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Clinical Cancer Research

Imaging, Diagnosis, Prognosis

PET Tumor Metabolism in Locally Advanced Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy: Value of Static versus Kinetic Measures of Fluorodeoxyglucose Uptake

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Abstract

Purpose: Changes in tumor metabolism from positron emission tomography (PET) in locally advanced breast cancer (LABC) patients treated with neoadjuvant chemotherapy (NC) are predictive of pathologic response. Serial dynamic [^{18}F]-FDG (fluorodeoxyglucose) PET scans were used to compare kinetic parameters with the standardized uptake value (SUV) as predictors of pathologic response, disease-free survival (DFS), and overall survival (OS).

Experimental Design: Seventy-five LABC patients underwent FDG PET prior to and at midpoint of NC. FDG delivery (K_1), FDG flux (K_i), and SUV measures were calculated and compared by clinical and pathologic tumor characteristics using regression methods and area under the receiver operating characteristic curve (AUC). Associations between K_1, K_i, and SUV and DFS and OS were evaluated using the Cox proportional hazards model.

Results: Tumors that were hormone receptor negative, high grade, highly proliferative, or of ductal histology had higher FDG K_i and SUV values; on an average, FDG K_1 did not differ systematically by tumor features. Predicting pathologic response in conjunction with estrogen receptor (ER) and axillary lymph node positivity, kinetic measures (AUC = 0.97) were more robust predictors than SUV (AUC = 0.84, $P = 0.005$). Changes in K_1 and K_i predicted both DFS and OS, whereas changes in SUV predicted OS only. In multivariate modeling, only changes in K_1 remained an independent prognosticator of DFS and OS.

Conclusion: Kinetic measures of FDG PET for LABC patients treated with NC accurately measured treatment response and predicted outcome compared with static SUV measures, suggesting that kinetic analysis may hold advantage of static uptake measures for response assessment. *Clin Cancer Res; 17(8); 2400–9. ©2011 AACR.*

Introduction

An advantage of positron emission tomography (PET) over other conventional oncologic imaging is the ability to quantify functional tumor biology. The most commonly used radiotracer in PET, [^{18}F]-fluorodeoxyglucose (FDG), targets tumor cells that exhibit increased glucose metabolism. The standardized uptake value (SUV) is the most commonly used measure of FDG tumor metabolism in clinical practice. The SUV is obtained semiquantitatively from a single (static) scan, conducted 60 minutes post-injection. Dynamic PET imaging over 60 minutes of tracer uptake allows use of a 2-compartment model to derive multiple quantitative parameters such as glucose metabolic rate estimated from FDG (MRFDG), glucose blood-to-tissue delivery (FDG K_1), and FDG flux constant (FDG K_i; refs. 1, 2).

One clinical oncologic indication for FDG PET in breast cancer is evaluation of treatment response among high-risk patient populations, such as those with locally advanced breast cancer (LABC), defined as any breast cancer that is greater than 5 cm in diameter, or invades the chest wall or skin, or has fixed lymph node metastases or is inflammatory (3–7). The standard of care for LABC patients is neoadjuvant (preoperative) chemotherapy with the goal of delivering early systemic therapy to micrometastases, improving tumor resectability, and assessing *in vivo* tumor response to systemic therapy agents (8). Patients who achieve a pathologic complete

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Translational Relevance

Positron emission tomography (PET) has been shown to be effective in monitoring treatment response for systemic therapy of locally advanced breast cancer. Using compartmental analysis of data from dynamic PET images, we estimated fluorodeoxyglucose (FDG) kinetics including glucose delivery (K_1) and glycolytic flux (K_i). We compared kinetic parameters versus static uptake measures, standardized uptake value (SUV), in their performance as a tumor response measure and predictor of patient outcome. We observed that mid-therapy changes in FDG K_1 and K_i were more robust predictors than SUV of pathologic response, relapse, and mortality. We observed a dependence on the change in SUV with therapy on pretherapy tumor uptake, implying reduced accuracy for low uptake tumors, not seen for kinetic parameters. These results provide an impetus for development of clinically practical approaches for obtaining FDG kinetic measures for tumor response evaluation as robust measures of response and predictors of patient outcome.

response (pCR) to neoadjuvant treatment have improved survival compared with patients achieving a less than pCR (9–11). Prior reports from our institution showed that changes in blood flow from [^{15}O]-water PET, and changes in MRFDG and FDG K_1, from FDG PET scans before the initiation of chemotherapy and at therapy midpoint, were associated with pathologic tumor response among LABC patients. Patients who achieved a pCR had, on average, a greater decrease in blood flow, MRFDG, and FDG K_1 from baseline to mid-therapy examinations (12, 13). In addition, higher recurrence or mortality risks have been associated with patients whose tumors had limited or no decline in blood flow or FDG K_1 over the course of therapy (13).

We present here a follow-up analysis investigating static SUV values versus kinetic measures (FDG K_1 and FDG K_i) from serial FDG PET scans in breast cancer patients undergoing chemotherapy, comparing pretherapy measures to tumor phenotypic features and changes in measures to pathologic response, relapse, and survival. This study differs from prior reports because it includes a larger patient population size, extended follow-up time, and has the primary focus of comparing FDG kinetic parameters versus static SUV measures as predictors of breast cancer phenotype and response to chemotherapy. The hypothesis tested was that the FDG kinetic measures would be more predictive than SUV as early indicators of pathologic response, disease-free survival (DFS), and overall survival (OS). Support for the hypothesis is based on earlier reports that have shown that kinetic analysis may be better suited to measuring treatment response, especially for patients with low pretherapy FDG uptake (4, 14, 15).

Materials and Methods

Patient selection

Patients who presented to the University of Washington Breast Cancer Specialty Center with histologically confirmed breast carcinoma scheduled to undergo neoadjuvant chemotherapy (NC) were eligible for the study. Patients were imaged as part of an ongoing prospective trial evaluating PET and LABC with an enrollment period from November 1995 to October 2007. Exclusion criteria included pregnancy, nonsurgical candidates, and patients unwilling, or unable to undergo PET examinations. Imaging performed for the study was primarily observational, and other than staging information from pretherapy PET scans, scan results were not intended to direct therapy. Prior enrollment periods yielded 53 patients with multiple PET scans who underwent surgery and have been previously described (12, 13). An additional 47 patients were enrolled since that time in the ongoing study that has now concluded, 22 are included in the current retrospective analysis, yielding a total of 75 patients. Of patients not included in the analysis, 25 of 47 were excluded because they did not have a mid-therapy examination ($n = 16$) or the baseline PET examination–identified metastatic disease ($n = 9$). The University of Washington Institutional Review Board approved the research protocol and written informed consent was obtained from all participants.

PET

PET radiotracer production, imaging methods, and data analysis have been previously described (12, 15–19). Briefly, images were acquired prior to and at the midpoint of NC on an Advance tomograph (General Electric Medical Systems) with a reconstructed spatial resolution of 10 to 12 mm (18). A dose range of 218 to 399 Mbq [^{18}F]-FDG was infused over 2 minutes in a 7- to 10-mL volume. Dynamic images were acquired for 60 minutes after the start of infusion. Regions of interest (ROI) were intended to measure "peak" uptake and were 1.5-cm diameter circles, drawn over the portion of the tumor with maximal uptake on summed images. Similar regions were drawn over the left ventricle to determine blood and tumor time–activity curves. [^{18}F]-FDG kinetic parameter estimates were obtained utilizing model optimization software (Berkeley Madonna; ref. (17). Of these, FDG K_1 (mL/min/g) and flux (K_i; mL/min/g) were the primary measures included in this analysis based on their value in prior studies (13, 17). Average FDG uptake from 45 to 60 minutes for the same ROIs were used to calculate weight-based SUV values that were not corrected for plasma glucose using standard definitions as in prior studies (15).

Tumor response assessment

A pCR was defined as the absence of invasive tumor by microscopic examination of the primary tumor postsurgical specimen. This response endpoint has been used in several prior studies of neoadjuvant treatment of LABC and has been shown to carry prognostic significance (20).

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Statistical analysis

Associations between tumor pathologic response and PET measures were evaluated using the Pearson's χ^2 test or Student's t test with unequal variances. Associations between prognostic factors and PET measures were evaluated using the Pearson's correlation coefficient (continuous variables), Student's t test for unequal variances (binary variables), or 1-way ANOVA (categorical variables). Changes in PET measures were examined using a 2-sample t test, comparing the 2 most prevalent chemotherapy regimens. Classification of pathologic response using different PET measures was compared using receiver operating characteristic (ROC) methods on probability of pathologic response estimated by logistic regression (predicting response by clinical prognostic factors and dynamic or static PET measures; refs. 21, 22).

Cox regression for survival analysis (23, 24) was used to calculate HRs and 95% CIs, measuring the association between PET parameters and breast cancer relapse or mortality risk. Time to recurrence (local/distant) was computed from date of surgery after NC to date of recurrence or date of death. Time-to-death was calculated from the date of diagnosis to the date of death, and times for women without recurrence or death were censored by date of last clinical follow-up or by May 4, 2009, whichever occurred first. Predictors with missing data were excluded casewise from Cox proportional hazards models. FDG K_1, FDG K_i, and SUV levels were log-transformed (base 2) so that a 1-unit difference in the HRs would be associated with a doubling of PET measures. After examining univariate models, multivariable Cox models were fitted for DFS and OS, holding constant clinical prognostic factors. The factors considered in the final models included tumor size, histologic subtype (ductal vs. lobular), number of positive axillary lymph nodes (ALN), estrogen receptor (ER), progesterone receptor (PR), and pathologic response. The proportional hazards assumption was validated by inspection of log–log survival curves. Analyses were performed using Stata/SE for Macintosh, version 10.1 (StataCorp) and SAS version 9.2 (SAS Institute).

Results

Treatment and response characteristics

More than 75% of patients presented with T3-T4 tumors (average tumor size = 5.2 cm; range = 1.1–14 cm) and N1 or greater nodal disease, reflecting common characteristics of LABC (Table 1). Only 1 patient had a tumor less than 1.5 cm, which was 1.1 cm by ultrasound and 2 cm by physical examination. Nine breast cancers were classified as inflammatory. Sixteen (21%) patients had histologically confirmed disease in the ALNs prior to the start of therapy.

The majority of patients (65/75, 87%) received weekly metronomic doxorubicin-based chemotherapy with daily oral cyclophosphamide and 27 of them followed it with weekly paclitaxel. The remaining patients received a variety of different regimens. The mean chemotherapy duration was 19 weeks (range = 8–38 weeks). Post–neoadjuvant therapy was performed per institutional standards and was based largely upon posttherapy surgical findings in the breast and axilla. Adjuvant treatment typically involved additional systemic therapy and regional radiotherapy if nodal disease was present. The baseline PET scan was performed for a mean of 9 days after the diagnostic biopsy (range = 1–72). Dynamic PET scans were performed before

Table 1. Subject demographic and clinical characteristics

Characteristics	$N = 75$	%
Age at diagnosis, y		
30–39	16	21
40–49	28	38
50–59	22	29
60+	9	12
Race		
Non-Hispanic white	63	84
African American	7	9
Asian/Pacific Islander	5	7
Histology		
Ductal	69	92
Lobular	6	8
Clinical tumor classification		
T1	2	3
T2	16	21
T3	43	57
T4	14	19
Clinical lymph node classification		
N0	14	19
N1	46	61
N2	13	17
N3	2	3
Tumor size, cm		
0–1.9	3	4
2–5	38	51
>5	34	45
ER		
Positive	41	55
Negative	34	45
PR		
Positive	34	45
Negative	41	55
HER-2/*neu*[a]		
Positive	19	26
Negative	55	74
Ki-67 proliferative index[b]		
Other than high	14	23
High[c]	48	77
Menopausal status		
Pre	47	63
Post	28	37

[a]Oncogene, unknown, $n = 1$.
[b]Unknown, $n = 13$ (17%).
[c]Greater than 20%.

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Table 2. Baseline FDG delivery, flux, and SUV measures versus clinical and pathologic breast tumor features

	K_1, mL/min/g			K_i, mL/min/g			SUV		
Characteristic	**Mean**	**SD**	***P***	**Mean**	**SD**	***P***	**Mean**	**SD**	***P***
Tumor histology									
Ductal	0.133	0.049	0.92	0.025	0.018	<0.0001	5.06	2.93	<0.0001
Lobular	0.130	0.070		0.006	0.002		2.25	0.52	
Clinically positive nodes									
No	0.123	0.050	0.40	0.025	0.021	0.67	5.14	3.31	0.70
Yes	0.135	0.051		0.023	0.018		4.77	2.85	
Menopausal status									
Pre	0.132	0.052	0.89	0.024	0.019	0.58	4.94	3.09	0.67
Post	0.134	0.050		0.022	0.017		4.65	2.64	
Tumor grade									
I	0.153	0.070	0.54	0.008	0.005	0.003	2.62	0.81	0.006
III	0.131	0.050		0.018	0.013		3.96	2.32	
III	0.131	0.050		0.029	0.020		5.67	3.12	
ER expression									
Positive	0.134	0.058	0.82	0.017	0.012	0.0008	3.82	2.21	0.001
Negative	0.131	0.041		0.031	0.021		6.06	3.22	
PR expression									
Positive	0.131	0.058	0.77	0.016	0.011	0.0009	3.62	1.80	0.0004
Negative	0.134	0.045		0.029	0.021		5.84	3.28	
HER-2/*neu*									
Positive	0.133	0.052	0.86	0.025	0.020	0.16	5.12	3.16	0.12
Negative	0.135	0.051		0.019	0.013		4.11	2.01	
Ki-67 proliferative index									
Other than high	0.142	0.060	0.46	0.012	0.009	0.0001	3.10	1.08	0.0002
High	0.129	0.050		0.026	0.019		5.16	2.94	

patients started chemotherapy and at mid-therapy, with an average 11 weeks of therapy (range = 6–27 weeks).

Surgical management was mastectomy (79%) or lumpectomy (21%), performed an average of 3.3 weeks following the last chemotherapy dose (range = 0.9–7.4 weeks) with the exception of 3 delays due to: patient request (9 weeks); plastic surgery coordination (10 weeks); and severe leukopenia (12 weeks).

Twenty-one (28%) patients achieved a primary tumor pCR to NC and 54 (72%) achieved other than pCR. Patients less likely to achieve a pCR were those with positive ALN posttherapy (6/45 = 13% pCR, compared with 15/30 = 50% for negative ALN posttherapy, P = 0.001) and ER^+ (5/41 = 12% vs. 16/34 = 47% for ER^-, $P = 0.002$) or PR^+ tumors (3/34 = 9% vs. 18/41 = 44% for PR^-, P = 0.002). Other clinical prognostic markers were not associated with tumor pathologic response.

The DFS median follow-up time was 4.2 years (range = 0.1–13.0 years) and the OS median follow-up time was 5.0 years (range = 0.6–13.4 years). Eighteen (24%) patients relapsed, presenting with metastases to the lung (31%), liver (31%), brain (19%), bone (13%), and lymph nodes (6%). Thirteen patients (17%) died; 10 deaths were due to metastatic breast cancer, 1 was probable and 2 were unknown.

PET measurements and association with tumor phenotypic features and pathologic response

Pretherapy K_i and SUV PET measures were associated with tumor histologic markers (Table 2, Fig. 1). Tumors that were of ductal origin, high grade, ER or PR negative, or highly proliferative had higher average FDG K_i and SUV. In contrast, baseline FDG K_1 was not associated with clinical or pathologic markers.

Baseline PET measures did not predict treatment response; however, changes in kinetic PET measures from baseline to mid-therapy were associated with tumor response. On an average, pCR patients had a 76% and 84% decrease in FDG K_1 and FDG K_i compared with 27% and 65%, respectively for other than pCR patients ($P \leq$ 0.0001 and $P = 0.004$). Changes in tumor uptake by SUV were similarly related to response (mean = 65% pCR vs. 50% non-pCR, $P \leq .01$). These changes were well beyond test/retest precision based on prior studies including our prior analysis (17). Multivariable logistic regression models were used to predict pCR by PET measures, adjusting for ER and pretherapy clinical axillary node positivity (additional clinical covariates resulted in overfitting). Predictions from a model including SUV had an area under the ROC curve (AUC) of 0.84 (95% CI = 0.74–0.95), whereas a model

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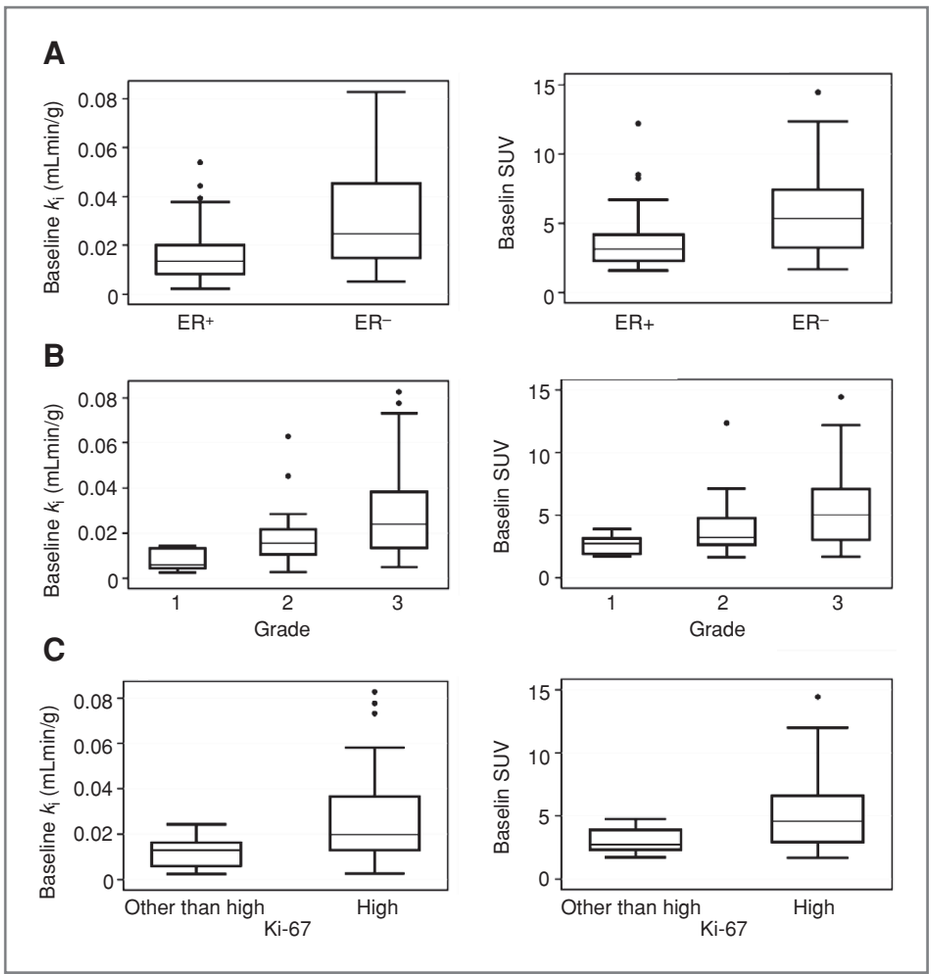

Figure 1. Comparison of baseline K_i and SUV values versus tumor pathologic markers. A, ER status ($P \leq 0.001$ for both). B, tumor grade ($P = 0.001$, K_i and $P = 0.002$, SUV). C, tumor proliferation ($P = 0.003$, K_i and $P = 0.001$, SUV).

including kinetic measures (FDG K_1 and FDG K_i) had an AUC of 0.97 (95% CI = 0.94–1.0). Using a nonparametric test comparing correlated ROC curves (with different markers predicting the same gold standard; ref. 22), the model using kinetic PET measures (AUC = 0.97) was superior to the model using the SUV (AUC = 0.84, $P = 0.005$).

Our prior analysis has shown that the level of tracer uptake in tumors pretherapy may affect the performance of SUV as a measure of change in FDG uptake with therapy (15). To this effect, we compared the percent change in SUV with the change in K_i for patients divided by tertiles of pretherapy uptake, similar to prior studies (15). For each group, we noted the maximum percent change in SUV, recorded as the absolute value of the y-intercept at K_i equal to −100% for the linear fit of percent change SUV versus percent change K_i. For patients whose tumors were in the lowest tertile of uptake pretherapy (pretherapy SUV < 3), the maximum percent change was 52%, compared with a maximum 81% change in SUV for patients whose tumors had higher pretherapy FDG uptake ($P \geq 0.0001$). This suggests that for tumors with low pretherapy uptake, SUV is relatively insensitive to change in FDG kinetics with treatment. We also compared the percent change in SUV, K_1, and K_i for the different tertiles of pretherapy FDG uptake (Fig. 2). Whereas there were no differences between tertiles in the mean change in K_1 (Fig. 2A) or K_i (Fig. 2B), changes in SUV were strongly related to magnitude of pretherapy uptake (Fig. 2C). Average change in uptake with therapy was lower for patients whose tumors had the lowest pretherapy SUV (−41% tertile 1 vs. −55% tertile 2 vs. −67% tertile 3; $P = 0.001$). This result indicates that SUV may underestimate the change in FDG uptake in response to therapy in patients with low pretherapy uptake.

PET measures association with relapse and survival

Pretherapy PET measures did not predict the likelihood of patient relapse or mortality (Table 3, univariate analysis). Mid-therapy functional imaging parameters were associated with DFS and OS in univariate Cox analyses. Patients whose tumors exhibited persistent, elevated FDG K_i on the mid-therapy examination had a 1.37-fold increased risk of

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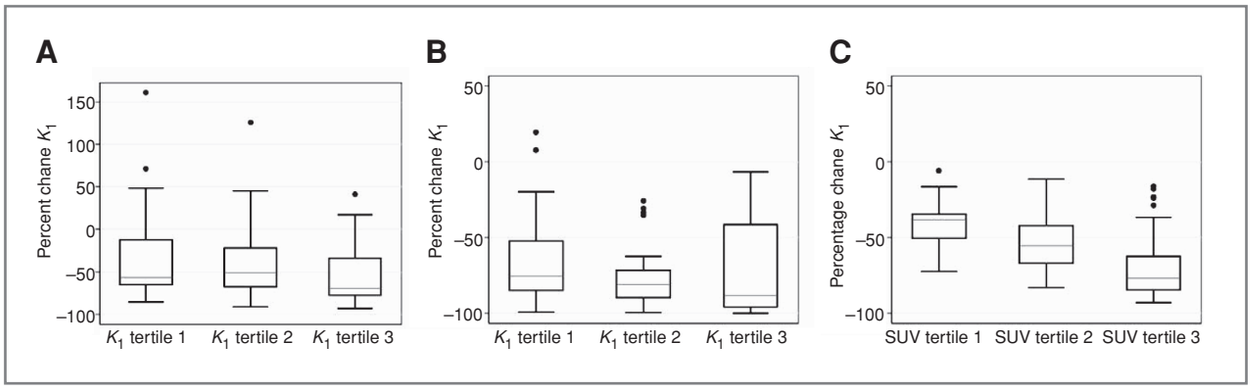

Figure 2. Comparison of the percent change measures from pretherapy to mid-therapy versus tertiles of pretherapy measures for: (A) FDG delivery (K_1; mL/min/g), (B) glycolytic flux (K_i; mL/min/g), and (C) SUV.

breast cancer recurrence and a 1.44-fold increased mortality risk for each doubling of FDG K_i, respectively. Although the change in K_1 and K_i were not necessarily correlated with each other, changes in both K_1 and K_i from baseline to mid-therapy were associated with earlier relapse or poorer OS. Changes in SUV were associated with OS only.

In multivariable Cox modeling (Table 3, multivariable adjusted analysis), the change in FDG K_1 delivery was associated with elevated relapse among patients with smaller declines or interval increases in FDG K_1 measured over the course of neoadjuvant treatment (HR = 1.37, 95% CI = 1.16–1.62). For example, a 10-percent point greater increase in FDG K_1 delivery to the primary tumor from baseline to mid-therapy examinations inferred a 37% higher recurrence risk to the patient. Greater mortality risks were also observed among patients with persistent or elevated FDG K_1 from baseline to mid-therapy PET examinations with a 33% greater risk of mortality for each 10% increase in FDG delivery (HR = 1.33, 95% CI = 1.12–1.58). The elevated recurrence and mortality risks that were observed univariately for change in FDG K_i were of borderline significance in multivariate models ($P = 0.06$ and $P = 0.07$ for DFS and OS, respectively). SUV changes during treatment were not significant in multivariable models ($P = 0.16$ and $P = 0.21$).

Discussion

Numerous studies have shown that FDG PET and PET/CT (computed tomography) are valuable and accurate clinical tools for measuring response to chemotherapy in LABC (3–5, 25). Most studies reported to date, and most PET procedures performed in the clinic, use static uptake measures, such as SUV, to quantify the level of FDG uptake in tumors and to track treatment changes as a measure of response. Some studies have also used FDG kinetic measures to quantify tumor metabolism in LABC treated with chemotherapy (3, 4, 13, 15) and found kinetic measures to be highly predictive of pathologic response and/or patient survival. Prior analyses from smaller patient populations suggested that kinetic measures might offer an advantage in response evaluation and predictive capability (4, 13, 15). The goal of our analysis was to test kinetic versus static measures of FDG uptake as predictors of response and outcome in a larger cohort of LABC patients treated with NC, for whom pathologic response, relapse, and mortality had been recorded. Our study posed 2 questions in comparing static uptake (SUV) to kinetic measures (delivery, K_1, and flux, K_i): (i) Do delivery and flux have the same relationship to pretherapy tumor phenotypic features compared with SUV? (ii) Are changes in SUV with therapy similar to changes in delivery and flux in the ability to predict response and outcome? Similar to prior reports (26–30), we found that pretherapy FDG SUV correlated with pathologic tumor characteristics; there were higher SUV values for ductal versus lobular tumors, and for high grade, highly proliferative, or hormone receptor–negative tumors. Nearly identical findings were observed for FDG K_i; however, no significant associations were found between FDG delivery and the phenotypic features tested. These results suggest that kinetic analysis does not add considerably to predicting tumor phenotype from FDG PET imaging, and consequently, that differences in performance as a response metric for static versus kinetic measures are not simply on the basis of association with tumor phenotype.

We did observe differences in the performance of SUV versus kinetic measures as predictors of patient response and outcome. Mid-therapy changes in FDG K_1 and K_i were highly predictive of pathologic response and had strong associations with relapse and OS in univariate analysis. On the other hand, SUV had a weaker, though still significant, association with pathologic response and OS, but not with relapse. In multivariate analysis that included known clinical and pathologic prognostic factors for LABC, the kinetic measures provided significantly incremental predictive capability, whereas SUV did not. These results suggest that the use of kinetic analysis in serial FDG PET applied to breast cancer treatment response offers significant advantages over static uptake measures such as SUV.

Why should kinetic measures be more predictive than SUV for serial FDG PET scans over the course of therapy? Our results suggest 2 factors and the first factor relates to

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Table 3. Risk of breast cancer recurrence and mortality associated with PET uptake measures

			DFS					
			Univariate analysis			Multivariate adjusted analysis[a]		
Characteristic	No. at risk	No. of recurrences	HR	95% CI	P[b]	HR	95% CI	P[b]
Baseline K_1[c]	75	18	0.63	0.32–1.23	0.18	0.19	0.06–0.61	0.003
Baseline K_i[c]	75	18	1.07	0.70–1.63	0.76	1.13	0.61–2.10	0.70
Baseline SUV[d]	75	18	0.91	0.49–1.70	0.77	0.92	0.41–2.07	0.84
Mid-therapy K_1[c]	75	18	1.49	0.96–2.32	0.07	1.55	0.79–3.04	0.19
Mid-therapy K_i[c]	75	18	1.37	1.06–1.77	0.01	1.36	0.97–1.90	0.05
Mid-therapy SUV[d]	75	18	1.52	0.91–2.54	0.14	1.45	0.72–2.91	0.31
Change in K_1[e]	75	18	1.16	1.07–1.27	0.001	1.37	1.16–1.62	<.0001
Change in K_i[e]	75	18	1.20	1.05–1.37	0.01	1.20	0.99–1.44	0.06
Change in SUV[e]	75	18	1.22	0.97–1.53	0.08	1.19	0.90–1.57	0.21
			OS					
			Univariate analysis			Multivariate adjusted analysis[a]		
Characteristic	No. at risk	No. of recurrences	HR	95% CI	P value[b]	HR	95% CI	P value[b]
Baseline K_1[c]	75	18	0.86	0.38–1.96	0.73	0.27	0.06–1.21	0.07
Baseline K_i[c]	75	18	1.13	0.68–1.87	0.64	1.31	0.59–2.91	0.50
Baseline SUV[d]	75	18	1.11	0.55–2.23	0.78	1.30	0.49–3.49	0.50
Mid-therapy K_1[c]	75	18	1.58	0.94–2.66	0.08	1.88	0.85–4.16	0.11
Mid-therapy K_i[c]	75	18	1.44	1.06–1.95	0.01	1.43	0.98–2.07	0.04
Mid-therapy SUV[d]	75	18	1.96	1.14–3.34	0.03	1.88	0.87–4.06	0.12
Change in K_1[e]	75	18	1.16	1.05–1.28	0.005	1.33	1.12–1.58	0.0003
Change in K_i[e]	75	18	1.26	1.08–1.47	0.006	1.21	0.98–1.49	0.07
Change in SUV[e]	75	18	1.38	1.04–1.84	0.02	1.27	0.91–1.78	0.16

[a]Multivariate adjusted HRs adjusted for ER, PR, tumor size (0–1.9, 2–5, and >5 cm), histology (ductal/lobular), pCR (pCR vs. other than pCR), and ALN positivity (0, 1–3, 4, or more).
[b]Likelihood ratio test.
[c]Log base 2, mL/min/g $\times 10^{-3}$.
[d]Log base 2.
[e]1 unit = 10 percent change.

tumors with low pretherapy FDG uptake. Prior reports have shown that SUV and other static measures have limited sensitivity for evaluating response in patients with low pretherapy FDG uptake (4, 14, 15, 31). Tumors with lower metabolic rates have a relatively larger proportion of non-metabolized FDG in tissue that contributes to the SUV compared with tumors with higher uptake (32–34). Static measures cannot distinguish between nonphosphorylated FDG, which does not provide specific information on glucose metabolic rate, and phosphorylated FDG (FDG-6P), which are FDG molecules that have committed to the glucose metabolism pathway. Kinetic analysis, on the other hand, can estimate the flux of FDG from the blood to FDG-6P, which is trapped within cells by phosphorylation during the commitment to the glucose metabolism pathway. As in our prior report (15), we found that low baseline SUV values were associated with lower maximum detectable SUV percent changes from pretherapy to mid-therapy scans. Furthermore, although pretherapy uptake was not associated with pathologic response, we did observe a clear trend for lower percent change in SUV with therapy for tumors that had low pretherapy uptake compared with tumors with higher uptake. A correlation between pretherapy uptake and change over the course of therapy was not observed for either K_1 or K_i. Taken together, these findings suggest that for SUV, but not for kinetic parameters, performance as a response measure depends upon the level of tumor uptake pretherapy.

A second factor underlying the advantage of kinetic measures over static measures is the ability of dynamic

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imaging to measure multiple aspects of FDG kinetics at the same time such as glucose delivery or glycolytic flux. This is in distinction to simple static measures that only indirectly reflect FDG kinetics. We observed that patients with greater reductions in both FDG K_1 and FDG K_i over the course of treatment were more likely to achieve a pCR and that changes in both K_1 and K_i were strongly associated with DFS and OS. This was not true for changes in SUV. In multivariate analysis that included known predictive and prognostic clinical and pathologic features, we found that the change in FDG delivery to the tumor over the course of therapy added significantly to predicting relapse and mortality. This was not the case for changes in SUV. Patients with persistent or incremental increases in FDG K_1 were more likely to relapse or experience mortality. For example, a patient that had a +20% change in FDG K_1 from baseline to mid-therapy examination had a 1.37-fold greater recurrence risk or a 1.33-fold greater mortality risk compared with a patient that had +10% change. Even after adjusting for standard clinical or pathologic markers, the change in glucose delivery to breast tumors remained an independent predictor of patient outcome. The ability to quantify changes in both glucose delivery and metabolic flux potentially offers significant advantages. Glucose delivery appears to provide an indirect measure of tumor perfusion (17, 35–37) as observed by perfusion-based imaging studies like ^{15}O-water PET and dynamic contrast-enhanced (DCE) MRI (12, 13, 38, 39) where perfusion measures were highly predictive in evaluating treatment response. Thus, a second important advantage of kinetic analysis over static uptake measures is the ability to quantify multiple aspects of tumor biology, and their changes in response to therapy.

Static acquisition is the most common clinical FDG PET imaging protocol from which SUV measures can easily be determined. However, SUV appears to have some important limitations as a measure of response. In addition to the factors identified in our analysis, there may be other factors in clinical imaging SUV estimation that may further limit its utility. SUV values are dependent on the time interval between tracer injection and imaging. Variations in this interval could confound comparisons between baseline and mid-therapy examinations in patients being scanned for therapy monitoring (40). Furthermore, the limited count statistic arising from a short static acquisition may have considerable statistical fluctuation. In our study, SUVs were highly optimized compared with standard clinical imaging; they were taken from fixed time intervals after injection (45–60 minutes), yielding high-count measures from a highly reproducible time interval. Even under these optimized conditions, kinetic analysis offered significant advantages over SUV.

Our results provide an impetus for clinically practical methods capable of estimating kinetic parameters from FDG PET studies. Some studies have suggested estimating tumor perfusion from a short dynamic image performed at the time of FDG injection (36). Dual time point imaging has also been tested and may provide additional data on FDG kinetics (41, 42); however, its values may be more limited in low uptake tumors where there is either a slight increase or minimal decrease in SUV over time (40). Further optimization of kinetic analysis measures may yield insights into practical alternatives that overcome the limitations of purely static measures and lead to the establishment of clinical scenarios where optimized kinetic analysis may be the most helpful, as in the case of low baseline tumor FDG uptake (15).

There are some important limitations to note for this study. The reported PET parameters measured only the most metabolically active portion of the tumor, as an indicator of the most aggressive behavior. LABC can be heterogeneous and analyzing heterogeneity of the entire tumor may further our understanding of its biological processes (43). Second, changes in clinical practice for LABC patients at this institution led to extended NC regimens over the duration of this study. However, the majority of patients did receive metronomic doxorubicin-based treatment and a comparison of the changes in PET parameters between the 2 prevalent neoadjuvant regimens showed no dependence on chemotherapy regimen (data not shown).

In conclusion, additional quantitative kinetic measures can be obtained from dynamic PET imaging compared with static SUV measures. Whereas FDG flux and SUV have similar correlation with tumor phenotypic features, the combination of measures of glucose delivery (K_1) and K_i from kinetic analysis of dynamic FDG PET offer significant advantages over SUV for predicting response, relapse, and survival from serial FDG PET studies. Changes in FDG delivery, and not SUV, during treatment predicted patient outcome, providing independent prognostic information that is distinct from pathology. These results provide an impetus for development of clinically practical approaches for obtaining FDG kinetic measures for tumor response evaluation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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