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Comparing the Performances of Magnetic Resonance Imaging Size vs Pharmacokinetic Parameters to Predict Response to Neoadjuvant Chemotherapy and Survival in Patients With Breast Cancer

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Purpose: To compare the value of dynamic contrast-enhanced magnetic resonance imaging-pharmacokinetic (PK) parameters vs tumor volume in predicting breast cancer neoadjuvant chemotherapy response (NACR) and patient survival.
Subjects and Methods: Sixty-six patients with locally advanced breast cancer who underwent breast MRI monitoring of NACR were retrospectively analyzed. We compared baseline transfer constant (K^{trans}), reflux rate contrast (k_{ep}), and extracellular extravascular volume fraction (v_e) with the same parameters obtained at early postchemotherapy MRI, and examined model-independent changes in time-intensity curves (maximum slope, contrast enhancement ratio, and IAUC90). Tumor size changes (tumor volume, single dimension, and Response Evaluation Criteria in Solid Tumors [RECIST]) were also analyzed. The Spearman correlation test was used to assess the association between size and PK parameters, and regression analysis to assess the association with 5-year disease-free survival.
Results: Higher v_e values at baseline were associated with greater decreases in tumor size ($P = 0.008$). Changes in K^{trans} and IAUC90 were the strongest predictors of NACR. Changes in IAUC90 ($P = 0.04$) and RECIST ($P = 0.003$) were independently associated with pathologic response. The only parameter significantly associated with 5-year survival was change in RECIST ($P = 0.001$). However, there was a trend toward statistical significance for changes in v_e and K^{trans}, with greater changes associated with longer survival.
Conclusion: Changes in PK and dynamic contrast-enhanced magnetic resonance imaging kinetic parameters may have a role in predicting NACR in breast tumors. Although changes in K^{trans} and IAUC90 are helpful in predicting NACR, they do not show significant association with survival. Early RECIST size change measured by MRI remains the strongest predictor of overall patient survival.

Introduction

An increasing number of patients with advanced breast tumors who are previously ineligible for breast conservation surgery have been receiving neoadjuvant chemotherapy.[1-4] Randomized trials comparing neoadjuvant chemotherapy with postoperative adjuvant chemotherapy have shown similar rates of recurrence-free and disease-free survival, and preoperative chemotherapy has allowed more patients to undergo breast-conserving treatment successfully. Furthermore, the pathologic response of breast cancer to neoadjuvant chemotherapy is a surrogate marker of patient outcome; patients who have a pathologic complete response after surgery survive longer than patients who do not.

Physical examination, mammography, and ultrasound have all been used to assess response to neoadjuvant chemotherapy, but each of these approaches has limitations.[5,6] Over the last decade, numerous studies assessed the use of breast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) for monitoring tumor response to neoadjuvant chemotherapy. Investigators have also used tumor volume calculations, in combination with the maximum tumor diameter, to assess response.[5-8] Some of the investigators observed that differences in tumor volume measured by MRI had a stronger association with recurrence-free survival rate in patients who received neoadjuvant chemotherapy than did other prognostic indicators, such as largest tumor diameter.[9,10]

Response assessments are usually based on tumor size or volume.[8-10] Previous studies found early volumetric changes based on both morphology and size were superior to the longest tumor

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diameter for predicting response.[10] However, changes in volume may occur long after physiological changes in a tumor. Pickles et al[11] found that changes in tumor volume and in the pharmacokinetic (PK) parameters transfer constant (K^{trans}), reflux rate contrast (k_{ep}), and extracellular extravascular volume fraction (v_e), measured by DCE-MRI early in treatment, differed significantly between responding and nonresponding patients, determined on the basis of their final tumor volume reduction. Previous investigators have suggested an association between PK parameters and response or patient survival.[12] However, it is unclear how PK parameters compare with previously established volumetric tumor changes in their precision for tumor response assessment, since a vis-à-vis comparison has not been performed. Our aim in this study was to investigate the usefulness of early changes in DCE-MRI-derived parameters K^{trans}, k_{ep}, and v_e along with model-independent time-intensity curve-derived metrics of maximum slope, initial (90 seconds) area under the time-intensity curve ($IAUC_{90}$), and contrast enhancement ratio for predicting disease-free survival rate. Based on the previously shown significance of early tumor size changes, we retrospectively compared the use of differences in tumor maximum diameter, tumor ellipsoid volume, and Response Evaluation Criteria in Solid Tumors (RECIST)[13] with the use of PK and model-independent DCE-MRI parameters for predicting pathologic tumor response and 5-year disease-free survival.

Patients and Methods

Patient Selection and Data Collection

Between January 1, 2000, and November 30, 2003, 93 patients with locally advanced invasive primary breast carcinoma enrolled in a prospective study monitoring response to neoadjuvant combination therapy consisting of either standard polychemotherapy, or, in some patients, intratumoral p53 adenovirus injection combined with chemotherapy. Patients underwent MRI evaluations at baseline, early during chemotherapy (MR1 = 1-12 cycles of Taxol), and late during chemotherapy or presurgery for assessment of response to primary neoadjuvant chemotherapy. Neoadjuvant chemotherapy received by the patients are in Appendix Table 1.

From the patients′ records, we collected and recorded data on age, imaging findings, tumor size, tumor histologic type and grade, treatment, and disease-free survival. The retrospective review of medical charts, reports, and MRI studies in this HIPAA-compliant study was approved by our Institutional Review Board.

Dynamic Contrast-Enhanced Magnetic Resonance Imaging

All MRI studies were performed with the patients lying prone in a 1.5-T scanner (Signa Excite HDx; GE Healthcare, Waukesha, WI) using a dedicated 7-channel breast array coil (MRI Devices Corporation, Pewaukee, WI). The breast MRI protocol consisted of a unilateral T1-weighted sequence and a T2-weighted fat-suppressed sagittal sequence followed by a 10-15 serial dynamic 3-dimensional fast spoiled-gradient echo image sets. Images were obtained during and following rapid intravenous bolus infusion of 0.1 mmoL/kg gadopentetate dimeglumine contrast medium (Magnevist; Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ) at a rate of 3 mL/sec with a power injector (Spectris Solaris MR Injector; Medrad, Warrendale, PA). Delayed postcontrast 3-dimensional fast spoiled-gradient echo images with fat suppression in both axial and sagittal planes were also obtained.

Image postprocessing was performed on a dedicated workstation (ADW 4.2; GE Healthcare, Waukesha, WI). The precontrast dynamic image set was subtracted from the postcontrast sets, and time-intensity curves were obtained from contrast-enhanced lesions with a hand-drawn region of interest (ROI) encompassing the lesion, with a maximum ROI size of at least 3 × 3 pixels. The time-intensity curve demonstrating maximal change was selected as representative for a lesion.

PK Analysis

A 3-parameter, 2-compartment model (K^{trans}, k_{ep}, and v_e) was used to derive PK parameters (Fig 1). CINETool software and the Kinmod analysis module (GE Healthcare, Waukesha, WI), using a generalized (extended) Tofts Kermode Model, as described in Tofts'1997 paper[14] for general kinetic modeling. A Weinmann arterial input function was used as the population model.[15] Parameters K^{trans} (min^{-1}), k_{ep} (min^{-1}), and v_e (unitless) were computed from the change in signal intensity data which was converted to gadolinium concentration pixel-by-pixel within a defined ROI. The mean values of these parameters were then recorded.

The parameters used for model-independent analysis were direct measurements of the slopes of signal intensity wash-in and wash-out curves (maximum slope), contrast enhancement ratio, and $IAUC_{90}$. A ROI was drawn to include the bulk of the lesion on the slice that demonstrated contrast uptake (Fig 2). ROI-based analysis was then performed to calculate the maximum slope (sec^{-1}), the contrast enhancement ratio, and the $IAUC_{90}$.

Tumor Size Assessment

Percentage change in tumor size was assessed using the following formula for ellipsoidal or sperical volume derived from mid-dynamic sequence subtraction series:

$$V\ (cm^3) = (4/3\ \pi) \times length/2 \times width/2 \times height/2$$

Percentage change in a single maximal dimension was assessed by subtracting the early chemotherapy maximum dimension from the baseline maximum dimension. Change in tumor size by RECIST 1.1 was assessed[13] as the net sum of percentage changes in the longest diameters of the target lesions . For multifocal and multicentric lesions, the sum of the dimensions of up to three lesions was used.[13] Each assessment of tumor response was expressed as a percentage decrease between the initial assessment and the subsequent assessment (Fig 2). Pathologic tumor response was considered as the gold standard and was assessed as the evidence of response from final pathology as no response, partial response, or complete response.

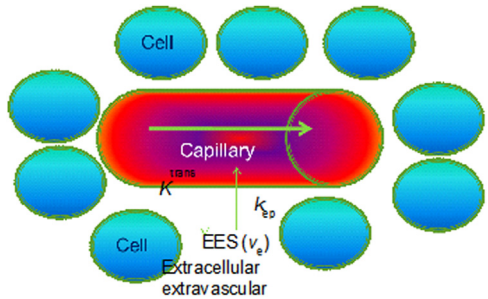

FIG 1. Compartmental modeling of tumor microvasculature. Blood flows through the tumor, potentially distributing contrast media molecules into 2 compartments: plasma and extravascular extracellular space (EES; v_e). Clinically available MRI contrast agents are extracellular agents. Contrast agent leakage is influenced by the difference in contrast agent concentrations in the plasma and the extracellular extravascular space and by the permeability and the surface area of the capillary endothelia. Transfer constant (K^{trans}), reflux rate contrast (k_{ep}), and extracellular extravascular volume fraction (v_e). (Color version of figure is available online.)

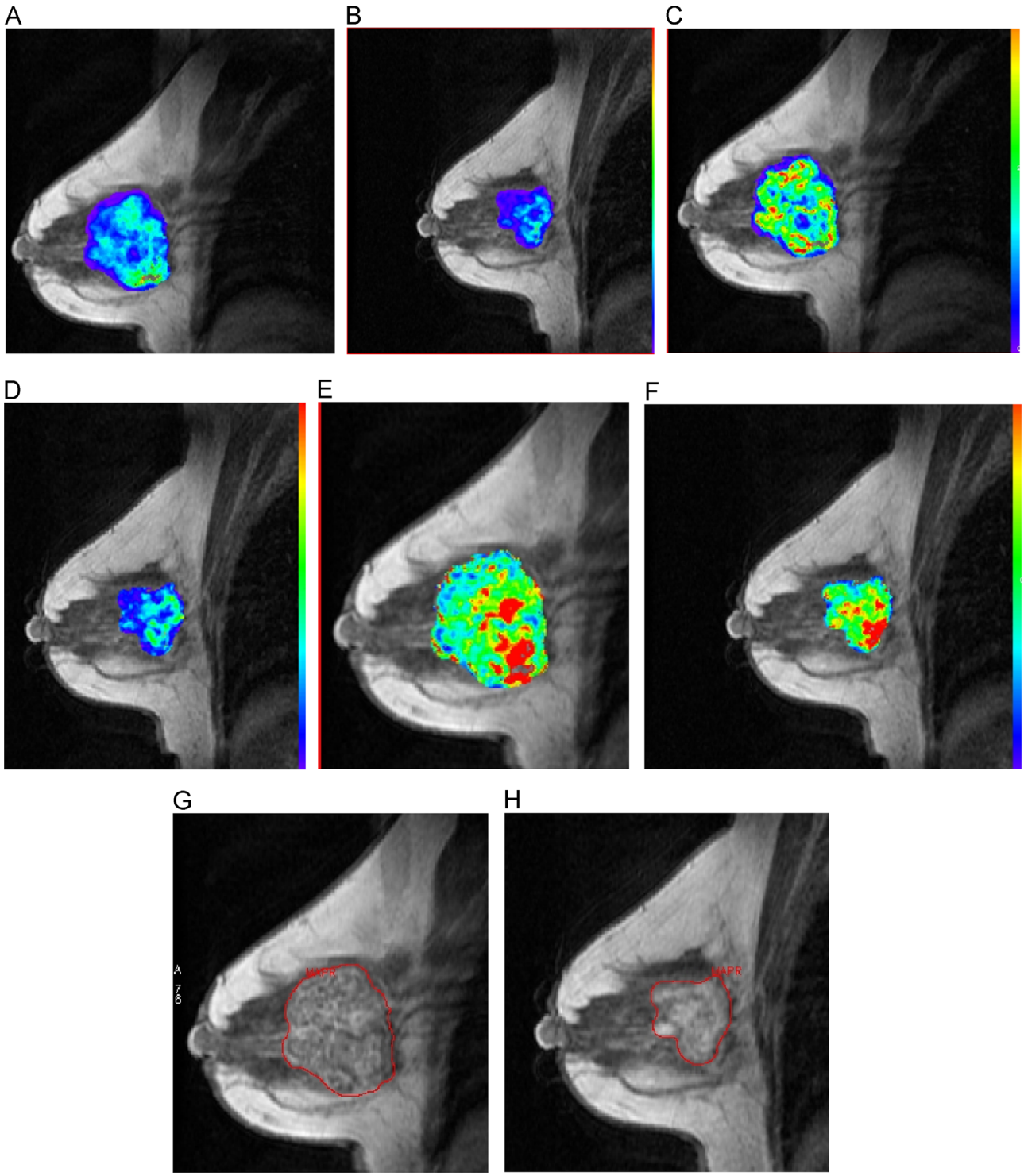

FIG 2. A 34 year-old woman with T3 N1 carcinoma, ER +, PR–, HER2 –negative. DCE-MRI PK parametric maps with color scale before and after, 2 cycles of neoadjuvant docetaxel + adriamycin. Prechemotherapyand postchemotherapy K^{trans} (A and B), k_{ep} (C and D), v_e (E and F) maps, and ROI placement (G and H). Baseline K^{trans}: 1.65 min^{-1}; k_{ep}: 9.668 min^{-1}; v_e: 0.17; MaxSLP: 0.48 sec^{-1}; CER: 1.11; IAUC90: 0.17. Change in PK parameters were as follows: ΔK^{trans}:−57%; Δk_{ep}: −85%; Δv_e: +170 %; ΔMaxSLP: +12%, ΔCER: +12%; ΔIAUC90: −35%. Change in tumor size parameters were ΔVolume : −64%; ΔMax diameter: −41%; ΔRECIST: −33%, demonstrating evidence of response. The patient proceeded to have a total of 6 cycles of docetaxel+adriamycin, followed by segmental mastectomy, adjuvant radiotherapy and tamoxifen. Segmental mastectomy pathology showed residual invasive carcinoma measuring 1.7 cm, with residual axillary metastasis in 3/24 removed nodes. The patient is in remission with no evidence of disease 5 years' postcompletion of breast-conserving therapy. (Color version of figure is available online.)

Statistical Analysis

Median, minimum, and maximum values were determined for patient age; tumor size change; and changes in baseline K^{trans}, k_{ep}, v_e, maximum slope, contrast enhancement ratio, and $IAUC_{90}$. Patients were also categorized in terms of survival status (alive, alive with disease, or dead with disease) to assess disease-free survival and response (complete, partial, or none), and percentages by category were determined.

A logistic regression model was used to estimate the probability (p) that a patient had a response (complete or partial). The model predicts the natural log of the odds $(\log[p/1-p])$ of a

patient having a response. The modeling was done in a univariate fashion. From this model, we estimated the odds ratio for each potential prognostic factor with a 95% confidence interval. We used the method of Kaplan and Meier to estimate median disease-free survival, calculated as the duration between the first study date and the last follow-up or death date. We used Cox proportional hazards regression analysis to assess the relationship between OS and PK parameters and tumor response.

Results

The mean patient age was 49 years (median, 52; range: 28-71). Of the 93 patients who were initially enrolled in the study, 66 completed their care at our institution. Excluded patients were as follows: 6 of the 93 patients were lost to follow-up due to transfer of clinical care elsewhere. Twenty patients did not have an early or late chemotherapy follow-up. One patient developed distant metastasis during the course of therapy and was excluded from the study. Patient clinicopathologic data are summarized in Table 1.

Pathologic Response and Patient Survival

Of the 66 eligible patients, 9 (13.6%) achieved complete, 51 (77.4%) partial response and the remaining 6 (9%) showed no pathologic response. At 5-year clinical and imaging follow-up, 20 (30.3%) were dead of disease, 1 (2%) alive with disease, and 45 (68%) alive without disease.

Pretreatment PK Parameters

Pretreatment PK parameters in the 66 patients were evaluated. The median K^{trans} was 0.74 min^{-1}, the median k_{ep} was 1.95 min^{-1}, and the median v_e was 0.38. None of the baseline PK parameters were significant in predicting complete or partial response or 5-year disease-free survival. However, higher baseline v_e values were associated with greater decreases in tumor size ($P < 0.01$) (Table 2).

TABLE 1
Patient clinicopathological data

Characteristic	No. (%) of patient ($n = 66$)
Tumor size	
T1 (< 2 cm)	2 (3.1)
T2 (2-5 cm)	33 (48.4)
T3 (> 5 cm)	16 (25)
T4	15 (23.4)
Nodal status	
N0 (negative)	17 (26.6)
N1	28 (43.8)
N2	12 (15.6)
N3	9 (14.1)
Histopathologic type	
IDC	63 (95.5)
Mixed IDC and ILC	1 (1.5)
ILC	1 (1.5)
Metaplastic	1 (1.5)
ER	
Negative	27 (40.9)
Positive	39 (59.1)
HER2 neu	
Negative	46 (69.7)
Positive	20 (30.3)

ER, estrogen receptor; HER2 neu, human epidermal growth factor receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

TABLE 2
Correlation of baseline PK parameters with decreases in tumor volume, tumor maximum dimension, and RECIST

Baseline parameter	Spearman correlation	P
Volume		
K^{trans}	−0.09	0.47
k_{ep}	0.13	0.30
v_e	−0.33	0.008
MaxSLP	0.01	0.91
CER	−0.24	0.06
$IAUC_{90}$	−0.06	0.64
Maximum size		
K^{trans}	−0.05	0.71
k_{ep}	0.17	0.18
v_e	−0.37	0.003
MaxSLP	−0.02	0.90
CER	−0.24	0.05
$IAUC_{90}$	−0.03	0.80
RECIST		
K^{trans}	−0.02	0.90
k_{ep}	0.20	0.11
v_e	−0.34	0.006
MaxSLP	0.06	0.63
CER	−0.18	0.15
$IAUC_{90}$	0.01	0.92

Transfer constant (K^{trans}); reflux rate contrast (k_{ep}); extracellular extravascular volume fraction (v_e); MaxSLP, maximum slope; CER, contrast enhancement ratio; $IAUC_{90}$, initial (90 sec) area under the time-intensity curve.

Association Between Changes in PK Parameters and Pathologic Response

Among the PK parameters, change in K^{trans} was more strongly associated with pathologic response ($P = 0.04$) than changes in v_e ($P = 0.7$) and k_{ep} ($P = 0.64$), although the association did not reach statistical significance. There was strong evidence that a decrease in $IAUC_{90}$ was associated with pathologic response ($P = 0.008$), but the association with contrast enhancement ratio ($P = 0.07$) and maximum slope ($P = 0.10$) did not reach statistical significance. In both cases, increases in these parameters were associated with a lower likelihood of a partial or complete response.

Association Between Changes in PK Parameters and Survival

Univariate modeling to estimate the association of survival with PK parameters was performed. Although a trend toward statistical significance was identified for changes in v_e ($P = 0.08$) and K^{trans} ($P = 0.06$), with decreasing values associated with longer

TABLE 3
Prediction of disease-free survival based on decreases in PK parameters and kinetic curve-derived metrics

Change	Hazard ratio	95% CI	P
K^{trans}	3.19	0.87, 11.7	0.08
k_{ep}	1.001	0.95, 1.05	0.95
v_e	9.01	0.92, 88.3	0.06
MaxSLP	2.99	0.50, 17.9	0.23
CER	3.19	0.69, 14.8	0.13
$IAUC_{90}$	2.99	0.14, 6.3×10^7	0.11

Transfer constant (K^{trans}); reflux rate contrast (k_{ep}); extracellular extravascular volume fraction (v_e); MaxSLP, maximum slope; CER, contrast enhancement ratio; $IAUC_{90}$, initial (90 seconds) area under the time-intensity curve.

TABLE 4
Prediction of disease-free survival based on decreases in tumor size

Change	Hazard ratio*	95% CI	*P
Volume	0.97	0.95, 0.99	< 0.0001
Maximum dimension	0.96	0.94, 0.99	0.003
RECIST	0.95	0.93, 0.98	0.001

* Cox regression model.

disease-free survival, none of the PK values were significantly associated with improved survival rate (Table 3), whereas it was significantly associated with tumor volume change (Table 4).

Multivariate Modeling for Predicting Pathologic Response and Disease-Free Survival

Multivariate analyses were conducted to develop a model for predicting pathologic response and disease-free survival. Significant factors from univariate analyses for PK changes and tumor response were fit jointly into a multivariate model. Changes in $IAUC_{90}$ and RECIST were both independently predictive of pathologic response (Appendix Table 2). No other covariates contributed to prediction of response. Multivariate modeling for predicting disease-free survival identified decrease in tumor volume ($P < 0.0001$) and RECIST ($P = 0.001$) as significant predictors of disease-free survival.

Discussion

Although the utility of breast MRI for monitoring response to neoadjuvant chemotherapy is already quite established, data on the utility of breast MRI to predict survival is scarce. Our findings on a moderately large number of patients indicate a stronger predictive value of volumetric tumor changes compared with PK parameters for neoadjuvant therapy response and patient survival. This conclusion is in agreement with prior studies that demonstrated a correlation between PK parameters and pathologic tumor response. Although a trend for an association of reductions in K^{trans} and v_e with longer survival was observed, no association between survival and PK or model-independent DCE-MRI parameters reached statistical significance. The most reliable predictor of 5-year disease-free survival was 3 dimensional volumetric reduction in tumor size and RECIST. Our results are in agreement with the previously published data from the ISPY2/ACRIN6657 trial, which indicated that early volumetric changes were correlated with pathologic response to neoadjuvant chemotherapy,[10] with implications for better disease-free survival and recurrence-free survival.

Quantitative DCE-MRI parameters and volumetric measurements have advantages over assessment of tumor size, with DCE-MRI parameters measuring angiogenic changes that may occur before tumor size reduction[16] and volumetric measurements potentially providing a more accurate representation of tumor burden.[10] Hence, it is plausible that decreases in K^{trans} and v_e may be more accurate markers of early response than a reduction in tumor size. Over the last decade, numerous studies have been conducted in several countries to assess the use of MRI in monitoring breast tumor response to neoadjuvant chemotherapy.[6-12,16-20] Although one study found an association of survival with semiquantitative parameters (E(max/1), and steepest slope) and baseline tumor stage (ie, size and nodal involvement), a correlation with volumetric data was not attempted.[12] Comparisons of published data are difficult, however, because of the different definitions of response and the different chemotherapy agents and regimens. Some of the previous studies suggested higher AUCs for sensitivity and specificity for K^{trans} than MRI-based single-dimension tumor size[17] with the use of study-specific thresholds. However, study-specific cut-offs likely overestimate the significance of the results, and were, therefore, avoided in our study. Although initial studies with small numbers of patients were promising,[12,17,18] the predictive accuracy of K^{trans} is likely affected by alterations in the tumor microenvironment independent of changes in tumor size. In a recent meta-analysis, PK analysis was reported to be similarly less conclusive compared to tumor diameter or volume assessment[19] in the assessment of tumor response. Cho et al[20] reported the parametric response map analysis performed using pixel by pixel assessment of signal intensity change after the first cycle of therapy is more helpful than PK parameter analysis in predicting NAC response, although none of these studies estimated predictive power for survival. Overall, due to modeling assumptions and lack of a standard MRI technique across studies, PK analysis may not be as robust as volume assessment for this purpose.

Another significant finding of our study was the association of higher baseline v_e values with greater decreases in tumor size, in agreement with the findings of other studies.[11] Because v_e is a reflection of the tumor extracellular, extravascular space, this finding may have implications for enhanced drug delivery to the tumor microenvironment in patients with higher v_e, with higher values suggesting better delivery of intravascular chemotherapeutic agents. We, however, did not find any significant association between baseline PK parameters and patient survival, in contrast to the findings reported by Pickles et al,[18] who suggested that shorter disease-free and disease-free survival durations are expected for patients who exhibit high levels of perfusion and vessel permeability, and hence high PK parameters, before commencement of neoadjuvant therapy.[18]

Limitations of our study include the single-center design and the retrospective analysis of the PK and size parameters. In addition, patients were administered differing chemotherapy regimens with or without trastuzumab depending on their immunohistochemical profiles. Lastly, the while all MRI examinations were performed before chemotherapy, assessment was performed following differing early time points in patients, while a standardized monitoring interval could not be maintained. Although this is a formal limitation, our findings suggest that DCE-breast MRI is robust enough to provide prognostic information even if used at variable early time points depending on the expected impact of administered therapy, and thus can be considered a strength.

In conclusion, PK analysis may have a role in predicting neoadjuvant chemotherapy response in breast tumors. However, PK parameters do not show a significant association with survival. Early tumor volume change and RECIST size change remained the strongest predictors of disease-free survival in this cohort of patients.

Appendix TABLE 1
Chemotherapy regimen

Initial	Total initial chemotherapy cycles	‡MRI- 1 (cycles)	Second regimen	Total delayed chemotherapy cycles	No. of patients
Paclitaxel	12	4-12	*FAC/†FEC	4	44
§Docetaxel + adriamycin	6	2-3	-	-	18
*FAC only‖	4	1-2	-	-	4

* FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide.
† FEC = 5-Fluorouracil, epirubicin, and cyclophosphamide.
‡ MRI-1: first MRI following initiation of chemotherapy. Performed median: post-4 cycles.
§ Nine patients also received intratumoral p53 adenoviral vector injection.
‖ Two patients also received Herceptin.

Appendix TABLE 2
Results of multivariate modeling for predicting pathologic response

Decreased parameter (baseline to early DCE-MRI)	Coefficient	SE	*P
RECIST	0.040	0.014	0.003
$IAUC_{90}$	−13.52	6.45	0.04

$IAUC_{90}$: initial (90 sec) area under the time-intensity curve.
SE, standard error.

* P value by logistic regression modeling ($P < 0.05$).

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