Quantitative Analysis of Clinical Dynamic Contrast-enhanced MR Imaging for Evaluating Treatment Response in Human Breast Cancer¹

Yanming Yu, BS
 Quan Jiang, PhD
 Yanwei Miao, MD
 Jun Li, BS
 Shanglian Bao, PhD
 Haoyu Wang, BS
 Chunxue Wu, MD
 Xiaoying Wang, MD
 Jiong Zhu, MD
 Yi Zhong, MS
 E. Mark Haacke, PhD
 Jiani Hu, PhD

¹From the Beijing Key Laboratory of Medical Physics and Engineering, Peking University, Beijing, China (Y.Y., J.L., H.W., S.B.); Department of Neurology, Henry Ford Health Sciences Center, Detroit, Mich (Q.J.); Department of Radiology, the First Affiliated Hospital, Dalian Medical University, Dalian, Liaoning, China (Y.M.); Department of Radiology, Peking University First Hospital, Beijing, China (C.W., X.W.); Department of Radiology, Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (J.Z.); Department of Sino-Dutch Biomedical & Information Engineering, Northeastern University, Shenyang, Liaoning, China (Y.Z.); Department of Radiology, Wayne State University School of Medicine, Harper University Hospital, MR Imaging Center/Concourse, 3990 John R St, Detroit, MI 48201 (E.M.H., J.H.); and MR Imaging Institute for Biomedical Research, Detroit, Mich (E.M.H.). Received November 18, 2009; revision requested January 12, 2010; revision received April 1; accepted April 19; final version accepted May 19. Supported in part by The Susan G. Komen Breast Cancer Foundation (grant IMG0402881) and the National Basic Research Program (2006CB705705) from the Ministry of Science and Technology of China, National Natural Science Foundation of China (grants 10527003, 60672104). **Address correspondence to** J.H. (e-mail: jhu@med.wayne.edu).

© RSNA, 2010

Purpose:

To develop a method that combines a fixed-T1, fuzzy c-means (FCM) technique with a reference region (RR) model (T1-FCM method) to estimate pharmacokinetic parameters without measuring the arterial input function or baseline T1, or T1(0), and to demonstrate its feasibility in the assessment of treatment response to neoadjuvant chemotherapy (NAC) in patients with breast cancer by using data from dynamic contrast material-enhanced magnetic resonance (MR) imaging.

Materials and Methods:

This study was approved by the human investigation committees of the two participating institutions. All patients gave written informed consent. A conventional dual-flip-angle gradient-echo method was used to evaluate the effects of noise and the T1 in the tissue itself on the accuracy of T1 estimation. Both conventional RR and fixed-T1 methods were used to evaluate the effects of noise and preselected T1(0) on the estimation of pharmacokinetic parameters by means of a simulation study. Thirty-three women (age range, 32–66 years; mean age, 45 years) with pathologically proved breast tumors were examined to evaluate the feasibility of using the T1-FCM method as a means of assessing treatment response to NAC. A non-parametric Mann-Whitney *U* test was used to assess the difference in each of the MR imaging parameters between patients with a major histologic response to treatment and those with a nonmajor histologic response.

Results:

With use of the dual-flip-angle method, the accuracy and distribution of T1 estimation are dependent on the T1 in the tissue itself. The T1-FCM method is more accurate than other methods and is relatively insensitive to the effects of noise and incorrect T1(0) selection. Preliminary clinical data revealed a significant difference ($P < .01$) in the change of the volume transfer constant after two cycles of NAC between the major and nonmajor histologic response groups.

Conclusion:

Results of the simulation study demonstrate that the T1-FCM method appears to be relatively insensitive to noisy dynamic contrast-enhanced MR imaging data. This method could prove useful in the evaluation of breast cancer therapy.

© RSNA, 2010

Neoadjuvant chemotherapy (NAC) has become more common for the treatment of breast cancer before surgery (1). Patients who respond to NAC have a better prognosis than those who do not (2). Nevertheless, patients who fail to respond to NAC should be identified as early as possible to minimize the side effects of ineffective therapy or enable alternative NAC or early surgery.

Magnetic resonance (MR) imaging has proved to be the most effective non-invasive technique for evaluating the response to NAC (3), and quantitative dynamic contrast material-enhanced MR imaging is useful for differentiating patients who respond to NAC after one or two cycles from those who fail

to respond (4). Quantitative dynamic contrast-enhanced MR imaging is superior to semiquantitative or qualitative options because of its ability to provide information about pharmacokinetic parameters such as volume transfer constant (K^{trans}) and extravascular extracellular volume fraction (v_e) (5), which not only facilitate a comparison before and after NAC but also help estimate breast tumor permeability. Nevertheless, quantitative dynamic contrast-enhanced MR imaging has not been routinely adopted in clinical practice because of several major practical limitations (6), including (a) the difficulty in obtaining an accurate arterial input function, (b) the long imaging time needed to acquire three-dimensional data with high spatial resolution and a high signal-to-noise ratio for accurate estimation of baseline T1, or T1(0), and (c) the often highly variable or even nonphysical results owing to the effects of noise.

Reference region (RR) models have been developed in an effort to overcome the difficulty in obtaining the arterial input function (7–11). In the RR model, the curves from the tissues of interest are compared with those from a well-characterized RR, thereby eliminating the need to directly measure arterial input function while at the same time losing the constraints on temporal resolution. For this reason, we chose an RR-based model for our study.

Fixed-T1 methods have been developed to overcome difficulties in measuring T1(0) (12). Instead of estimating T1(0) from specially acquired data, fixed-T1 methods use a preselected T1(0) to estimate pharmacokinetic parameters, thus eliminating the need to measure and estimate T1(0) along with associated errors. This preselected T1(0) is typically based on data from similar patients or values in the literature. Although the usefulness and effectiveness

of fixed-T1 methods have recently been documented (13,14), one major question remains: Can these methods still estimate pharmacokinetic parameters with acceptable accuracy when data from dynamic contrast-enhanced MR imaging are noisy and the preselected T1(0) is considerably different from the true value? The heterogeneous nature of breast cancer (including T1) is well recognized. In this study, we propose using a modified RR model to minimize the effect of incorrect T1(0) selection by taking advantage of the relationship between the T1(0) in the tumor and the T1(0) in the RR.

Fuzzy c-means (FCM) is an automated learning technique used for pattern recognition that has proved to be both effective and efficient for segmenting and classifying breast lesions on the basis of the uptake curves obtained with dynamic contrast-enhanced MR imaging (15,16); however, its practicality for quantitative dynamic contrast-enhanced MR imaging has not been fully recognized. In addition to automatically differentiating tumors from nontumor tissues, the FCM algorithm also groups

Advances in Knowledge

- Results of a simulation study showed that with a preselected baseline T1, or T1(0), of less than 15% off the true T1(0), the original fixed-T1 method improved accuracy by more than 40% and precision by more than 60% compared with the conventional reference region method.
- The modified fixed-T1 method further improved accuracy from 11% to 1.1% but had little effect on precision.
- The modified fixed-T1 method with the fuzzy c-means (FCM) technique (T1-FCM method) improved precision from 13% to 2.7% but had no major effect on accuracy by using the simulated dynamic contrast-enhanced MR imaging data at 80% of typical noise.
- Using the T1-FCM method to quantitatively assess treatment response to neoadjuvant chemotherapy (NAC) in patients with breast cancer, we found a significant difference ($P < .01$) in the change of the volume transfer constant after NAC between the patients with major histologic response and those with nonmajor histologic response.

Implication for Patient Care

- This method could prove useful for the assessment of treatment response to therapy in patients with breast cancer.

Published online before print
10.1148/radiol.10092169

Radiology 2010; 257:47–55

Abbreviations:

FCM = fuzzy c-means
 K^{trans} = volume transfer constant
 NAC = neoadjuvant chemotherapy
 RR = reference region
 T1(0) = baseline T1
 v_e = extravascular extracellular volume fraction

Author contributions:

Guarantors of integrity of entire study, Y.Y., S.B., C.W., J.Z., Y.Z., E.M.H., J.H.; 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, Y.Y., J.L., S.B., H.W., C.W., X.W., J.Z., Y.Z., J.H.; clinical studies, Y.Y., Y.M., S.B., C.W., X.W., J.Z., J.H.; statistical analysis, Y.Y., S.B., C.W., X.W., Y.Z., J.H.; and manuscript editing, Y.Y., S.B., C.W., E.M.H., J.H.

Funding:

This research was supported by the National Institutes of Health (grant R21 CA118569-01A1).

Authors stated no financial relationship to disclose.

contrast material uptake curves with similar patterns into a single cluster. The number of clusters (N_{cluster}) is determined with the empirical equation (15)

$$N_{\text{cluster}} = \begin{cases} 2 & \text{if } N \leq 160 \\ \lceil N/60 \rceil & \text{if } N > 160 \end{cases} \quad (1)$$

where N is the number of pixels. Because there are far fewer clusters than pixels in a given image according to Equation (1), the use of FCM should markedly reduce noise effects, making it an important adjunct to quantitative dynamic contrast-enhanced MR imaging.

The purpose of this study was to develop a quantitative dynamic contrast-enhanced MR imaging method that combines the fixed-T1 method, the FCM algorithm, and an RR model (the T1-TCM method) to estimate pharmacokinetic parameters without measuring arterial input function or T1(0) and to demonstrate its feasibility in assessing treatment response to NAC in patients with breast cancer with use of routinely acquired clinical dynamic contrast-enhanced MR imaging data.

Materials and Methods

Modified RR Model

There are two key components to the modified RR model: (a) reconstruction of the baseline signal intensity $S(0)$ in the region of the suspected tumor and (b) use of the reconstructed baseline signal intensity $S(0)_{\text{rec}}$ instead of the measured baseline signal intensity to estimate pharmacokinetic parameters in a fixed-T1-based method. The signal intensity for a spoiled gradient-echo sequence with a short repetition time is given by the following equation (17):

$$S(0) = \frac{\rho_b \sin \theta (1 - e^{-\text{TR}/\text{T1}(0)})}{(1 - e^{-\text{TR}/\text{T1}(0)}) \cos \theta}, \quad (2)$$

where θ is the flip angle, ρ the proton density, and TR the repetition time. In the modified RR model, “reconstructing” the baseline signal intensity simply means replacing the true T1 in Equation

(2) with the preselected T1(0), or T1(0)_{fix}, as follows:

$$\begin{aligned} S(0)_{\text{rec}} &= \frac{\rho_b \sin \theta (1 - e^{-\text{TR}/\text{T1}(0)_{\text{fix}}})}{(1 - e^{-\text{TR}/\text{T1}(0)_{\text{fix}}}) \cos \theta} \\ &= S(0) \cdot \frac{x_{\text{true}}}{x_{\text{fix}}}, \end{aligned} \quad (3)$$

where x_{true} and x_{fix} are calculated from Equation (4) by using the true T1(0) and preselected T1(0), respectively, and

$$x = \frac{1 - \cos \theta \cdot e^{-\text{TR}/\text{T1}(0)}}{1 - e^{-\text{TR}/\text{T1}(0)}}. \quad (4)$$

To estimate the true T1(0), we first establish the relationship between the T1(0) in the tumor [T1(0)_{tumor}] and that in the RR [T1(0)_{RR}] by dividing the signal intensity in the tumor by that in the RR according to Equation (2), as follows:

$$\begin{aligned} \frac{S(0)_{\text{tumor}}}{S(0)_{\text{RR}}} &= \frac{\rho_{\text{tumor}}}{\rho_{\text{RR}}} \cdot \frac{1 - \cos \theta e^{-\text{TR}/\text{T1}(0)_{\text{RR}}}}{1 - \cos \theta e^{-\text{TR}/\text{T1}(0)_{\text{tumor}}}} \cdot \frac{1 - e^{-\text{TR}/\text{T1}(0)_{\text{tumor}}}}{1 - e^{-\text{TR}/\text{T1}(0)_{\text{RR}}}}, \end{aligned} \quad (5)$$

where ρ_{tumor} and ρ_{RR} are the proton density in the tumor and RR, respectively. Then, the T1 in the tumor can be estimated from that in the RR by simplifying the exponent $-\text{repetition time}/\text{T1}$ in Equation (5) as $(1 - \text{repetition time})/\text{T1}$, specifying that $\text{repetition time}/\text{T1} \ll 1$:

$$\begin{aligned} \text{T1}(0)_{\text{tumor}} &= \frac{\text{T1}(0)_{\text{RR}} - \cos \theta \cdot \text{T1}(0)_{\text{RR}} + \cos \theta \cdot \text{TR} - \cos \theta \cdot \text{TR} \cdot N_{\text{RR},t} \cdot \frac{S(0)_{\text{tumor}}}{S(0)_{\text{RR}}}}{N_{\text{RR},t} \cdot \frac{S(0)_{\text{tumor}}}{S(0)_{\text{RR}}} \cdot (1 - \cos \theta)}, \end{aligned} \quad (6)$$

where $N_{\text{RR},t}$ is the proton density ratio ($\rho_{\text{RR}}/\rho_{\text{tumor}}$) between RR and tumor (t). $N_{\text{RR},t}$ can be estimated (a) with proton density-weighted MR imaging, (b) with data obtained from patients with similar lesions, (c) with values stated in the literature, and (d) by averaging $\rho_{\text{tumor}}/\rho_{\text{RR}}$ from Equation (5) by using T1 values for tumor and RR in the literature. In our preliminary study, we used the averaging method with a tumor T1 of 1151 msec and a muscle T1 of 869 msec (18).

Simulation Study

For the simulation study, we first compared estimates of K^{trans} and v_e obtained with four different quantitative dynamic contrast-enhanced MR imaging methods with the true values we used to generate the dynamic contrast-enhanced MR imaging data (along with a true T1[0]) and then used this comparison to determine the accuracy and precision of each method at various noise levels by using estimated or preselected values of T1(0) (depending on the method). In this study, accuracy was defined as $|\text{true value} - \text{estimated value}|/\text{true value}$, and precision was defined as standard deviation/mean value. Nonphysical values of K^{trans} were defined as those that were less than 0 or larger than 5.

Figure 1 illustrates the procedure used to generate the dynamic contrast-enhanced MR imaging data at five different noise levels (no noise and 40%, 80%, 120%, and 160% of the typical noise level for unenhanced T1-weighted breast MR imaging with our unit) for the comparison study. The first method (conventional RR) involves a two-compartment RR model, which does not call for measurement of arterial input function but does require estimation of T1(0) with use of a conventional dual-flip-angle method (7,21). In this study, whenever the first method was involved, two optimal flip angles for a true T1(0) of 1000 msec were used to estimate T1(0) for a fair comparison with the other methods (22). The second method (the original fixed-T1 method) is basically the same as the conventional RR model but uses a preselected T1(0) without measuring either arterial input function or T1(0) (12–14). The third and fourth methods (modified fixed-T1 without and with FCM) replace the original RR model with a modified version. Note that all fixed-T1 methods eliminate the need to measure arterial input function and T1(0) but still require preselection of T1(0). A series of preselected T1(0) values of 800, 900, 1000, 1100, and 1200 msec were used to study the T1(0) dependence of each of the three fixed-T1 methods. We wanted to answer the following questions: (a) Does the true T1 have

any effect on the accuracy and distribution of T_1 as estimated with the conventional dual-flip-angle method? (b) Can the modified fixed- T_1 method help improve the accuracy of K^{trans} and v_e estimation in the event that the pre-selected $T_1(0)$ is not equal to the true $T_1(0)$? (c) Can use of the FCM algorithm reduce the effect of noise on the estimation of K^{trans} and v_e ? and (d) Can use of the T_1 -FCM method improve accuracy and precision over that with other methods?

Clinical Study

MR imaging.—All patients underwent MR imaging with a 1.5-T whole-body unit (Signa Excite 1.5T; GE Health Care, Milwaukee, Wis) by using a four-channel phased-array breast coil. Dynamic contrast-enhanced MR images were obtained with a T_1 -weighted fast three-dimensional short-repetition-time spoiled gradient-echo sequence with fat suppression by using a standard clinical breast MR imaging protocol (6.65/1.56 [repetition time msec/echo time msec], 15° flip angle, 3-mm-thick sections, 512×512 matrix, and 50-second temporal resolution) before and after two cycles of NAC. One series was performed before contrast material administration and seven series were performed after contrast material administration. The median interval between pretreatment MR imaging and chemotherapy was 1 day. Data from dynamic contrast-enhanced MR imaging were processed with software developed in-house and written in Matlab 7.6 (MathWorks, Natick, Mass). Figure 2 illustrates steps for the T_1 -FCM method.

Patients.—This prospective study was approved by the human investigation committees of each of the participating institutions (Dalian Medical University and Shanghai Jiao Tong University School of Medicine). Written informed consent was obtained from all patients. Thirty-three women (age range, 32–66 years; mean age, 45 years) with biopsy-proved breast cancer participated in the study. The 33 patients were from two institutions: 26 patients were from Dalian Medical University, and seven were from Shanghai Jiao Tong

Figure 1

Step 1: Generating $C_t(t)$ in tumor and reference tissue with given AIF (See Ref 19) and (K_{trans}, V_e) using Toft model as detailed in Ref 7.

Step 2: Converting $C_t(t)$ in tumor to $T_1(t)$ with known baseline $T_1(0)$ value (1000ms) (See Ref 12).

Step 3: Constructing tumor DCE-MRI $S(t)$ with $T_1(t)$ by Equation 2.

Step 4: Adding different levels of noise to DCE-MRI.

Figure 1: Flowchart of the procedure for generating dynamic contrast-enhanced MR imaging (DCE-MRI) data with a true K^{trans} of 0.4 minute^{-1} , true v_e of 0.4, true $T_1(0)$ of 1000 msec, repetition time of 3.8 msec, 13° flip angle, proton density of 10 000 arbitrary units, 64×64 matrix, and temporal resolution of 50 seconds. One series was obtained before the administration of contrast material, and seven series were obtained after the administration of contrast material. Different levels of noise (0, 20, 40, 60, and 80 arbitrary units, which are 0%, 40%, 80%, 120%, and 160%, respectively, of our typical noise level for unenhanced T_1 -weighted breast MR imaging) were added to the dynamic contrast-enhanced MR images. AIF = arterial input function, $C_t(t)$ = contrast material concentration, $S(t)$ = signal intensity in the tumor, $T_1(t)$ = T_1 in the tumor.

University School of Medicine. All MR images were obtained between January 2007 and February 2009. The specific NAC regimen used in each patient was determined on an individual basis by their oncologists. Seventeen patients were treated with 80 mg/m² perarubicin, 800 mg/m² cytoxan, and 120 mg/m² taxinol once every 3 weeks for four cycles. The other 16 patients received 80 mg/m² perarubicin, 800 mg/m² cytoxan, and 1 g/m² fluorouracil once every 3 weeks for four cycles. Each patient underwent three MR examinations: one before NAC, one after two cycles of treatment, and one before surgery. All patients underwent lumpectomy or mastectomy

Figure 2

Step 1: Tumor segmentation using a FCM based segmentation algorithm (See Ref 16).

Step 2: Reference Region (Muscle) Selection.

Step 3: Determine an optimized fixed- T_1 value for tumor by averaging the estimated $T_1(0)$ value from modified RR model.

Step 4: Obtain the reconstructed baseline signal intensity $S_{rec}(0)$ over tumor area, and convert signal intensity of tumor and RR to concentration following the steps as Ref 12.

Step 5: Automatically clustering tumor CA concentration $C_t(t)$ into pre-defined number (See Equation 1) of clusters by FCM technique.

Step 6: Fitting the clusters to an empirical formula (See Ref 21).

Step 7: Estimating K_{trans} and V_e for each cluster using RR model with linear regression method, and K_{trans} and V_e for each pixel were given by corresponding cluster with the greatest similarity (or the largest membership grade) for the pixel.

Figure 2: Flowchart for the T_1 -FCM method. CA = contrast agent, $C_t(t)$ = contrast material concentration, $S_{rec}(0)$ = reconstructed baseline signal intensity.

after the completion of NAC. For all patients, surgery was performed within 1 day of the final MR imaging examination. In this study, we analyzed images from only two of the three dynamic contrast-enhanced MR imaging examinations:

those obtained before therapy and those obtained after two cycles of therapy.

The histopathologic response to NAC was assessed on the basis of excised specimens according to the five-grade scheme proposed by Ogston et al (23). A grade of 4 or 5 was classified as a major histologic response (24), and a grade of 1–3 was classified as a nonmajor histologic response (25). All histopathologic specimens were processed at the First Affiliated Hospital of Dalian Medical University, and assessments were independently performed by two pathologists with 8 and 10 years of experience in the evaluation of breast cancer. There was disagreement about one case owing to the difficulty in judging the actual reduction in tumor cells (determined to be 85% or grade 3 by one pathologist but 95% or grade 4 by the other). For this case, the final assessment was decided by the chief pathologist of the department as grade 3.

The peak enhancement ratio of the time–signal intensity curve, a semi-quantitative parameter, was calculated as follows: $(S^* - S[0]) / (S[0] \times \tau)$, where S^* is the maximum value of the time–signal intensity curves and τ the time needed for S^* .

Statistics.—Median tumor values of K^{trans} and v_e were obtained for each patient as suggested in the literature (24). Tumor volumes were assessed for each patient by using a FCM-based method (16). Changes in the K^{trans} , v_e , tumor volume, and peak enhancement ratio before and after two cycles of NAC were calculated with the following formula: $[(\text{value before NAC} - \text{value after NAC}) / \text{value after NAC}] \times 100\%$.

Considering the limited samples for each group, we chose a nonparametric method (Mann-Whitney U test) to assess the statistical difference in each of the parameters between major and nonmajor histologic response groups by using software (Matlab 7.6). One patient with grade 5 response did not show a visible tumor at MR imaging after two cycles of NAC and therefore was excluded from statistical analysis. A P value of .05 was used to determine statistical significance. Two cutoff values (85% for change of K^{trans} and 0.39 minute⁻¹

for pretreatment K^{trans}) were chosen to compare the performance of the two parameters after reviewing the data.

Results

Simulation Study

Effects of noise and T1 on the distribution of T1 as estimated with the dual-flip-angle gradient-echo method.—Figure 3 shows a histogram of T1 estimated with two flip angles. As illustrated in Figure 3, the higher the noise level, the broader the distribution of estimated T1 values. The figure also shows that the distribution of estimated T1 with the dual-flip-angle method became worse as the true T1 increased from 500 to 1000 msec, even though the two flip angles were optimized for a T1 of 1000 msec (2.07° and 12.01°, respectively) (22).

Minimizing T1-related effects on K^{trans} estimation with the modified RR

model.—Figure 4 shows K^{trans} as estimated with the original and modified fixed-T1 methods by using preselected T1(0) values of 800, 900, 1000, 1100, and 1200 msec. The accuracy of K^{trans} estimated with both methods was within 2% of the true K^{trans} of 0.4 minute⁻¹ when using a preselected T1(0) equal to the true T1(0) of 1000 msec. The accuracy of the modified RR method was within 7% of the true K^{trans} of 0.4 minute⁻¹ for the range of preselected T1(0) values as the preselected T1(0) increased or decreased away from 1000 msec, unlike the original fixed-T1 method, where the estimated K^{trans} could be off the true value by more than 50%. Moreover, estimations of K^{trans} with the modified fixed-T1 method were more accurate than those with the original fixed-T1 method in every case. Compared with the original fixed T1-method, the modified fixed-T1 method is less sensitive to preselected T1(0).

Figure 3

Figure 3: Graph shows the effects of noise and T1 on T1 estimation with the conventional dual-flip-angle gradient-echo method at two different levels of noise: a standard deviation of 40 arbitrary units (80% of typical noise, solid lines) and a standard deviation of 80 arbitrary units (160% of typical noise, dashed lines), which were generated from pseudorandom Gaussian noise. Data were obtained with a spoiled gradient-echo sequence with the following parameters: 128 × 128 matrix, 3.8-msec repetition time, 2.07° and 12.01° flip angles (optimal for a T1 of 1000 msec), proton density of 10 000 arbitrary units, and a true T1(0) of 500 (green), 1000 (red), or 1500 (black) msec.

Figure 4

Figure 4: Bar chart illustrates the insensitivity to preselected $T_1(0)$ values associated with estimating K^{trans} with the modified versus original fixed- T_1 method at a noise level of 80%. The data from dynamic contrast-enhanced MR imaging were generated with the procedure illustrated in Figure 1. The mean K^{trans} values and standard deviations with the two methods were compared for each preselected $T_1(0)$ ranging from 800 to 1200 msec.

Reducing noise-related effects on K^{trans} and v_e estimation with FCM.—Figure 5 shows the mean K^{trans} values and standard deviations estimated with the modified fixed- T_1 method with and without FCM at five noise levels (no noise and 40%, 80%, 120%, and 160% of the noise level typical with unenhanced T_1 -weighted MR imaging) by using the same procedure and parameters as in Figure 1. Clearly, use of the FCM algorithm can improve precision for noisy data. For example, the precision was improved from 21.7% to 3.4% by adding FCM to the modified fixed- T_1 method at a noise level of 120%.

Improving accuracy and precision and reducing nonphysical values with T_1 -FCM.—Table 1 illustrates the accuracy and precision of K^{trans} as estimated with the conventional RR method, the original fixed- T_1 method, and the modified fixed- T_1 method with and without FCM at two noise levels (80% and 160% of typical noise). In addition, the percentage of nonphysical values generated with each method is shown. At 80% of typical noise and a preselected $T_1(0)$ of

Figure 5

Figure 5: Bar chart illustrates the effectiveness of the FCM method in reducing noise-related effects. The data from dynamic contrast-enhanced MR imaging were obtained with the steps outlined in Figure 1. The mean K^{trans} values and standard deviations obtained with the modified fixed- T_1 method with and without FCM are compared at noise levels of 0%, 40%, 80%, 120%, and 160% by using a preselected $T_1(0)$ equal to the true $T_1(0)$ of 1000 msec.

Table 1

Comparison of MR Imaging Methods at Two Different Noise Levels for a True K^{trans} of 0.4 Minute⁻¹

Noise Level and Parameter	Conventional RR Method	Fixed-T1 Method	Modified Fixed-T1 Method	
			Without FCM	With FCM
80% of typical noise				
Accuracy	20	11	1.1	1.4
Precision	69	23	13	2.7
Nonphysical values	3.3	0.0	0.0	0.0
160% of typical noise				
Accuracy	45	14	2.5	3.0
Precision	110	32	23	4.7
Nonphysical values	21.3	3.0	0.2	0.0

Note.—Data are given as percentages. Nonphysical values are those that are less than 0 or more than 5.

less than 15% of the true $T_1(0)$, the original fixed- T_1 method improved accuracy by more than 40% and precision by more than 60% compared with that at conventional RR. The modified fixed- T_1 method further improved accuracy from 11% to 1.1% but had little effect on precision. Conversely, the modified fixed- T_1 method with FCM improved precision from 13% to

2.7% but had no substantial effect on accuracy.

Clinical study.—Figure 6 shows the relationship between changes in K^{trans} , v_e , tumor volume, and peak enhancement ratio after two cycles of NAC and the histopathologic response from 32 of our 33 patients with use of the T_1 -FCM method. Seventeen of the 33 patients had a major histologic response and 16 had

Table 2

Summary of Patient Characteristics

Patient No./ Age (y)	Tumor Type*	Tumor Grade	Pathologic Response Grade†
1/39	IDC	II	1
2/55	IDC	II	1
3/48	IDC	II	1
4/32	IDC	II	1
5/44	DCIS	III	2
6/49	IDC	II	2
7/47	IDC	II	2
8/32	DCIS	III	2
9/52	IDC	III	2
10/50	IDC	II	2
11/66	IDC	II	3
12/55	IDC	II	3
13/51	IDC	II	3
14/41	IDC	II	3
15/46	IDC	III	3
16/45	IDC	III	3
17/38	IDC	III	4
18/56	IDC	III	4
19/37	IDC	II	4
20/45	IDC	III	4
21/52	IDC	II	4
22/38	IDC	II	4
23/40	DCIS	II	4
24/52	IDC	III	4
25/32	IDC	III	4
26/50	IDC	III	4
27/45	IDC	II	4
28/54	IDC	II	4
29/45	IDC	III	4
30/34	IDC	II	5
31/55	IDC	III	5
32/34	IDC	III	5
33/39	IDC	III	5

* DCIS = ductal carcinoma in situ, IDC = invasive ductal carcinoma.

† A grade of 1–3 is indicative of a nonmajor response, and a grade of 4 or 5 is indicative of a major response.

a nonmajor histologic response. Table 2 lists patient characteristics. The difference between the pretreatment K^{trans} and that after two cycles of NAC between the major and nonmajor histologic response groups was statistically significant (Table 3). A cutoff value of 85% for changes in K^{trans} would help correctly predict the histologic response in 14 of the 16 patients with a nonmajor response and 13 of the 17 with a major response. These numbers yield a sensitivity of 81% (13 of 16 patients), specificity

Figure 6

Figure 6: Box plot of changes in (a) K^{trans} , (b) v_e , (c) volume, and (d) peak enhancement ratio between patients with major histologic response (MHR) and those with nonmajor histologic response (NMHR). The boundaries of the box denote the 25th and 75th percentiles, and the line within the box marks the median value. Whiskers show 95th and fifth percentiles. Outliers (●) are also shown.

of 88% (14 of 16 patients), positive predictive value of 87% (13 of 15 patients), negative predictive value of 82% (14 of 17 patients), and accuracy of 84% (27 of 32 patients). Conversely, a pretreatment K^{trans} cutoff of 0.39 minute^{-1} could enable the correct prediction of the histologic response in 10 of the 16 patients with a nonmajor response and 12 of the 17 with a major response, yielding a sensitivity of 75% (12 of 16 patients), specificity of 63% (10 of 16 patients), positive predictive value of 67% (12 of 18 patients), negative predictive value of 71% (10 of 14 patients), and accuracy of 69% (22 of 32 patients).

Discussion

In general, the technical requirements for accurately assessing responses to

chemotherapy are more demanding than those required for diagnosis because of potential changes in the experimental conditions between different MR imaging examinations for a longitudinal study (14). Chemotherapy can alter MR imaging tissue properties such as $T1(0)$, and absolute noise levels can change from one session to another. Our method, which we call T1-FCM, combines fixed-T1, FCM, and modified RR models to estimate the K^{trans} and v_e from clinical dynamic contrast-enhanced MR imaging data without the need to measure $T1(0)$ or arterial input function. Moreover, the T1-FCM method offers improved precision when evaluating noisy dynamic contrast-enhanced MR imaging data and is relatively insensitive to the incorrect selection of $T1(0)$. The results of our clinical study of

Table 3

Comparison of Vascular Data, Patient Age, and Diagnostic Tumor Grade between Major and Nonmajor Histologic Response Groups

Parameter	Histologic Response		P Value
	Nonmajor	Major	
K^{trans} (min^{-1})			
Before treatment	0.34 ± 0.23	0.55 ± 0.22	.024
After two cycles of treatment	0.28 ± 0.22	0.28 ± 0.12	.651
Change	45.4 ± 41.0	123.6 ± 70.7	<.01
v_e			
Before treatment	0.75 ± 0.52	0.91 ± 0.36	.175
After two cycles of treatment	0.65 ± 0.51	0.66 ± 0.33	.651
Change	29.6 ± 37.3	55.0 ± 52.7	.109
Tumor volume (mL)			
Before treatment	46.74 ± 45.82	36.44 ± 26.70	.706
After two cycles of treatment	31.05 ± 27.32	19.57 ± 15.12	.407
Change	62.2 ± 102.3	96.2 ± 115.9	.118
Peak enhancement ratio			
Before treatment	0.29 ± 0.13	0.32 ± 0.11	.522
After two cycles of treatment	0.17 ± 0.08	0.17 ± 0.09	.940
Change	75.5 ± 36.2	103.2 ± 45.1	.080
Mean patient age (y)	46.9 ± 8.7	44.2 ± 8.2	.450
Pretreatment tumor grade*	II (11), III (5)	II (7), III (9)	.167

Note.—Except where indicated, data are given as means $\pm$ standard deviations. Data were obtained in only 32 patients. Change was calculated as average [(value before treatment – value after treatment)/value after treatment] $\times$ 100%.

* Numbers in parentheses are numbers of patients.

33 patients with breast cancer before and after treatment confirm that the T1-FCM method is capable of assessing the response to NAC in a typical clinical setting and can also be used for retrospective pharmacokinetic modeling of previously acquired clinical data. This finding suggests that changes in K^{trans} and/or pretreatment K^{trans} should be used to assess treatment response to NAC in patients with breast cancer. Although the peak enhancement ratio did not show a significant difference between patients with a major histologic response and those with a nonmajor histologic response, it was second to K^{trans} in the assessment of treatment response. This finding supports the common consensus that quantitative kinetic parameters are the most useful endpoints for dynamic contrast-enhanced MR imaging (3,11) as far as accurate results can be obtained, although semiquantitative approaches to kinetic analysis with dynamic contrast-enhanced MR imaging have been used. To our knowledge, this is the first study in which a fixed-T1-based method was

used to quantitatively assess treatment response to NAC in patients with breast cancer.

The improved accuracy and sensitivity with the T1-FCM method stem from several factors. The measurement of three-dimensional T1 mapping in the breast is prone to errors due to inconsistency in flip angles and lipid suppression as well as motion during data acquisition. Moreover, errors associated with the estimation of T1 can be considerably large, even if the measurements themselves are free of errors. We found that the conventional dual-flip-angle method is sensitive to both noise and true tissue T1(0), which is likely because of the trade-off between the distance between two given points in the regression line and the signal-to-noise ratio with each pair of flip angles (ie, a long T1 has a small Ernst angle) (21). A broad distribution of estimated T1(0) values for a long true T1(0) (ie, ~ 1000 msec) could explain our results: Even the original fixed-T1 method can offer better results than the original

RR method in terms of accuracy, precision, and nonphysical values if the preselected T1(0) is not too different from the true value (ie, within 15%). Unfortunately, the T1 of breast tumors is typically longer than that of healthy fibrous tissues (approximately 1000 vs 500 msec, respectively) (18,27,28).

Use of the fixed-T1 method eliminates the need to measure T1(0) with its attendant errors. However, the accuracy of K^{trans} and v_e as estimated with the original fixed-T1 method is heavily dependent on correct T1(0) selection. To overcome this problem, we suggest replacing the original RR model with the modified fixed-T1 method. The modified fixed-T1 method appears to work well, most likely because of three interrelated factors: the reconstructed baseline signal intensity, the relationship between the T1 in the tumor and RR, and the linear relationship between contrast material concentration and the longitudinal relaxation rate.

The T1-FCM method combines the modified fixed-T1 method with the FCM technique to use the inherent characteristics of FCM to reduce noise-related effects. Our results clearly show that the modified fixed-T1 method with FCM was better than that without FCM. FCM improved precision but not accuracy, consistent with the knowledge that non-systematic random noise will impair precision but have a smaller influence on accuracy. It is worth noting that, in the absence of noise, the conventional RR method gave the best estimate among the four methods. Its effectiveness stems from (a) automatically differentiating tumors from nontumor tissues on the basis of kinetic curve patterns and (b) automatically grouping concentration-time curves with a similar pattern into a single cluster. However, we should note that the T1-FCM method increases precision due to the “clustering” effect, which could decrease if the number of pixels for the tumor is too small (eg, <4 mm in diameter).

Our study had several limitations. Systematic error will occur if the two-compartment model is not an appropriate pharmacokinetic model with which to accurately assess treatment response to NAC. When adopting an RR model,

we assume that the arterial input function of the tumor and the RR is the same. This assumption can be incorrect, particularly if the RR is located far from the tumor. In generating contrast material uptake curves, we assumed that the T1 of muscle was 869 msec for all patients; this does not take into consideration individual diversity. Another limitation is the small number of patients in this study. In addition, the sensitivity and specificity we obtained were based on thresholds produced by our own population and, thus, may overrepresent the values that could be obtained in a different sample. More patient studies with rigorous design are needed to validate the prognostic value and reproducibility of the T1-FCM method before embarking on routine clinical applications (27), including the determination of the cutoff values for predicting treatment outcome while blinded to the treatment result.

In conclusion, a quantitative dynamic contrast-enhanced MR imaging method has been developed to assess treatment response to NAC in patients with breast cancer by using standard clinical dynamic contrast-enhanced MR imaging data without measuring either the arterial input function or the T1(0). This method is relatively insensitive to the effects of noise and incorrect T1(0) selection and should prove useful for evaluating treatment response to NAC in patients with breast cancer.

References

- Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998;16(8):2672-2685.
- Machiavelli MR, Romero AO, Pérez JE, et al. Prognostic significance of pathological response of primary tumor and metastatic axillary lymph nodes after neoadjuvant chemotherapy for locally advanced breast carcinoma. *Cancer J Sci Am* 1998;4(2):125-131.
- Padhani AR. Dynamic contrast-enhanced MRI in clinical oncology: current status and future directions. *J Magn Reson Imaging* 2002;16(4):407-422.
- Padhani AR, Hayes C, Assersohn L, et al. Prediction of clinicopathologic response of breast cancer to primary chemotherapy at contrast-enhanced MR imaging: initial clinical results. *Radiology* 2006;239(2):361-374.
- Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T1-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999;10(3):223-232.
- Yankeelov TE, Gore JC. Dynamic contrast enhanced magnetic resonance imaging in oncology: theory, data acquisition, analysis, and examples. *Curr Med Imaging Rev* 2009;3(2):91-107.
- Yankeelov TE, Luci JJ, Lepage M, et al. Quantitative pharmacokinetic analysis of DCE-MRI data without an arterial input function: a reference region model. *Magn Reson Imaging* 2005;23(4):519-529.
- Kovar DA, Lewis M, Karczmar GS. A new method for imaging perfusion and contrast extraction fraction: input functions derived from reference tissues. *J Magn Reson Imaging* 1998;8(5):1126-1134.
- Yang C, Karczmar GS, Medved M, Stadler WM. Estimating the arterial input function using two reference tissues in dynamic contrast-enhanced MRI studies: fundamental concepts and simulations. *Magn Reson Med* 2004;52(5):1110-1117.
- Walker-Samuel S, Leach MO, Collins DJ. Reference tissue quantification of DCE-MRI data without a contrast agent calibration. *Phys Med Biol* 2007;52(3):589-601.
- Yang C, Karczmar GS, Medved M, Stadler WM. Multiple reference tissue method for contrast agent arterial input function estimation. *Magn Reson Med* 2007;58(6):1266-1275.
- Haacke EM, Filletti CL, Gattu R, et al. New algorithm for quantifying vascular changes in dynamic contrast-enhanced MRI independent of absolute T1 values. *Magn Reson Med* 2007;58(3):463-472.
- Guo JY, Reddick WE, Rosen MA, Song HK. Dynamic contrast-enhanced magnetic resonance imaging parameters independent of baseline T10 values. *Magn Reson Imaging* 2009;27(9):1208-1215.
- Huang W, Wang Y, Panicek DM, Schwartz LH, Koutcher JA. Feasibility of using limited-population-based average R10 for pharmacokinetic modeling of osteosarcoma dynamic contrast-enhanced magnetic resonance imaging data. *Magn Reson Imaging* 2009;27(6):852-858.
- Chen WJ, Giger ML, Bick U, Newstead GM. Automatic identification and classification of characteristic kinetic curves of breast lesions on DCE-MRI. *Med Phys* 2006;33(8):2878-2887.
- Chen WJ, Giger ML, Bick U. A fuzzy c-means (FCM)-based approach for computerized segmentation of breast lesions in dynamic contrast-enhanced MR images. *Acad Radiol* 2006;13(1):63-72.
- Haase A. Snapshot FLASH MRI: applications to T1, T2, and chemical-shift imaging. *Magn Reson Med* 1990;13(1):77-89.
- Bottomley PA, Hardy CJ, Argersinger RE, Allen-Moore G. A review of 1H nuclear magnetic resonance relaxation in pathology: are T1 and T2 diagnostic? *Med Phys* 1987;14(1):1-37.
- Benjaminsen IC, Graff BA, Brurberg KG, Rofstad EK. Assessment of tumor blood perfusion by high-resolution dynamic contrast-enhanced MRI: a preclinical study of human melanoma xenografts. *Magn Reson Med* 2004;52(2):269-276.
- Walker-Samuel S, Parker CC, Leach MO, Collins DJ. Reproducibility of reference tissue quantification of dynamic contrast-enhanced data: comparison with a fixed vascular input function. *Phys Med Biol* 2007;52(1):75-89.
- Deoni SCL, Rutt BK, Peters TM. Rapid combined T1 and T2 mapping using gradient recalled acquisition in the steady state. *Magn Reson Med* 2003;49(3):515-526.
- Schabel MC, Morrell GR. Uncertainty in T(1) mapping using the variable flip angle method with two flip angles. *Phys Med Biol* 2009;54(1):N1-N8.
- Ogston KN, Miller ID, Payne S, et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. *Breast* 2003;12(5):320-327.
- van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer Trial 10902. *J Clin Oncol* 2001;19(22):4224-4237.
- Martincich L, Montemurro F, De Rosa G, et al. Monitoring response to primary chemotherapy in breast cancer using dynamic contrast-enhanced magnetic resonance imaging. *Breast Cancer Res Treat* 2004;83(1):67-76.
- Roberts C, Issa B, Stone A, Jackson A, Waterton JC, Parker GJ. Comparative study into the robustness of compartmental modeling and model-free analysis in DCE-MRI studies. *J Magn Reson Imaging* 2006;23(4):554-563.
- Rakow-Penner R, Daniel B, Yu H, Sawyer-Glover A, Glover GH. Relaxation times of breast tissue at 1.5T and 3T measured using IDEAL. *J Magn Reson Imaging* 2006;23(1):87-91.
- Merchant TE, Obertop H, de Graaf PW. Advantages of magnetic resonance imaging in breast surgery treatment planning. *Breast Cancer Res Treat* 1993;25(3):257-264.