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ORIGINAL REPORT

Tumor Metabolism and Blood Flow Changes by Positron Emission Tomography: Relation to Survival in Patients Treated With Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer

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ABSTRACT

Purpose
Patients with locally advanced breast carcinoma (LABC) receive preoperative chemotherapy to provide early systemic treatment and assess in vivo tumor response. Serial positron emission tomography (PET) has been shown to predict pathologic response in this setting. We evaluated serial quantitative PET tumor blood flow (BF) and metabolism as in vivo measurements to predict patient outcome.

Patients and Methods
Fifty-three women with primary LABC underwent dynamic [^{18}F]fluorodeoxyglucose (FDG) and [^{15}O]water PET scans before and at midpoint of neoadjuvant chemotherapy. The FDG metabolic rate (MRFDG) and transport (FDG K_1) parameters were calculated; BF was estimated from the [^{15}O]water study. Associations between BF, MRFDG, FDG K_1, and standardized uptake value and disease-free survival (DFS) and overall survival (OS) were evaluated using the Cox proportional hazards model.

Results
Patients with persistent or elevated BF and FDG K_1 from baseline to midtherapy had higher recurrence and mortality risks than patients with reductions. In multivariable analyses, BF and FDG K_1 changes remained independent prognosticators of DFS and OS. For example, in the association between BF and mortality, a patient with a 5% increase in tumor BF had a 67% higher mortality risk compared with a patient with a 5% decrease in tumor BF (hazard ratio = 1.67; 95% CI, 1.24 to 2.24; $P < .001$).

Conclusion
LABC patients with limited or no decline in BF and FDG K_1 experienced higher recurrence and mortality risks that were greater than the effects of clinical tumor characteristics. Tumor perfusion changes over the course of neoadjuvant chemotherapy measured directly by [^{15}O]water or indirectly by dynamic FDG predict DFS and OS.

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INTRODUCTION

Up to 20% of breast cancer patients present with locally advanced breast cancer (LABC) without distant metastases.[1] The current standard of care for LABC is preoperative chemotherapy. A limited number of LABC patients achieve a pathologic complete primary tumor response (pCR) to neoadjuvant chemotherapy. These patients have improved survival compared with patients achieving a less than pCR.[2-4]

Positron emission tomography (PET) evaluates in vivo tumor biology by measuring tumor perfusion and tumor glucose utilization using radiotracers [^{15}O]water and [^{18}F]fluorodeoxyglucose (FDG), respectively, and has been useful for evaluating breast cancer response.[5-8] In previous reports, we showed that PET measures of tumor blood flow (BF) and glucose metabolism (measured as FDG metabolic rate [MRFDG]) obtained before initiation of neoadjuvant chemotherapy and at midtherapy predicted response among LABC patients.[9,10] Patients with high pretherapy MRFDG relative to BF were more likely to have tumors resistant to therapy and were more likely to experience relapse. We also reported that resistant tumors were

more likely to have an increased BF over the course of therapy and that patients whose tumors failed to have a decline in perfusion at midtherapy were more likely to have higher recurrence and mortality risks. We documented that changes in PET measures also predicted the likelihood of achieving a pCR to treatment.[10] Further studies from our institution[11] examined the relationship between tumor glucose metabolism and BF using more detailed analyses of [^{18}F]FDG kinetics and found that FDG glucose blood-to-tissue transport (K_1) correlated with [^{15}O]water BF, in accord with other reports.[12]

We now present follow-up data to determine whether PET measures of tumor perfusion and metabolism were associated with disease-free survival (DFS) or overall survival (OS) among LABC patients. Such an assessment of in vivo tumor biology may provide knowledge regarding the prognostic utility of quantitative PET measurements and insight into factors associated with disease resistance and recurrence.

PATIENTS 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 were eligible for the study. Patients were clinically staged according to the TNM classification of malignant tumors.[13] The enrollment period was from November 1995 to December 2005. Patients were excluded if they were pregnant, unwilling, or unable to undergo PET examinations. Patients were also excluded if they were not surgical candidates. Prior enrollment periods yielded 35 patients with multiple PET scans who underwent surgery and have been previously described.[10] Since those reports, 30 additional patients were eligible for the study. Eleven patients underwent pretherapy imaging only as follows: two elected not to receive chemotherapy; three sought medical care elsewhere; four completed their neoadjuvant treatment and definitive surgery but were unwilling to undergo midtherapy imaging; and two had distant disease observed by computed tomography. One patient with lobular histology had little or no tracer uptake on pretherapy examination. Eighteen patients underwent serial PET scans and were analyzed with 35 patients from prior analyses to yield a total of 53 patients included in the study. Written informed consent for PET studies and follow-up was obtained according to the University of Washington Human Subjects Committee guidelines.

PET

PET radiotracer production, imaging methods, and data analysis have been previously described.[9-11,14,15] Briefly, images were acquired on the Advance tomograph (General Electric Medical Systems, Waukesha, WI) before and at the midpoint of neoadjuvant chemotherapy. For [^{15}O]water studies, patients received 725 to 1,902 MBq in a 1- to 4-mL volume via bolus intravenous injection. Dynamic images were acquired for 7.75 minutes after injection. For [^{18}F]FDG studies, 218 to 396 MBq was infused over 2 minutes in a 7- to 10-mL volume, and dynamic images were acquired for 60 minutes after the start of infusion. Regions of interest were 1.5-cm diameter circles, drawn over the tumor and the left ventricle of the heart to determine blood and tumor time-activity curves. BF estimates from [^{15}O]water and [^{18}F]FDG kinetic parameter estimates (MRFDG and K_1) were obtained using model optimization software (Berkeley Madonna, Berkeley, CA) as previously reported.[11] Average FDG standardized uptake values (SUVs) of the tumor region were also calculated as previously reported.[16]

Statistical Analysis

Our aims were to assess whether PET measures before neoadjuvant chemotherapy, PET measures at midtherapy, or changes in PET measures would predict DFS and OS. We also considered other patient and tumor characteristics as potential predictors of patient outcome and then assessed the effect of controlling for other factors in a multivariable model.

The primary outcomes were breast cancer recurrence and mortality. Disease recurrence was classified as local or distant. Local recurrence was defined as invasive disease limited to the ipsilateral breast, chest wall, or axillary lymph nodes, and distant recurrence was defined as metastases to other parts of the body. DFS was calculated in years, using the patient's date of surgery and one of the following: date of known recurrence, date of death, date last known to have no evidence of disease, or date of most recent clinical follow-up. OS was calculated in years, using the patient's breast cancer diagnosis date and one of the following: date of death, date last known to be alive, or date of most recent clinical follow-up. Chart review for patient clinical follow-up dates and disease

Table 1. Selected Characteristics Among Patients With Locally Advanced Breast Cancer

Characteristic	No. of Patients (N = 53)	%
Age at diagnosis, years		
30-39	12	23
40-49	22	41
50-59	14	26
60-69	4	8
70-79	1	2
Race		
Non-Hispanic white	43	81
African American	6	11
Asian/Pacific Islander	4	8
Tumor histology		
Ductal	49	92
Lobular	4	8
Clinical tumor classification		
T1	2	4
T2	11	21
T3	29	54
T4	11	21
Clinical lymph node classification		
N0	11	21
N1	31	58
N2	10	19
N3	1	2
Tumor size, cm		
0-1.9	3	6
2-5	25	46
> 5	26	48
ER		
Positive	31	58
Negative	22	42
PR		
Positive	28	53
Negative	25	47
HER-2/*neu**		
Positive	12	24
Negative	39	76
Ki-67 proliferative index†		
Other than high	13	29
High	32	71
Palpable axillary lymph nodes		
No	19	36
Yes	34	64
Menopausal status		
Premenopausal	37	70
Postmenopausal	16	30

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
*Oncogene; unknown, n = 2.
†Unknown, n = 8.

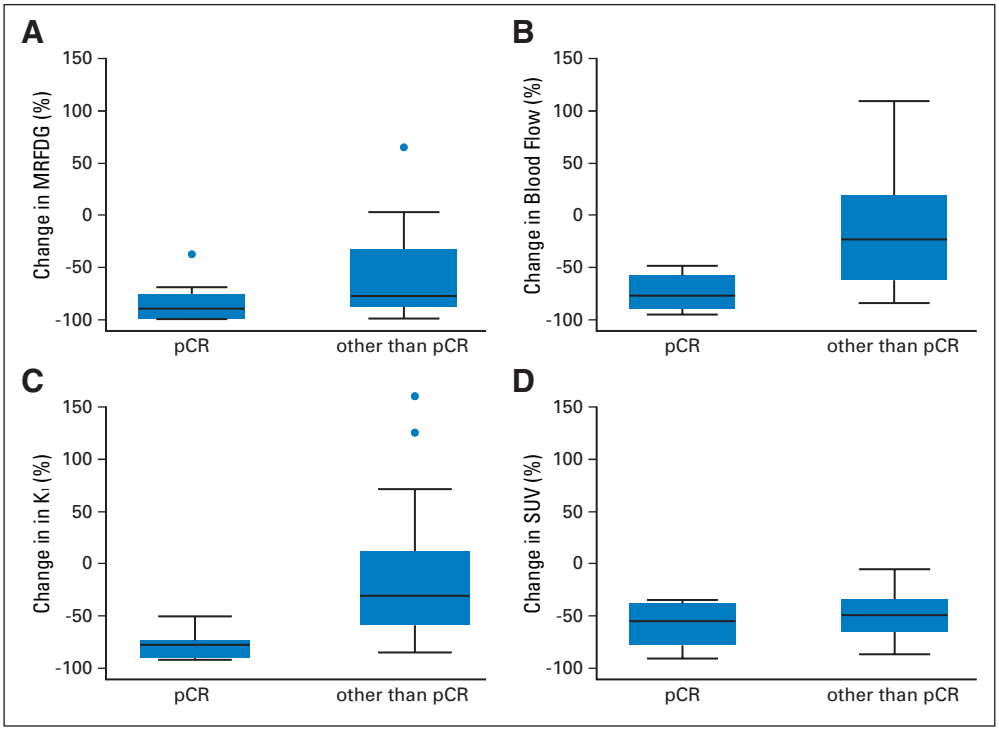

Fig 1. Percent change in serial positron emission tomography measurements versus pathologic response to neoadjuvant chemotherapy (pathologic complete response [pCR] or other than pCR) for (A) fluorodeoxyglucose metabolic rate (MRFDG), (B) blood flow, (C) fluorodeoxyglucose transport (FDG K_1), and (D) standardized uptake value (SUV; *P* values from two-sample *t* test).

status determination was completed as of June 30, 2006. Dates of death were also extracted from the Social Security Death Index.[17]

Established breast cancer prognostic factors associated with DFS and OS[4,18-23] that were assessed included diagnosis age (continuous), tumor size (0 to 1.9, 2 to 5, or > 5 cm), tumor grade (Nottingham histologic grading system, grades I to III), stage (American Joint Committee on Cancer classification system grouping, stages I to IV), axillary lymph node status (none, one to three, or ≥ 4 nodes), and pathologic tumor characteristics such as estrogen receptor (ER; positive or negative), progesterone receptor (PR; positive or negative), c-erb-b2 overexpression (HER-2/*neu*, yes or no), *p53* overexpression (yes or no), Ki-67 proliferation index (high or other), and pathologic response (pCR or other than pCR). We also assessed the possible influence of tumor histology (ductal *v* lobular) because tracer uptake varies by tumor type and tumor histology is associated with survival.[24] Associations between pathologic response and PET measures or prognostic factors were evaluated using the *t* test and Pearson's χ^2 test.

Kaplan-Meier curves were examined with continuous PET measures dichotomized above and below median values. Associations between PET predictors and breast cancer DFS and OS were estimated using the Cox proportional hazards model.[25,26] Predictors with missing data were excluded casewise from Cox models. MRFDG, BF, FDG K_1, and SUV levels were log transformed (base 2) so that hazard ratios based on a one-unit difference would be associated with a doubling of PET measures. After examining univariate models, we evaluated the contribution of PET parameters to multivariable models that controlled for the effects of prognostic factors selected based on prior research[4,18-23] and univariate results. The proportional hazards assumption was validated by inspection of log-log survival curves. Analyses were performed using Stata for Macintosh, version 9.2 (StataCorp, College Station, Texas) and R version 2.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients and Response

The characteristics of the 53 women included in the study are listed in Table 1. The mean age at diagnosis was 47 years (range, 32 to 76 years), and the average tumor size was 5.0 cm (range, 1.1 to 11 cm). Most patients had tumors with a high proliferative index; however, most tumors did not overexpress HER-2/*neu*. Patients were primarily premenopausal and had clinically palpable axillary lymphadenopathy. Five of 11 T4 carcinomas were inflammatory.

The majority of patients (83%) underwent weekly metronomic doxorubicin-based chemotherapy with daily oral cyclophosphamide (n = 40), daily oral cyclophosphamide and fluorouracil (n = 2), or doxorubicin only (n = 2). Four (7%) of 53 patients received nonweekly doxorubicin/cyclophosphamide. Three (6%) of 53 patients received weekly cyclophosphamide, methotrexate, and fluorouracil. One (2%) of 53 patients received paclitaxel/trastuzumab, and one (2%) of 53 patients received docetaxel/vinorelbine. Mean chemotherapy duration was 17 weeks (range, 8 to 28 weeks).

Surgery was performed a mean of 3.0 weeks after the last chemotherapy dose (range, 0.9 to 6.7 weeks) except for one patient whose surgery was 12 weeks after treatment as a result of severe leukopenia. Eleven (21%) of 53 patients underwent breast conservation surgery (lumpectomy) and axillary lymph node dissection, and 42 (79%) of 53 patients underwent total mastectomy and axillary lymph node dissection. Eleven patients (20%) achieved a pCR to neoadjuvant therapy, and 42 patients (80%) achieved other than pCR. Thirty-four of 53 patients had residual axillary nodal disease after therapy (median number of nodes positive, four nodes; range, one to 18 nodes).

The median follow-up time for DFS was 3.6 years (range, 0.1 to 9.7 years). Twelve patients had tumor recurrences; three patients experienced recurrence with both local and distant disease, and nine patients presented with distant metastases. The OS median follow-up time was 4.4 years (range, 0.5 to 10.4 years) with 10 deaths recorded. Seven deaths were confirmed to be caused by breast carcinoma, two were probable, and one was unknown. The estimated 4-year DFS and OS probabilities for the entire cohort were 80% and 84%, respectively.

Among patients who achieved a pCR, the estimated probability of surviving disease free for 4 years was 90% compared with 78% among patients who achieved other than pCR. For OS, 4-year survival probability among patients with a pCR was 100% compared with 79% for the other than pCR group.

PET Imaging

Pretherapy PET imaging was performed a mean of 5 days (range, 0 to 21 days) before the first chemotherapy dose, and midtherapy PET imaging occurred a mean of 9 weeks (range, 6 to 20 weeks) after the first chemotherapy dose. Changes in PET measures from baseline to midtherapy examinations were associated with tumor response (Fig 1 and Appendix Fig A1 [online only]). Patients who achieved a pCR had, on average, an 84%, 76%, and 79% decrease in MRFDG, BF, and FDG K_1 from baseline to midtherapy scans, respectively, whereas the average changes for patients with other than pCR were 62%, 14%, and 19%, respectively ($P < .01$ or less for MRFDG, BF, and FDG K_1). Percent change in average SUV was not related to response (60% pCR *v* 50% other than pCR; $P = .12$). In addition, pCR patients had lower pretherapy MRFDG:BF ratios compared with other than pCR patients ($P = .003$; Table 2). Other known prognostic markers were not associated with tumor pathologic response in this small cohort. High-grade, ER-negative, and PR-negative tumors had trends for improved response.

Survival Analysis: Univariate

Individual pretherapy PET values did not predict relapse or mortality; however, patients with a high pretherapy MRFDG:BF ratio were more likely to experience relapse (Table 3). Also, changes in PET values from baseline to midtherapy predicted those patients more likely to experience recurrence.

Persistent or elevated MRFDG and BF at midtherapy were indicators of poorer OS, with 1.4-fold and 1.7-fold increased mortality risks observed for each doubling of MRFDG and BF, respectively. For example, a patient whose tumor MRFDG is 4.0 has a 40% greater mortality risk compared with a patient whose tumor MRFDG is 2.0. Changes in PET values over the course of chemotherapy were also associated with outcome, in that patients who did not experience a decline in MRFDG, BF, FDG K_1, or SUV from baseline to midtherapy scans had elevated mortality risks compared with patients with decreased values between scans (Fig 2). Each 10% difference in the percent change of MRFDG, BF, FDG K_1, or SUV was associated with a 1.0- to 1.9-fold higher mortality risk compared with smaller increases or greater decreases in PET parameters. Although elevations in

Table 2. Association Between Clinical, Pathologic, and Baseline PET Data Versus Therapy Response

Parameter	No. of Patients		Test Statistic*	*P*
	pCR (n = 11)	Other Than pCR (n = 42)		
Age	11	42	$t = -0.43$	.66
Tumor size	11	42	$t = -0.22$	.82
Positive nodes†			$\chi^2 = 2.10$	.14
Yes	6	13		
No	5	29		
Menopausal status			$\chi^2 = 0.94$	.33
Premenopausal	9	28		
Postmenopausal	2	14		
Tumor grade			$\chi^2 = 4.63$	.09
I	1	4		
II	1	18		
III	9	20		
ER expression			$\chi^2 = 2.79$	.09
Positive	4	27		
Negative	7	15		
PR expression			$\chi^2 = 3.63$	.05
Positive	3	25		
Negative	8	17		
HER-2/*neu*‡			$\chi^2 = 0.10$	.74
Negative	8	31		
Positive	3	9		
Ki-67 proliferative index§			$\chi^2 = 0.10$	.74
Other than high	3	10		
High	6	26		
Baseline MRFDG	11	42	$t = 0.01$	.98
Baseline blood flow	11	42	$t = 1.96$	.07
Baseline MRFDG:blood flow	11	42	$t = -3.18$	.003

Abbreviations: PET, positron emission tomography; pCR, pathologic complete response; ER, estrogen receptor; PR, progesterone receptor; MRFDG, fluorodeoxyglucose metabolic rate.
*t = Student's t test; χ^2 = Pearson's χ^2 statistic.
†Binary: yes or no.
‡Unknown, n = 2.
§Unknown, n = 8.

Table 3. Univariate Cox Proportional Hazard Analyses of Breast Cancer Recurrence and Mortality Risk Among Women With LABC

Characteristic	Disease-Free Survival					Overall Survival				
	No. of Patients at Risk	No. of Recurrences	Hazard Ratio	95% CI	*P*	No. of Patients at Risk	No. of Deaths	Hazard Ratio	95% CI	*P**
Age at diagnosis	53	12	0.96	0.90 to 1.03	.28	53	10	0.95	0.88 to 1.03	.18
Tumor size, cm					.83					.91
0-1.9	3	1	1.00			3	1	1.00		
2-5	25	5	0.49	0.05 to 4.30		25	4	0.63	0.07 to 5.67	
> 5	25	6	0.54	0.06 to 4.64		25	5	0.76	0.09 to 6.57	
Tumor grade					.95					.90
I	5	1	1.00			5	1	1.00		
II	19	5	1.18	0.14 to 10.38		19	3	0.82	0.08 to 7.98	
III	29	6	0.98	0.12 to 8.34		29	6	1.12	0.13 to 9.46	
Tumor stage					.62					.84
I	2	1	1.00			2	1	1.00		
II	11	1	0.15	0.01 to 2.48		11	1	0.29	0.02 to 4.67	
III	29	6	0.32	0.04 to 2.70		29	5	0.55	0.06 to 4.82	
IV	11	4	0.38	0.04 to 3.75		11	3	0.59	0.06 to 5.73	
No. of axillary lymph node positive					.10					.09
0	19	2	1.00			19	1	1.00		
1-3	16	3	1.86	0.31 to 11.24		16	3	4.04	0.42 to 38.87	
≥ 4	18	7	4.44	0.92 to 21.46		18	6	6.96	0.84 to 57.98	
ER					.36					.14
Positive	31	6	1.00			31	4	to		
Negative	22	6	1.70	0.54 to 5.31		22	6	2.53	0.71 to 9.00	
PR					.26					.07
Positive	28	5	1.00			28	3	1.00		
Negative	25	7	1.93	0.61 to 6.11		25	7	3.16	0.81 to 12.24	
HER-2/*neu*†					.66					.96
Negative	39	8	1.00			39	7	1.00		
Positive	12	4	1.32	0.38 to 4.52		12	3	1.04	0.26 to 4.21	
p53‡					.29					.13
Negative	25	5	1.00			25	3	1.00		
Positive	19	5	1.98	0.57 to 6.88		19	5	2.96	0.70 to 12.47	
Ki-67 proliferative index§					.88					.82
Other than high	13	4	1.00			13	3	1.00		
High	32	7	1.10	0.32 to 3.81		32	6	1.17	0.29 to 4.72	
Tumor histology					.86					.81
Ductal	49	11	1.00			49	9	1.00		
Lobular	4	1	1.22	0.15 to 9.63		4	1	1.30	0.16 to 10.38	
Primary tumor pathologic response					.75					.93
pCR	10	2	1.00			11	2	1.00		
< pCR	43	11	1.27	0.28 to 5.86		42	8	1.06	0.22 to 5.04	
Baseline MRFDG‖	53	12	1.14	0.63 to 2.04	.66	53	10	1.25	0.69 to 2.26	.47
Baseline BF‖	53	12	0.51	0.24 to 1.08	.07	53	10	0.79	0.36 to 1.73	.54
Baseline FDG K_1‖	53	12	0.51	0.23 to 1.12	.10	53	10	0.76	0.30 to 1.92	.56
Baseline MRFDG:BF	53	12	1.04	1.01 to 1.06	.007	53	10	1.03	1.00 to 1.06	.06
Baseline SUV‖	53	12	0.86	0.39 to 1.91	.71	53	10	1.10	0.50 to 2.43	.81
Midtherapy MRFDG‖	53	12	1.32	0.95 to 1.85	.08	53	10	1.40	0.99 to 1.99	.04
Midtherapy BF‖	53	12	1.60	0.94 to 2.73	.09	53	10	1.74	1.00 to 3.02	.05
Midtherapy FDG K_1‖	53	12	1.61	0.90 to 2.90	.10	53	10	1.70	0.92 to 3.15	.08
Midtherapy SUV‖	53	12	1.41	0.74 to 2.67	.32	53	10	1.84	1.00 to 3.39	.07
Change in MRFDG¶	53	12	1.14	1.01 to 1.29	.06	53	10	1.15	1.02 to 1.30	.04
Change in BF¶	53	12	1.19	1.07 to 1.31	.001	53	10	1.17	1.05 to 1.31	.005
Change in FDG K_1¶	53	12	1.19	1.08 to 1.32	.001	53	10	1.18	1.06 to 1.32	.004
Change in SUV¶	53	12	1.31	0.95 to 1.80	.08	53	10	1.49	1.03 to 2.16	.03

Abbreviations: LABC, locally advanced breast cancer; ER, estrogen receptor; PR, progesterone receptor; pCR, pathologic complete response; MRFDG, fluorodeoxyglucose metabolic rate; BF, blood flow; MRFDG:BF, MRFDG/BF ratio; FDG K_1, fluorodeoxyglucose transport; SUV, standardized uptake value.

*Likelihood ratio test.

†Unknown, n = 2.

‡Unknown, n = 9.

§Unknown, n = 8.

‖Log base 2.

¶1 unit = 10% change.

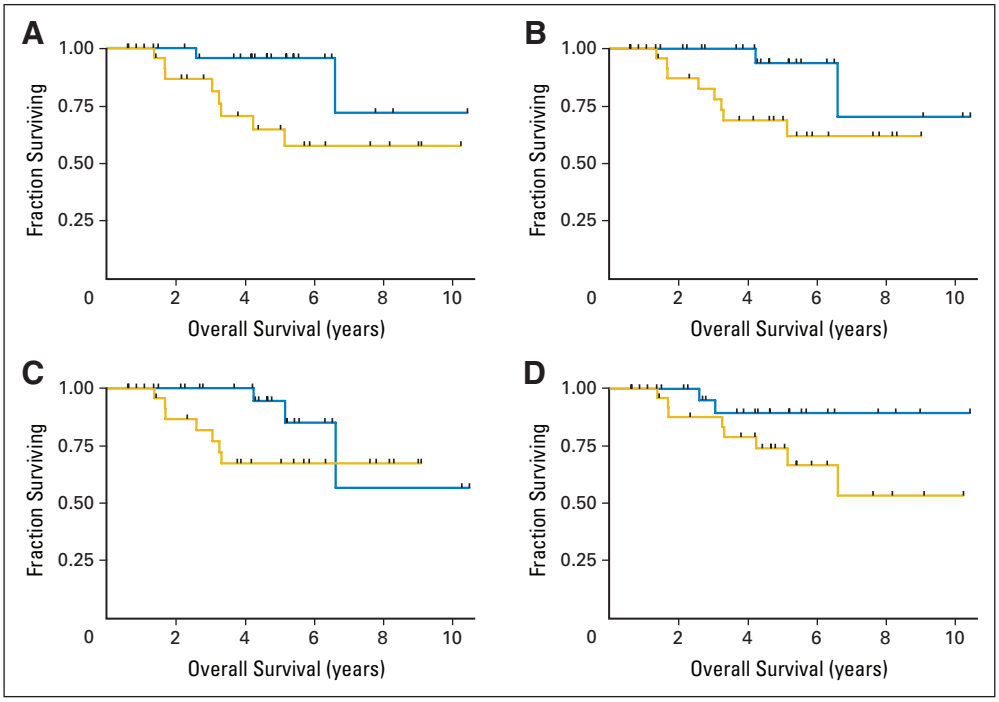

Fig 2. Kaplan-Meier curves of change in positron emission tomography measures divided greater than (blue) and less than (yellow) median values for (A) fluorodeoxyglucose metabolic rate, (B) blood flow, (C) fluorodeoxyglucose transport, and (D) standardized uptake value.

tumor recurrence and mortality risk were observed among women whose tumors were ER-negative, PR-negative, HER-2/*neu*-positive, or highly proliferative or whose tumors achieved other than pCR, these elevations were within the limits of chance in this cohort.

Survival Analysis: Multivariable

The risks of recurrence and mortality associated with MRFDG, BF, FDG K_1, and SUV, each adjusted for tumor ER and PR status, size, histology, pathologic response, and axillary lymph node status are listed in Table 4. The baseline MRFDG:BF ratio predicted relapse, and a one-unit increase inferred a 5% greater risk. BF and FDG K_1 changes from baseline to midtherapy also remained prognostic indicators of the likelihood of tumor recurrence. Each 10% lesser decrease (or greater increase) in BF or FDG K_1 was associated with a 1.4-fold greater relapse risk.

Elevated mortality risk was observed for higher midtherapy BF. Each doubling of tumor BF was associated with a 3.4-fold higher mortality risk. Greater mortality risks were observed for patients with little to no change or a proportionate increase in tumor BF or FDG K_1. Specifically, a 10% smaller decline in BF from baseline to midtherapy examination (or a 10% greater increase) was associated with a 1.67-fold higher mortality risk (95% CI, 1.24 to 2.24), and each 10% lesser decrease (or greater increase) in FDG K_1 was associated with a 1.77-fold higher mortality risk (95% CI, 1.12 to 2.78). Changes in SUV were univariately related to OS; however, multivariably, the risks were within the limits of chance (hazard ratio = 1.25; 95% CI, 0.80 to 1.96; $P = .31$).

DISCUSSION

In prior studies, we reported that MRFDG and BF PET measures before and at the midpoint of neoadjuvant chemotherapy predicted response among LABC patients.[9] This study expands on our previous studies by exploring the long-term end points of breast cancer recurrence and mortality. We observed that patients whose tumors had increases or small reductions in BF and FDG K_1 from pretherapy to midtherapy examinations had elevated recurrence and mortality risks compared with patients with greater reductions in BF and FDG K_1. We also found evidence for higher mortality risk associated with higher BF on midtherapy examinations. Differences in DFS and OS by PET parameters were observed even after adjusting for multiple prognostic factors, such as tumor ER and PR status, size, histology, and pathologic response. Our results suggest that PET data, especially changes in tumor perfusion over the course of neoadjuvant chemotherapy, measured directly by [^{15}O]water or indirectly by dynamic FDG PET as FDG K_1, provide information distinct from standard markers.

PET as a predictor of patient outcome has been reported for numerous other cancers including sarcoma and head and neck, esophageal, and lung cancers.[27-30] For breast cancer in the metastatic setting, qualitatively positive FDG PET tumor uptake after treatment was associated with shorter median DFS or OS.[31-33] Prior studies have not examined and compared PET measures of breast tumor BF and FDG tumor kinetics with breast cancer recurrence or mortality risk in the neoadjuvant setting. To our knowledge, our study is the first to show that parameters estimated from kinetic analysis of dynamically acquired PET examinations predict outcome among LABC patients. The standard clinical and pathologic factors also evaluated did not correlate with DFS or OS in this relatively small study, suggesting that quantitative PET imaging provides predictive data independent of these established factors. We observed that persistent MRFDG uptake could indicate tumor resistance to therapy and that greater decreases in BF predicted favorable survival. The standard static measure used

Table 4. Multivariable Cox Proportional Hazard Analyses of Breast Cancer Recurrence and Mortality Risk Among Women With LABC

Characteristic	Disease-Free Survival			Overall Survival		
	HR	95% CI	P*	HR	95% CI	P
Tumor size, cm†			.65			.81
0-1.9	1.00			1.00		
2-5	0.32	0.02 to 4.24		0.64	0.03 to 12.99	
> 5	0.56	0.05 to 5.39		1.15	0.09 to 14.22	
No. of axillary lymph node positive‡			.04			.01
0	1.00			1.00		
1-3	2.45	0.37 to 16.06		6.69	0.66 to 67.55	
≥ 4	7.32	1.28 to 41.73		14.96	1.39 to 160.53	
ER§			.94			.89
Positive	1.00			1.00		
Negative	0.91	0.08 to 10.16		1.19	0.07 to 17.92	
PR‖			.94			.14
Positive	1.00			1.00		
Negative	6.01	0.47 to 76.70		9.88	0.56 to 173.86	
Tumor histology¶			.78			.56
Ductal	1.00			1.00		
Lobular	1.39	0.13 to 14.26		2.11	0.16 to 26.82	
Primary tumor pathologic response#			.14			.19
pCR	1.00			1.00		
< pCR	4.22	0.52 to 34.14		4.36	0.39 to 48.25	
Baseline MRFDG:BF	1.05	1.02 to 1.08	.01	1.04	1.00 to 1.07	.03
Midtherapy MRFDG**	1.22	0.82 to 1.81	.29	1.51	0.94 to 2.42	.05
Midtherapy BF**	1.53	0.79 to 2.94	.19	3.42	1.07 to 10.93	.01
Midtherapy FDG K_1**	1.44	0.67 to 3.13	.34	2.30	0.85 to 6.24	.08
Midtherapy SUV**	1.19	0.46 to 3.05	.72	2.90	0.80 to 10.55	.07
Change in MRFDG††	1.12	0.91 to 1.38	.26	1.24	0.92 to 1.67	.11
Change in BF††	1.48	1.20 to 1.83	< .001	1.67	1.24 to 2.24	< .001
Change in K_1††	1.43	1.13 to 1.80	< .001	1.77	1.12 to 2.78	< .001
Change in SUV††	1.20	0.82 to 1.76	.34	1.25	0.80 to 1.96	.31

Abbreviations: LABC, locally advanced breast cancer; HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor; pCR, pathologic complete response; MRFDG, fluorodeoxyglucose metabolic rate; BF, blood flow; MRFDG:BF, MRFDG/BF ratio; FDG K_1, fluorodeoxyglucose transport; SUV, standardized uptake value.
*Likelihood ratio test.
†HRs adjusted for ER, PR, histology (ductal *v* lobular), pCR (pCR *v* other than pCR), and axillary lymph node status (0, 1-3, or ≥ 4 nodes).
‡HRs adjusted for ER, PR, tumor size (0-1.9, 2-5, or > 5 cm), histology, and pCR.
§HRs adjusted for PR, tumor size, histology, pCR, and axillary lymph node status.
‖HRs adjusted for ER, tumor size, histology, pCR, and axillary lymph node status.
¶HRs adjusted for ER, PR, tumor size, pCR, and axillary lymph node status.
#HRs adjusted for ER, PR, tumor size, histology, and axillary lymph node status.
**Log base 2; HRs adjusted for ER, PR, tumor size, histology , pCR, and axillary lymph node status.
††1 unit = 10% change; HRs adjusted for ER, PR, tumor size, histology, pCR, and axillary lymph node status.

for most FDG PET studies, SUV, did not retain predictive value after accounting for other risk factors associated with DFS or OS.

Although a number of tumor and host factors play a role in tumor sustainability, tumor vasculature is necessary for growth and spread. Several different imaging modalities, such as dynamic contrast-enhanced magnetic resonance imaging (MRI), [^{99m}Tc]sestamibi (MIBI), Doppler ultrasound, and dynamic FDG PET have the ability to assess in vivo tumor BF and vascularity and have shown utility in measuring treatment response.[34-40] Our observations of higher relapse and mortality risks associated with higher tumor BF at therapy midpoint parallel our previous work using MIBI imaging[41] and MRI findings that evaluated LABC response to antivascular treatment.[42] Persistent MIBI uptake, MRI contrast enhancement, and BF in breast tumors after therapy may all indicate the inability of the chemotherapeutic agent to disrupt tumor vasculature, thus allowing continued tumor growth and potential spread, portending a poorer prognosis.

In accordance with previous works that demonstrated a relationship between BF and FDG K_1 both before and after therapy,[11,12] we observed similar relapse and mortality risks associated with proportionate changes in tumor BF and FDG K_1 over the course of chemotherapy. These results suggest that it may be feasible to substitute K_1, the transport rate constant of [^{18}F]FDG from blood to tissue, for [^{15}O]water studies, which require an on-site cyclotron.

[^{18}F]FDG scans acquired in the clinical setting are typically static whole-body images in which semiquantitative tumor uptake measures are dependent on the time interval between tracer injection and scanning,[43] which are factors important to replicate when using [^{18}F]FDG studies for monitoring patient therapy response. Dynamic [^{18}F]FDG data acquisition is not dependent on image time. Full kinetic analysis provides insights into tumor patterns of glucose metabolism that include transport and phosphorylation measures,[44] which are predictive indicators that may not be visualized by static whole-body imaging.

Potential limitations to our study include a relatively small cohort with a recruitment time frame spanning 10 years. Second, although the majority of patients received similar neoadjuvant chemotherapy, there was some heterogeneity of treatment regimens. Third, there was some variability in scan timing and length of treatment before definitive surgery. The difference in treatment lengths and the broad time point range for midtherapy PET examinations is reflective of the ongoing changes in our clinical practice for LABC patients. These findings may not be necessarily generalizable to other populations; further analysis in a larger series is warranted.

Our findings suggest that a small group of breast cancer patients identified by PET experience poor outcome. Early response monitoring would play a critical role for these patients. Prior PET studies indicate that early response monitoring is feasible.[7,8] Our study also suggests that targeting tumor vasculature of patients who have resistant tumors may be helpful. Current studies at our institution are evaluating the role of dynamic FDG PET and dynamic contrast-enhanced MRI in early response prediction of antivascular therapies for breast cancer.

Our results suggest that information provided by PET imaging is complementary to standard clinical end points based on surgical pathology.[27-30] Therefore, functional imaging may be helpful in clinical trials as an adjunct in measuring tumor response and predicting patient outcome.

Overall, we observed that patients with smaller declines in BF and FDG K_1 experienced higher risks of recurrence and mortality that were largely independent of patient and tumor characteristics assessed in this study. Our findings suggest that changes in tumor perfusion over the course of neoadjuvant chemotherapy measured directly by [^{15}O]water or indirectly by dynamic FDG PET are predictive of outcome in LABC patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).