Radiology

Use of Dynamic Contrast-enhanced MR Imaging to Predict Survival in Patients with Primary Breast Cancer Undergoing Neoadjuvant Chemotherapy[1]

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Purpose: To investigate whether early changes in vascular parameters determined with dynamic contrast material–enhanced magnetic resonance (MR) imaging after two cycles of neoadjuvant chemotherapy (NAC) are predictive of disease-free and overall survival in primary breast cancer.

Materials and Methods: Institutional ethics approval and informed consent were obtained. Patients with primary breast cancer (median age, 45 years; age range, 22–70 years) recruited from January 2001 to September 2008 underwent dynamic contrast-enhanced MR imaging before and after two cycles of NAC. Quantitative and semiquantitative kinetic parameters were calculated, including the volume transfer constant (K^{trans}) and the initial area under the gadolinium concentration–time curve over 60 seconds ($IAUGC_{60}$). Cut points optimized to the receiver operating characteristic curve were used to dichotomize MR imaging data for Kaplan-Meier survival analysis. MR imaging parameters and known prognostic indicators in primary breast cancer were correlated with disease-free and overall survival by using the Cox proportional hazards model for univariate and multivariate analyses.

Results: MR imaging was performed before (n = 62) and after (n = 58) two cycles of NAC. The median follow-up time was 43.9 months for disease-free survival and 60.3 months for overall survival. There were 28 recurrences; 26 patients had distant metastases (two had additional local recurrence) and two had local recurrence only. There were 20 deaths, all of which were related to breast cancer. At univariate analysis, progesterone receptor status, the type of surgery performed, higher posttreatment K^{trans} (P = .048), and larger posttreatment $IAUGC_{60}$ (P = .035) were significant predictors of worse disease-free survival. At multivariate analysis, progesterone receptor status (P = .002) and mean transit time (P = .025) were significant predictors of disease-free survival. Univariate analysis showed that clinical tumor stage (P = .005), progesterone receptor status (P = .025), and type of surgery performed (P = .017) were significant predictors of overall survival. Higher posttreatment K^{trans} (P = .043), larger $IAUGC_{60}$ (P = .029), and larger tumor size at posttreatment MR imaging were predictive of worse overall survival (P = .018). Of these variables, K^{trans} remained an independent indicator of overall survival (P = .038).

Conclusion: Higher posttreatment tumor vascularization as depicted with dynamic contrast-enhanced MR imaging may be associated with higher recurrence and lower survival rates. Dynamic contrast-enhanced MR imaging parameters, in conjunction with traditional prognostic factors, have the potential to be prognostic biomarkers for disease-free and overall survival in primary breast cancer.

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The role of neoadjuvant chemotherapy (NAC) in the treatment of primary breast cancer is well established. The ability to downstage tumors and increase the likelihood of breast-conserving surgery while targeting occult micrometastatic disease has made this an attractive therapeutic option. Patients who achieve a clinical or pathologic response to chemotherapy have better disease-free and overall survival (1,2). Therefore, the ability to identify those who may not be responding early on in their treatment has the potential to influence patient outcome.

Dynamic contrast material–enhanced magnetic resonance (MR) imaging has the ability to yield detailed insights into underlying tumor angiogenesis by way of parameters relating to tumor perfusion and permeability (3) and has been shown to be predictive of both clinical and pathologic response to NAC as early as after two cycles of treatment. We have previously demonstrated that reductions in the inflow transfer constant (K^{trans}) correlate well with improved response to anthracycline-based NAC (4). However, the ability of K^{trans} and other dynamic MR imaging parameters to help predict long-term outcome in breast cancer is, to our knowledge, not well described in the literature. Several studies of breast cancer have shown elevated pretreatment dynamic contrast-enhanced MR imaging–derived parameters, consistent with higher levels of tumor blood perfusion and permeability, to be predictive of lower disease-free and overall survival (5,6); however, there is a paucity of data regarding whether these parameters after treatment with chemotherapy are predictive of long-term outcome. The early identification of potential prognostic imaging biomarkers may enable patients to benefit from more individualized, targeted treatment.

We hypothesize that breast tumors with persistent levels of abnormal vascularization after two cycles of chemotherapy as a result of a poor antiangiogenic response to treatment carry a worse prognosis. Conventional cytotoxic treatment exerts both indirect and direct effects on tumor vasculature by way of loss of proangiogenic support secondary to tumor cell kill and also directly on endothelial cell function (7). Hence, persistent cytokine support from poorly responding tumors may explain the presence of greater levels of residual angiogenic activity, thus leading to higher values of K^{trans} after two cycles of neoadjuvant therapy.

The objective of this study was to test the hypothesis that dynamic contrast-enhanced MR imaging–derived vascular parameters, in particular K^{trans}, after two cycles of NAC are predictive of disease-free and overall survival alongside traditional prognostic variables in breast cancer.

Advances in Knowledge

- Breast carcinomas displaying a high volume transfer constant (K^{trans}) and a large initial area under the gadolinium-time curve over 60 seconds ($IAUGC_{60}$) after two cycles of neoadjuvant chemotherapy (NAC) are associated with worse disease-free survival (K^{trans}: $P = .048$; $IAUGC_{60}$: $P = .035$) and overall survival (K^{trans}: $P = .043$; $IAUGC_{60}$: $P = .029$) at univariate analysis.
- When traditional prognostic variables are taken into account at multivariate analysis, progesterone receptor status ($P = .002$) and mean transit time before treatment ($P = .025$) were significant predictors for disease-free survival, and posttreatment K^{trans} ($P = .038$) and outflow rate constant ($P = .038$) were significant predictors of overall survival.

Implications for Patient Care

- Dynamic contrast-enhanced MR imaging–derived vascular parameters in combination with traditional prognostic factors in breast cancer are potential biomarkers of disease-free and overall survival.
- Patients whose tumors display persistent, higher values of K^{trans} after two cycles of NAC as a result of a poor antiangiogenic response to treatment may benefit from therapies directed at the tumor vasculature.

Materials and Methods

Study Design

Institutional ethics committee approval was given and informed consent obtained from all participants. Seventy-three female patients with histologically proved breast cancer were recruited consecutively to undergo dynamic MR imaging before (pretreatment MR imaging) and after (posttreatment MR imaging) two cycles of NAC between January 2001 and September 2008 as part of two sequential prospective studies (West Hertfordshire Hospitals protocol EC2001–26). Patients received anthracycline-based chemotherapy sessions with intravenous 5-fluorouracil (600 mg/m^2), epirubicin (60 mg/m^2), and cyclophosphamide (600 mg/m^2) or adriamycin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) three times weekly, which was the standard of care at that time in our institution. A study extension was granted to allow the recruitment of patients receiving

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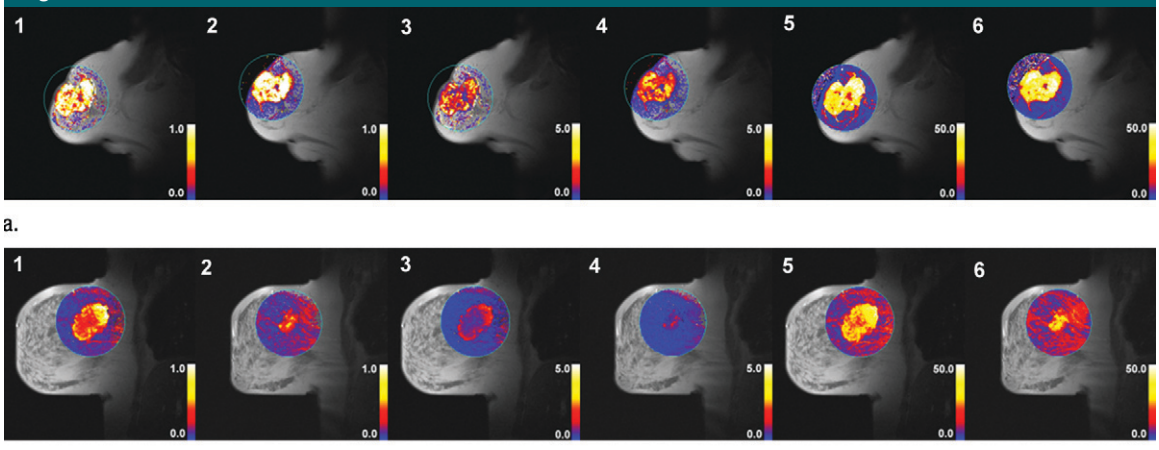
Abbreviations:
HR = hazard ratio
$IAUGC_{60}$ = initial area under the gadolinium concentration–time curve over 60 seconds
k_{ep} = outflow rate constant
K^{trans} = inflow transfer constant
MTT = mean transit time
NAC = neoadjuvant chemotherapy
v_e = extravascular volume fraction

Author contributions:
Guarantors of integrity of entire study, S.P.L., A.M., A.R.P.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, S.P.L., A.M., M.J.B., J.J.S., D.J.C., A.R.P.; clinical studies, S.P.L., A.M., M.J.B., N.J.T., M.L.W.A., J.J.S., A.R.P.; statistical analysis, S.P.L., A.M., N.J.T., J.A.D., D.J.C., R.K.; and manuscript editing, S.P.L., A.M., M.J.B., N.J.T., M.L.W.A., J.J.S., J.A.D., D.J.C., A.R.P.

Potential conflicts of interest are listed at the end of this article.

Figure 1



a.

b.

Figure 1: **(a)** Dynamic T1-weighted MR images of a 60-mm grade 2 breast carcinoma in the right breast (T3 N0 M0, estrogen receptor positive, progesterone receptor positive, HER2 negative) of a 70-year-old woman whose disease relapsed distally 38.8 months after diagnosis. The patient died 47.2 months after initial radical treatment. Her tumor displayed high values for K^{trans}, k_{ep}, and $IAUGC_{60}$ after two cycles of NAC. *1*, K^{trans} before treatment (median, 0.403 $minute^{-1}$), *2*, K^{trans} after treatment (median, 0.603 $minute^{-1}$), *3*, k_{ep} before treatment (median, 1.212 $minutes^{-1}$), *4*, k_{ep} after treatment (median, 1.816 $minutes^{-1}$), *5*, $IAUGC_{60}$ before treatment (median, 19.49 mmol/sec), and, *6*, $IAUGC_{60}$ after treatment (median, 23.41 mmol/sec). **(b)** Dynamic T1-weighted MR images of a 57-mm grade 2 breast carcinoma in the right breast (T3 N0 M0, estrogen receptor negative, progesterone receptor positive, HER2 negative) of a 61-year-old woman who had no evidence of disease recurrence more than 5 years after diagnosis. The patient was still alive at the time this manuscript was written. Tumor displayed lower values for K^{trans}, k_{ep}, and $IAUGC_{60}$ after treatment. *1*, K^{trans} before treatment (median, 0.271 $minute^{-1}$), *2*, K^{trans} after treatment (median, 0.146 $minute^{-1}$), *3*, k_{ep} before treatment (median, 0.708 $minute^{-1}$), *4*, k_{ep} after treatment (median, 0.403 $minute^{-1}$), *5*, $IAUGC_{60}$ before treatment (median, 16.47 mmol/sec), and *6*, $IAUGC_{60}$ after treatment (median, 12.19 mmol/sec).

neoadjuvant docetaxel (100 mg/m^2 every 21 days). Inclusion criteria included *(a)* age of 18–70 years, *(b)* World Health Organization performance status of 0–1, *(c)* no contraindications to chemotherapy, and *(d)* adequate bone marrow function. Patients were excluded if they were pregnant or if they had any contraindications to MR imaging. At completion of NAC, patients subsequently received further treatment with surgery (wide local excision or mastectomy with axillary nodal clearance), postoperative external beam radiation therapy to the breast or chest wall, endocrine therapy if the patient had positive hormone receptor status, and trastuzumab if the patient had positive HER2 status.

MR Imaging Data Acquisition and Analysis

MR imaging was performed with a 1.5-T unit (Symphony; Siemens Healthcare, Erlangen, Germany) by using a dedicated bilateral breast coil. Initial diagnostic T1- and T2-weighted images were obtained through the center of the tumor. Then, proton density–weighted gradient-recalled echo images were acquired (350/4.7 [repetition time msec/echo time msec], 6° flip angle, 8-mm-thick sections) for four sections (three through tumor and one through the contralateral normal breast). Forty sets of dynamic T1-weighted images were then obtained by using a sequence based on two-dimensional fast low-angle shot imaging (11/4.7, 35° flip angle, 256 × 256 matrix) at the same section positions as those used for proton density–weighted images every 12 seconds for a total imaging time of 8 minutes. Gadopentetate dimeglumine (0.1 mmol per kilogram body weight; Magnevist, Bayer-Schering, Newberry, United Kingdom) was injected intravenously at 4 mL/sec by using a power injector during the fifth acquisition time point; this was followed by 20 mL of normal saline. The proton density– and T1-weighted dynamic series of images were acquired to calculate tissue T1 and contrast agent concentration (8).

Following this, 60 sets of dynamic T2*-weighted images (based on the two-dimensional fast low-angle shot sequence; 30/20, 40° flip angle, 128 × 128 matrix, one section) were obtained by using a second intravenous injection of gadopentetate dimeglumine (0.2 mmol/kg injected at 4 mL/sec after 20 seconds) every 2 seconds over 2 minutes through the central tumor section after the 10th acquisition. This T2*-weighted sequence was performed to quantify susceptibility effects and first-pass kinetics.

Images were analyzed by using specialist dynamic contrast-enhanced MR imaging software (MR Imaging Workbench, version 4.3; Institute of Cancer Research, London, England) (9) with whole tumor regions of interest drawn on T1-weighted subtraction images by one observer (A.R.P.), an oncologically trained radiologist with a special interest in breast cancer MR imaging and more than 15 years of experience. Dynamic contrast-enhanced MR imaging analysis was performed by using pharmacokinetic modeling of contrast kinetics according to the Tofts model (10) and a modified Fritz-Hansen assumed

arterial input function (11–13). The following quantitative kinetic parameters were calculated: K^{trans} (measured in minutes^{-1}), extracellular extravascular volume fraction (v_e), and outflow rate constant ($k_{ep,}$ measured in minutes^{-1}). In addition, we measured the initial area under the gadolinium concentration–time curve over 60 seconds ($IAUGC_{60}$, measured in millimoles per second), a semiquantitative parameter, and determined the relative blood volume (measured in arbitrary units), mean transit time (MTT, measured in seconds), and relative blood flow (measured in arbitrary units) at pre- and posttreatment time points of the T2*-weighted data set; percentage changes with treatment were also calculated. Maximum tumor size was measured from initial diagnostic MR images by using electronic calipers, and the change in size after two cycles of NAC was calculated. Representative parametric MR images are shown in Figure 1.

Statistical Analysis

The primary outcomes were disease-free and overall survival (calculated in months). Disease-free survival was defined as the time from radical treatment to the date of first breast cancer recurrence, date of death, date last known to have no evidence of disease, or date of most recent follow-up. Breast cancer recurrence was either local (limited to ipsilateral breast or chest wall and/or axillary, infraclavicular, or supraclavicular lymph nodes) or distant (metastasis to other parts of the body). Overall survival was calculated from the time of first diagnosis to the date of death, the date last known to be alive, or the date of most recent follow-up. The last date of data collection was June 1, 2010, and patients for whom no event had occurred or who were lost to follow-up were censored accordingly.

Cut points were determined by means of optimization of maximum test sensitivity and specificity at receiver operating characteristic curve analysis to dichotomize MR imaging parameters for survival analysis (Youden index [14]). Survival curves were estimated by using Kaplan-Meier analysis, and significance was determined with log-rank tests. Traditional prognostic factors, such as age, grade of tumor, clinical tumor and nodal stage, and estrogen receptor, progesterone receptor, and HER2 receptor status, were analyzed in a univariate analysis of survival by using the Cox proportional hazards model. Other potential prognostic variables were also examined, including clinical and pathologic response to NAC, pathologic tumor and nodal stage, type of surgery performed at completion of chemotherapy (breast-conserving surgery vs mastectomy vs no surgery), and adjuvant therapy. Parameters significant at $P \leq .10$ were then entered into a multivariate model for the prediction of outcome. Cases with missing data were excluded from the Cox model. Given the small numeric values for K^{trans}, v_e, and k_{ep}, these were scaled accordingly so that a change in hazard ratio (HR) was associated with a 0.01-unit difference in MR imaging parameters.

Statistical significance was otherwise set at a two-tailed P value of less than .05. All statistical analyses were performed by using R statistical software (version 2.10.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics and Response to NAC

Among the 73 patients recruited to the study, three were found to have metastatic disease after enrollment, eight were not able to undergo their first MR imaging examination, and four did not undergo their second MR imaging examination. Patient and disease characteristics of the 62 women included in this study are shown in Table 1. The median age at diagnosis was 45 years (range, 22–70 years), and the median tumor size was 50 mm (range, 10–100 mm). Most women were premenopausal, with most exhibiting tumors of the invasive ductal subtype.

Most patients received intravenous anthracycline-based NAC with 5-fluorouracil, epirubicin, and cyclophosphamide (n = 47) or adriamycin and cyclophosphamide (n = 4) three times weekly; 30 patients received docetaxel either sequentially (n = 19) or alone (n = 11). All patients who received docetaxel alone received anthracycline-based chemotherapy in the adjuvant setting. The median number of cycles of NAC received was six (range, 2–8). All but two of the patients who received fewer than six cycles of NAC went on to receive further chemotherapy after surgery; the

Table 1

Clinical Characteristics of Study Population

Characteristic	No. of Patients (n = 62)
Age at diagnosis (y)	
<50	39 (63)
≥50	23 (37)
Menopausal status	
Premenopausal	39 (63)
Postmenopausal	21 (34)
Perimenopausal	1 (2)
Unevaluable	1 (2)
Histologic characteristic*	
IDC	50 (81)
ILC	9 (14)
Other or NOS	3 (5)
Grade	
I	3 (5)
II	30 (48)
III	24 (39)
Unknown or unevaluable	5 (8)
Clinical tumor stage	
T2	34 (55)
T3	19 (31)
T4	9 (14)
Clinical nodal stage	
Positive	28 (45)
Negative	34 (55)
Estrogen receptor status	
Positive	40 (64)
Negative	22 (35)
Progesterone receptor status	
Positive	31 (50)
Negative	28 (45)
Unknown or unevaluable	3 (5)
HER2 status	
Positive	12 (19)
Negative	45 (73)
Unknown or unevaluable	5 (8)

Note.—Numbers in parentheses are percentages.

* IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, NOS = not otherwise specified.

Figure 2

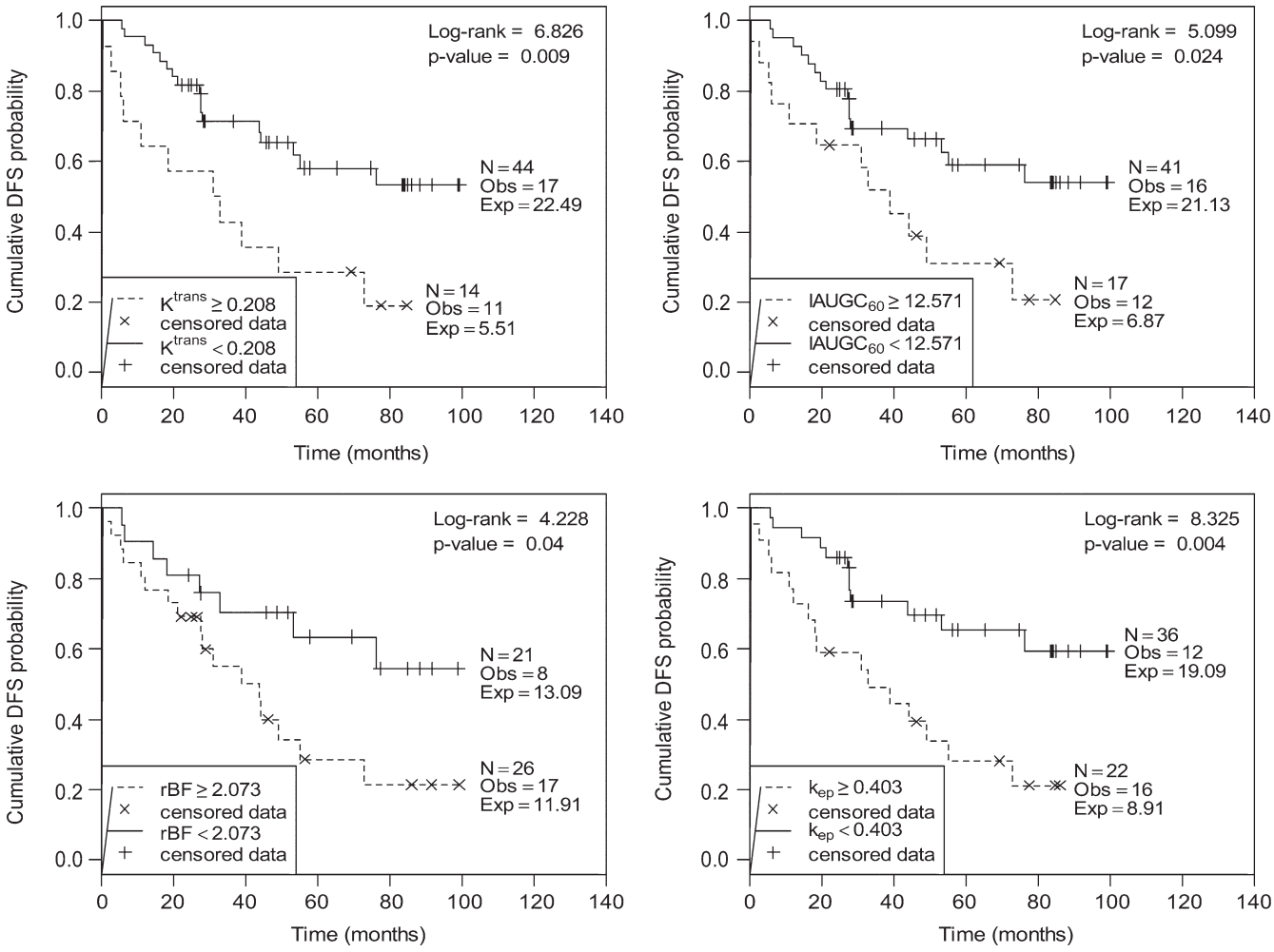


Figure 2: Kaplan-Meier curves for disease-free survival (*DFS*) on the basis of dynamic contrast-enhanced MR imaging kinetic parameters after two cycles of NAC, with values dichotomized above and below the receiver operating characteristic–derived Youden index (*P* values determined with log-rank tests). *Exp* = expected number of events, *N* = number of patients, *Obs* = observed number of events, *rBF* = relative blood flow.

two patients who did not receive further chemotherapy experienced substantial toxicity (one patient underwent two cycles of NAC and the other underwent four cycles of NAC).

Twenty-eight patients underwent breast-conserving surgery and 30 underwent a total mastectomy. Four patients did not undergo surgery but instead received a radical dose of external beam radiation therapy due to patient or physician choice. Two of these four patients had a complete radiologic and clinical response, and the other two patients had clinically palpable minimal residual disease at the completion of NAC. Overall, 38 of the 62 patients (61%) showed a pathologic response and were classified as pathologic responders; 24 of the 62 patients (39%) were classified as nonresponders. Forty-seven of the 62 patients (76%) showed a clinical response (partial or complete) and were classified as clinical responders; 15 of the 62 patients (24%) were classified as nonresponders (stable or progressive disease). Ten of the 62 patients (16%) achieved a complete pathologic response to chemotherapy and 52 (84%) did not.

The median follow-up time was 43.9 months (range, 0.3–99.2 months) for disease-free survival and 60.3 months (range, 10.9–104.1 months) for overall survival. There were 28 recurrences; 26 patients had distant metastases (two also had additional local recurrence) and two had local recurrence only. There were 20 deaths, all of which were related to breast cancer.

Disease-Free Survival

Estimates of disease-free survival at Kaplan-Meier analysis revealed statistically significant differences in posttreatment values for K^{trans} ($P = .009$), k_{ep} ($P = .004$), $IAUGC_{60}$ ($P = .024$), and relative blood flow ($P = .040$), with higher values corresponding to worse outcomes (Fig 2).

Table 2

Survival with Univariate Cox Proportional Hazard Analysis

Characteristic	No. of Patients	Disease-Free Survival			Overall Survival		
		P Value	HR	95% CI*	*P* Value	HR	95% CI*
Age at diagnosis (y)		.086	...	...	.544	...	...
<50	39	...	1.00	...	...	1.00	...
≥50	23	...	0.48	0.21, 1.11	...	0.75	0.30, 1.89
Clinical tumor stage		.057	...	...	.005†	...	...
T2	34	...	1.00	...	...	1.00	...
T3	19	...	0.778	0.30, 2.00	...	0.96	0.30, 3.13
T4	9	...	2.885	1.17, 7.11		5.78	2.08, 16.08
Clinical nodal stage		.234	...	...	.193	...	...
Negative	34	...	1.00	...	...	1.00	...
Positive	28	...	1.57	0.75, 3.30	...	1.80	0.74, 4.36
Tumor grade		.743	...	...	.756	...	...
I	3	...	1.00	...	...	1.00	...
II	30	...	1.67	0.22, 12.82	...	1.09	0.14, 9.67
III	24	...	2.00	0.26, 15.61	...	1.54	0.19, 12.46
Estrogen receptor status		.348	...	...	.205	...	...
Negative	22	...	1.00	...	...	1.00	...
Positive	40	...	0.69	0.32, 1.50	...	0.56	0.23, 1.38
Progesterone receptor status		.032†	...	...	.025†	...	...
Negative	28	...	1.00	...	...	1.00	...
Positive	31		0.43	0.20, 0.93	...	0.35	0.14, 0.87
HER2 status		.384	...	...	.160	...	...
Negative	45	...	1.00	...	...	1.00	...
Positive	12	...	1.46	0.62, 3.45	...	0.35	0.08, 1.52
Type of NAC		.271	...	...	.414	...	...
Anthracycline only	32	...	1.00	...	...	1.00	...
Anthracycline/taxane	19	...	1.47	0.61, 3.58	...	1.95	0.61, 6.22
Taxane only	11	...	0.52	0.15, 1.77	...	0.71	0.16, 3.24
Type of surgery		.033†	...	...	.017†	...	...
Breast-conserving surgery	28	...	1.00	...	...	1.00	...
Mastectomy	30	...	2.40	1.03, 5.57	...	3.61	1.18, 11.09
None	4	...	4.84	1.27, 18.37	...	6.43	1.43, 28 85
Clinical response		.819	...	...	.297	...	...
Nonresponder	15	...	1.00	...	...	1.00	...
Responder	47	...	0.91	0.38, 2.13	...	0.60	0.23, 1.57
Pathologic response		.135	...	...	.141	...	...
Nonresponder	24	...	1.00	...	...	1.00	...
Responder	38	...	0.57	0.27, 1.19	...	0.51	0.21, 1.25
Pathologic response		.335	...	...	.407	...	...
No complete response	52	...	1.00	...	...	1.00	...
Complete response	10	...	0.49	0.12, 2.09	...	0.42	0.06, 3.23
Pathologic tumor stage		.096	...	...	.094	...	...
pT0	10	...	1.00	...	...	1.00	...
pT1	22	...	1.54	0.33, 7.17	...	1.89	0.23, 15.64
pT2	21	...	1.90	0.41, 8.83	...	1.76	0.20, 15.23
pT3	5	...	6.22	1.21, 32.11	...	8.96	1.00, 80.27
Pathologic nodal stage		.080	...	...	.073	...	...
pN0	25	...	1.00	...	...	1.00	...
pN1	13	...	1.56	0.53, 4.66	...	1.50	0.37, 6.06
pN2	8	...	2.17	0.63, 7.43	...	1.14	0.21, 6.30
pN3	9	...	4.14	1.44, 11.88	...	5.14	1.44, 18.28

Table 2 (continues)

Table 2 (continued)

Survival with Univariate Cox Proportional Hazard Analysis

Characteristic	No. of Patients	Disease-Free Survival			Overall Survival		
		P Value	HR	95% CI*	*P* Value	HR	95% CI*
Adjuvant chemotherapy		.227	...	...	.973	...	...
No	51	...	1.00	...	...	1.00	...
Yes	11	...	0.48	0.14, 1.58	...	0.97	0.28, 3.39
Baseline/pretreatment parameters							
Tumor size at MR imaging	56	.622	1.01	0.98, 1.03	.120	1.02	0.99, 1.04
K^{trans}	62	.252	1.03	0.98, 1.07	.392	1.02	0.97, 1.08
v_e	62	.254	1.02	0.99, 1.06	.389	1.02	0.97, 1.07
k_{ep}	62	.765	1.00	0.99, 1.02	.763	1.00	0.99, 1.02
$IAUGC_{60}$	62	.360	1.04	0.96, 1.14	.673	1.02	0.92, 1.14
Relative blood volume	52	.567	1.00	0.99, 1.00	.407	1.00	0.99, 1.00
Relative blood flow	52	.815	0.98	0.85, 1.13	.590	0.95	0.80, 1.14
MTT	52	.013†	0.92	0.87, 0.98	.020†	0.92	0.86, 0.99
Parameters after two cycles of NAC							
Tumor size at MR imaging	52	.145	1.02	0.99, 1.04	.018†	1.03	1.01, 1.06
K^{trans}	58	.048†	1.03	1.01, 1.06	.043†	1.04	1.01, 1.07
v_e	58	.723	0.99	0.97, 1.02	.432	0.99	0.95, 1.02
k_{ep}	58	.044†	1.01	1.00, 1.02	.084	1.01	0.99, 1.02
$IAUGC_{60}$	58	.035†	1.08	1.01, 1.17	.029†	1.10	1.01, 1.21
Relative blood volume	47	.399	1.00	0.99, 1.00	.142	1.00	1.00, 1.01
Relative blood flow	47	.125	1.05	0.99, 1.12	.272	1.05	0.96, 1.15
MTT	47	.950	1.00	0.94, 1.07	.409	1.05	0.94, 1.17
Percentage change with two cycles of NAC							
Tumor size at MR imaging	52	.532	1.77	0.30, 10.57	.374	2.84	0.28, 28.39
K^{trans}	58	.222	1.01	0.99, 1.02	.194	1.01	0.99, 1.02
v_e	58	.462	0.99	0.99, 1.01	.196	0.99	0.98, 1.01
k_{ep}	58	.110	1.01	0.99, 1.02	.108	1.01	1.00, 1.03
$IAUGC_{60}$	58	.112	1.01	0.99, 1.02	.077	1.01	1.00, 1.03
Relative blood volume	47	.039†	1.01	1.00, 1.01	.002†	1.01	1.00, 1.02
Relative blood flow	47	.094	1.00	1.00, 1.00	.616	1.00	1.00, 1.00
MTT	47	.043†	1.02	1.00, 1.03	.013†	1.02	1.00, 1.04

* CI = confidence interval.

† *P* value is statistically significant.

Pretreatment v_e (P = .027) and MTT (P = .002) were predictive of worse disease-free survival, as was the percentage change in MTT (P = .025) after two cycles of chemotherapy.

Univariate analysis of MR imaging parameters as continuous variables by using the Cox model demonstrated that posttreatment K^{trans} (HR = 1.03, P = .048), k_{ep} (HR = 1.01, P = .044), and $IAUGC_{60}$ (HR = 1.08, P = .035) were significant predictors of early recurrence, as were pretreatment MTT (HR = 0.92, P = .013) and percentage changes in MTT (HR = 1.02, P = .043) and relative blood volume (HR = 1.01, P = .039) (Table 2). Progesterone receptor positivity (HR = 0.43, P = .032) was associated with better disease-free survival, whereas no surgery (HR = 4.84) or a mastectomy (HR = 2.40) appeared to be associated with worse disease-free survival (P = .033). Multivariate analysis revealed progesterone receptor positivity (HR = 0.10, P = .002) and pretreatment MTT (HR = 0.79, P = .025) to be significantly associated with outcome (Table 3).

Overall Survival

There were statistically significant differences in posttreatment values at Kaplan-Meier analysis for tumor size at MR imaging (P = .031) and k_{ep} (P = .016) in the prediction of overall survival, but only a trend for K^{trans} (P = .070) and $IAUGC_{60}$ (P = .067) (Fig 3). Neither pretreatment parameters nor percentage change in dynamic contrast-enhanced MR imaging parameters with treatment were significantly associated with mortality.

Univariate analysis of MR imaging parameters as continuous variables revealed posttreatment tumor size at MR imaging (HR = 1.03, P = .018), K^{trans} (HR = 1.04, P = .043), and $IAUGC_{60}$ (HR = 1.10, P = .029) to be significant predictors of overall survival. Pretreatment MTT (HR = 0.92, P = .020) and percentage changes in relative blood volume (HR = 1.01, P = .002) and

Table 3

Survival with Multivariate Cox Proportional Hazard Analysis

Characteristic	Disease-Free Survival			Overall Survival		
	P Value	HR	95% CI*	*P* Value	HR	95% CI*
Age at diagnosis	.093	0.94	0.86, 1.01	...	...	...
Clinical tumor stage	.160	0.42	0.13, 1.41	.099	0.15	0.02, 1.42
Progesterone receptor	.002†	0.10	0.02, 0.42	.709	0.35	0.00, 83.63
Type of surgery	.173	2.98	0.62, 14.31	.467	4.22	0.09, 204.83
Pathologic tumor stage	.180	1.79	0.78, 4.16	.764	0.48	0.01, 56.13
Pathologic nodal stage	.415	1.33	0.67, 2.68	.526	0.53	0.07, 3.80
Baseline/pretreatment MTT	.025†	0.79	0.65, 0.97	.072	0.67	0.43, 1.04
Parameters after two cycles of NAC						
Tumor size at MR imaging	...	...	...	.298	1.15	0.89, 1.49
K^{trans}	.549	1.11	0.78, 1.59	.038†	4.11	1.08, 15.62
k_{ep}	.804	1.01	0.93, 1.10	.038†	0.72	0.52, 0.98
$IAUGC_{60}$	.634	0.89	0.57, 1.41	.154	0.39	0.11, 1.42
Percentage changes with NAC						
$IAUGC_{60}$	...	...	...	.579	0.98	0.91, 1.06
Relative blood volume	.087	0.99	0.98, 1.00	.387	1.01	0.98, 1.05
Relative blood flow	.298	1.00	0.99, 1.00	...	...	...
MTT	.927	1.00	0.96, 1.05	.890	0.99	0.79, 1.23

* CI = confidence interval.

† *P* value is statistically significant.

MTT (HR = 1.02, *P* = .013) were also associated with overall survival. Higher clinical T stage (*P* = .005) and a mastectomy (HR = 3.61) or no surgery (HR = 6.43) (*P* = .017 for both) were significant predictors of worse overall survival compared with progesterone receptor positivity (HR = 0.35, *P* = .025) (Table 2). Of these variables, only posttreatment K^{trans} (*P* = .038) remained an independent prognostic indicator (Table 3), with k_{ep} becoming a significant prognosticator (*P* = .038) at multivariate analysis.

Discussion

Dynamic MR imaging has been shown to be an important tool in the early identification of patients whose breast cancer does not respond to NAC (4,15). However, the ability to identify imaging biomarkers that could also provide prognostic information would be invaluable, particularly in individualizing patient therapy. We observed that patients whose tumors remained highly vascular at dynamic contrast-enhanced MR imaging after two cycles of NAC, as evidenced by elevated values of K^{trans} and $IAUGC_{60}$, were at higher risk of recurrence and mortality. Higher posttreatment K^{trans} and $IAUGC_{60}$ retained their significance as predictors of breast cancer relapse and death when analyzed as continuous variables in the Cox model. In this study, every increment of 0.01 in values for posttreatment K^{trans} between patients conferred an additional 3% increase in risk of recurrence and a 4% increase in risk of death; the same was true for $IAUGC_{60}$, with an 8% increase in recurrence risk and 10% increase in mortality risk. Although $IAUGC_{60}$ and K^{trans} are similar parameters—both reflect underlying tumor perfusion and permeability—the former is a semiquantitative parameter and does not rely on kinetic modeling of dynamic contrast-enhanced MR imaging data. Posttreatment K^{trans} remained an independent predictor for overall survival, even after adjusting for other prognostic indicators.

We observed that posttreatment k_{ep} may also be a potential prognosticator for overall survival at multivariate analysis, although the HR unexpectedly indicated the opposite (HR = 0.72). Although this result cannot be explained physiologically in the context of this study, it highlights the limitations of a multivariate model involving numerous covariates, particularly when some may be co-linearly dependent (eg, K^{trans} and k_{ep}). Notably, k_{ep} was not significantly associated with survival in a univariate model, whereas K^{trans} was consistently so. We also observed at univariate analysis that smaller reductions in tumor blood volume may be associated with poorer disease-free and overall survival, although changes in perfusion did not retain their importance alongside other prognostic variables. The baseline MTT, a measure of the time it takes for blood to perfuse the tumor, was also significantly associated with disease-free survival at both univariate and multivariate analyses. Not unexpectedly, prolonged tumor perfusion times (increased MTT) occurring in treatment-naïve breast tumors that are less well perfused (with lower blood flow and volume) and, therefore, less aggressive, may also be associated with better long-term outcomes.

Traditional prognostic indicators in breast cancer have included TNM stage (16), tumor grade, and hormonal and

Figure 3

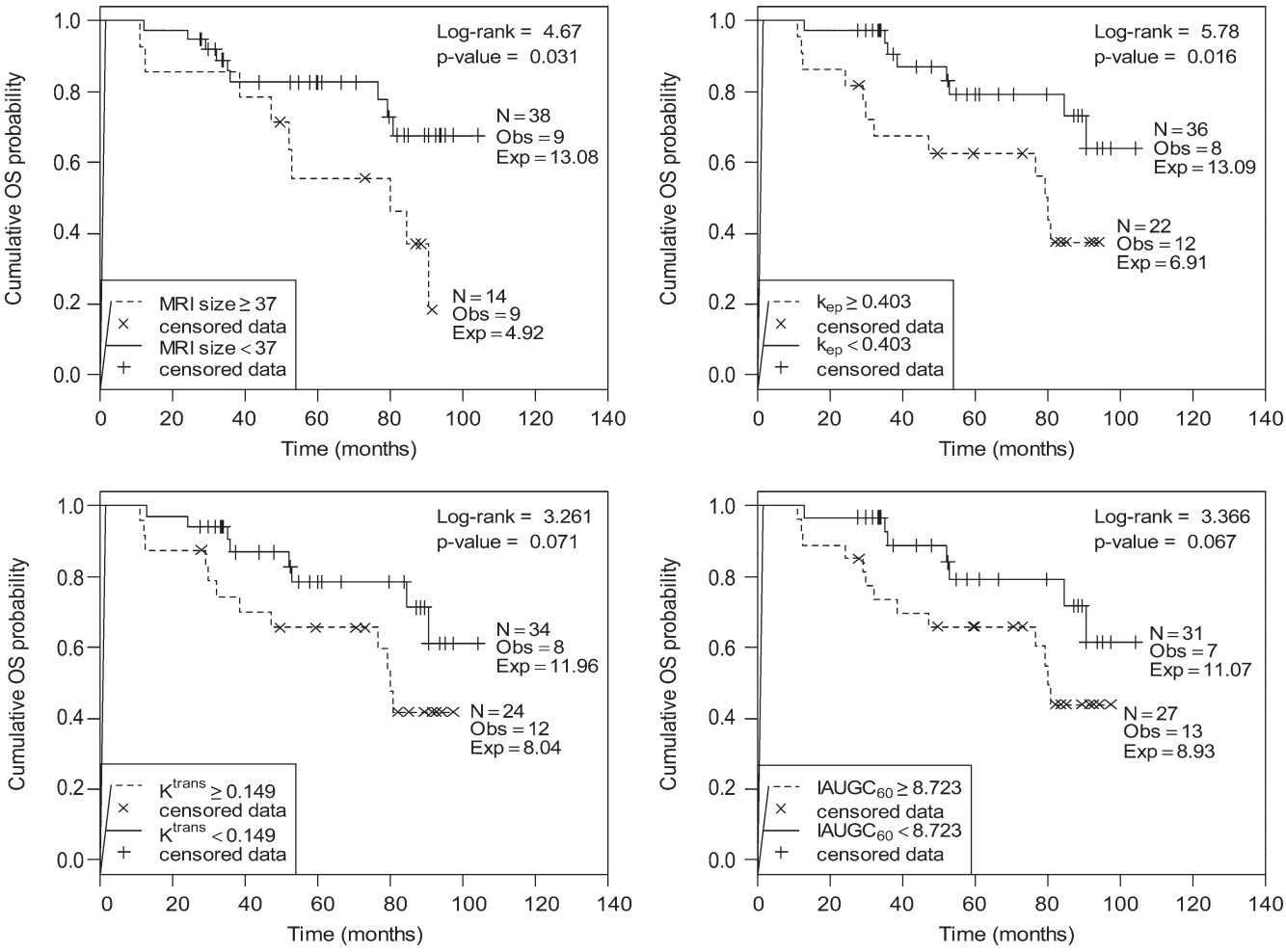


Figure 3: Kaplan-Meier curves for overall survival (*OS*) based on dynamic contrast-enhanced MR imaging kinetic parameters after two cycles of NAC, with values dichotomized above and below the receiver operating characteristic–derived Youden index (*P* values determined with log-rank tests). *Exp* = expected number of events, *MRI size* = size of tumor at MR imaging (in millimeters), *N* = number of patients, *Obs* = observed number of events.

HER2 receptor status. The Nottingham prognostic index, which is based on tumor size and grade, and nodal involvement have been shown to be predictive of patient outcomes (17–19). In our study, clinical tumor stage, progesterone receptor status, and type of surgery performed were all important determinants of outcome. Patients who required a mastectomy at the completion of chemotherapy had a poorer prognosis. In addition, patients with complete clinical response or minimal residual disease who underwent radical radiation therapy instead of surgery also had a worse outcome, although there were only four patients in this category. Surprisingly, known prognostic factors such as estrogen receptor status and tumor grade (20) did not affect outcome in our patient cohort. Although complete pathologic response was associated with better disease-free and overall survival, more than halving the risks of recurrence and mortality, this also did not reach statistical significance. The small number of patients in this study could explain the discrepancy between the observations seen in our cohort and those seen in other larger studies.

MR imaging as a predictor of patient outcome has been reported in breast as well as other cancers, including renal cell, lung, and head and neck cancers (21,22). However, previous studies of breast cancer have principally investigated pretreatment variables without taking into account the effects of treatment (5,6). To our knowledge, only one study has explored the changes that occur in MR imaging parameters with NAC in relation to long-term outcome. Johansen et al (23) evaluated the role of dynamic contrast-enhanced MR imaging in the early prediction of both response and 5-year overall survival in 24 patients with locally advanced breast cancer. By assessing the signal intensity and area under the contrast enhancement curve before and after one cycle of NAC, they demonstrated that

pretreatment values could help predict 5-year overall survival; changes with treatment could not. However, the methods used in dynamic contrast-enhanced MR imaging analysis were different and did not involve any compartmental modeling. To our knowledge, our study is the first to describe the ability of quantitative dynamic contrast-enhanced MR imaging parameters to help identify those patients receiving NAC who may fare better prognostically.

Previous studies have shown that higher values for the proliferation antigen Ki67 after NAC, which imply a heavier residual disease burden, have greater value in predicting worse outcome compared with baseline assessment (24–27). These findings are consistent with our observations that tumors that exhibit greater perfusion and permeability and are larger at the completion of two cycles of NAC may also experience worse outcomes. Chemotherapeutic agents possess antiangiogenic properties in addition to their cytotoxic action, acting both directly by means of endothelial cell death and indirectly by way of loss of endothelial cytokine support (7). This suggests that tumors with a poor angiogenic response to chemotherapy early on, which thereby remain highly vascular, have a greater potential for continued growth and ability to metastasize, leading to a poorer prognosis. Therefore, earlier intervention with drugs directed at the tumor vasculature may be beneficial in this patient population who may fail to respond.

Although this study demonstrates the potential role of dynamic contrast-enhanced MR imaging in predicting long-term outcome, results should be interpreted with caution given the relatively small study size; further exploration with larger studies is warranted. In addition, this study was exploratory in nature, and a formal prospective power analysis was not performed. Therefore, given the relatively small number of events and the subsequent wide confidence intervals, results should be viewed with caution. We are aware of the potential limitations of using optimized cut points derived from our own study for Kaplan-Meier analysis of survival and imaging parameters, as this may lead to overly optimistic results; however, these parameters retained their significance when analyzed as continuous variables in the Cox model. There was some heterogeneity in patient treatment; although most patients went on to receive radical surgery, four patients received a radical dose of radiation therapy instead. Furthermore, quantitative dynamic contrast-enhanced MR imaging analysis involves pharmacokinetic modeling, which is based on a number of underlying assumptions—including a simplified two-compartmental model of contrast kinetics and an assumed arterial input function. Nevertheless, our observations in this study are in keeping with evidence supporting the detrimental effects of higher residual vascularization and disease activity after NAC.

In conclusion, the results of this study demonstrated that patients with breast carcinomas exhibiting higher levels of vascularization after two cycles of NAC experience worse disease-free and overall survival. Taken in conjunction with traditional prognostic variables in breast cancer, dynamic contrast-enhanced MR imaging–derived measures of vascularity after treatment may act as predictors of disease outcome in patients undergoing NAC. Functional dynamic contrast-enhanced MR imaging parameters have the potential to become valid surrogate determinants of long-term outcome, although further prospective evaluation is required.

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