A clinically feasible method to estimate pharmacokinetic parameters in breast cancer

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(Received 2 June 2008; revised 17 May 2009; accepted for publication 18 May 2009; published 20 July 2009)

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is the MRI technique of choice for detecting breast cancer, which can be roughly classified as either quantitative or semi-quantitative. The major advantage of quantitative DCE-MRI is its ability to provide pharmacokinetic parameters such as volume transfer constant (K^{trans}) and extravascular extracellular volume fraction (v_e). However, semiquantitative DCE-MRI is still the clinical MRI technique of choice for breast cancer diagnosis due to several major practical difficulties in the implementation of quantitative DCE-MRI in a clinical setting, including (1) long acquisition necessary to acquire 3D $T_1(0)$ map, (2) challenges in obtaining accurate artery input function (AIF), (3) long computation time required by conventional nonlinear least square (NLS) fitting, and (4) many illogical values often generated by conventional NLS method. The authors developed a new analysis method to estimate pharmacokinetic parameters K^{trans} and v_e from clinical DCE-MRI data, including fixed $T_1(0)$ to eliminate the long acquisition for $T_1(0)$ map and “reference region” model to remove the requirement of measuring AIF. Other techniques used in our analysis method are (1) an improved formula to calculate contrast agent (CA) concentration based on signal intensity of SPGR data, (2) FCM clustering-based techniques for automatic segmentation and generation of a clustered concentration data set (3) an empirical formula for CA time course to fit the clustered data sets, and (4) linear regression for the estimation of pharmacokinetic parameters. Preliminary results from computer simulation and clinical study of 39 patients have demonstrated (1) the feasibility of their analysis method for estimating K^{trans} and v_e from clinical DCE-MRI data, (2) significantly less illogical values compared to NLS method (typically less than 1% versus more than 7%), (3) relative insensitivity to the noise in DCE-MRI data; (4) reduction in computation time by a factor of more than 30 times compared to NLS method on average, (5) high statistic correlation between the method used and NLS method (correlation coefficients: 0.941 for K^{trans} and 0.881 for v_e), and (6) the potential clinical usefulness of the new method. © 2009 American Association of Physicists in Medicine. [DOI: [10.1118/1.3152113](https://doi.org/10.1118/1.3152113)]

Key words: DCE-MRI, breast cancer, reference region model, fixed $T_1(0)$, fuzzy C-means cluster, pharmacokinetic parameters, K^{trans} and v_e

I. INTRODUCTION

Breast cancer is the second most common type of cancer after lung cancer¹ and the fifth most common cause of cancer death worldwide.² The diagnostic accuracy of breast cancer, however, is still not satisfactory in clinical practice. Mammography, the most commonly used breast imaging modality, for example, can miss up to 50% of cancers in women with dense breasts. Magnetic resonance imaging (MRI) has gained acceptance as an important adjunct breast imaging modality because of its high sensitivity in detecting breast cancer, superior to mammography, clinical examination, and ultrasonography.³ Dynamic contrast enhancement (DCE) is the MRI technique of choice for breast cancer imaging.

DCE-MRI can be classified as either semiquantitative or quantitative. While semiquantitative DCE-MRI only needs one measurement, dynamic data acquisition to characterize the kinetics of the contrast agent (CA) entry and exit into tissues, a quantitative DCE-MRI data acquisition typically requires two extra measurements: A T_1 map before contrast administration [$T_1(0)$] and the estimation of the time rate of change in the CA concentration in the blood plasma or arterial input function (AIF). The major advantage of the quantitative DCE-MRI is its ability to provide pharmacokinetic parameters such as volume transfer constant (K^{trans}) and extravascular extracellular volume fraction (v_e). It has been well documented that the information on K^{trans} and v_e can

improve diagnostic accuracy of tumors.⁴ However, semi-quantitative DCE-MRI is still the clinical MRI technique of choice for breast cancer diagnosis due to several major practical difficulties in the implementation of quantitative DCE-MRI in a clinical setting. It is impractical to obtain accurate 3D $T_1(0)$ map and AIF in a typical clinical setting; conventional nonlinear least square (NLS) fitting is time consuming and often generates many illogical values due to effects of noise.

Recently several milestones have been achieved in the area. It has been demonstrated by both simulation and *in vivo* human study that fixing $T_1(0)$ not only eliminates the need of absolute $T_1(0)$ map but also helps to achieve more consistent results because it eliminates most of effects associated with the noise from the calculation of the $T_1(0)$ map.⁵ It is a common understanding that most of the DCE errors are related to the noise in absolute $T_1(0)$ estimation.⁵

It is accepted that the most technically demanding portion of the data acquisition process in a conventional quantitative DCE-MRI is to acquire the AIF, particularly for the AIF near a suspected breast tumor. To date, three methods have been proposed for AIF measurement, each with its own advantages and disadvantages.⁶⁻⁸ In efforts to eliminate the AIF problem, Yankeelov *et al.* developed the reference region (RR) model⁶ that does not require any direct measurement of AIF. The RR model, based on the Kety equation⁹ derived from a two-compartment model, uses a well characterized tissue (e.g., muscle) as the reference tissue to estimate pharmacokinetic parameters in a tissue of interest (TOI) (e.g., tumor) and has demonstrated its value as an alternative approach to solve the AIF problem.⁶

There are, however, a few problems with the RR model that prevents its routine application. To obtain accurate pharmacokinetic parameter values, the RR model typically adopts NLS to fit DCE-MRI data. But because of the convergence issues and consistency problems associated with the need to specify starting values, it is inefficient in terms of computation time,^{10,11} particularly for estimating pharmacokinetic parameters at a pixel-by-pixel level. Moreover, the NLS method typically needs more time points than the typical clinical DCE-MRI dataset in order to obtain an acceptable fitting result. Because there is a trade-off between temporal resolution, spatial resolution, and signal-to-noise ratio (SNR) in MRI pulse sequence design, high temporal resolution generally means poor spatial resolution or low SNR, which, in turn, can result in more illogical values for pharmacokinetic parameters. Fuzzy C-means (FCM) clustering-based techniques can circumvent these problems. FCM clustering, as an unsupervised learning technique in pattern recognition field,¹² has proven its usefulness in MR image segmentation,^{13,14} analysis of functional MRI of human brain,^{15,16} and analysis of uptake curves in DCE-MRI.¹⁷

In this work, we reported our preliminary results on a new analysis method that combines several recently developed techniques, including fixed $T_1(0)$, RR model, and FCM clustering, to accurately and speedily estimate K^{trans} and v_e . The method calculates K^{trans} and v_e values directly from clinical

DCE-MRI data pixel by pixel in 3D space while still preserves the clinical morphologic and uptake kinetic information. To improve the accuracy of results, we derived an analytical formula to transform signal intensity (SI) change to CA concentration change using fixed $T_1(0)$ and the linear relationship between R_1 ($1/T_1$) and CA concentration. In addition, we used FCM clustering to classify concentration curves into a few clusters automatically, so that both the noise level and computation time could be reduced significantly. Then we fitted the clustered data to an empirical formula to overcome the often insufficient temporal resolution in clinical DCE-MRI data. Finally, by applying these data sets to the RR model and linear regression algorithm, the 3D map of the relative values for K^{trans} and v_e were generated. We tested our method through computer simulation and 39 clinical breast cancer cases.

II. THEORY

II.A. Calculations of CA concentration

Spoiled gradient (SPGR) pulse sequence is often adopted in clinical DCE-MRI acquisition protocols, especially for breast MRI. According to the linear relationship between the tissue longitudinal relaxation time T_1 and CA concentration in a homogeneous tissue with fast water exchange, we can derive the CA concentration as follows (see the Appendix):

$$C(t) = \frac{1}{r_1} \cdot \frac{\Delta S(t) \cdot R_1(0) \cdot (1 - \cos \theta + R_1(0) \cdot \cos \theta \cdot TR)}{1 - \cos \theta - \Delta S(t) \cdot R_1(0) \cdot \cos \theta \cdot TR}, \quad (1)$$

where r_1 is the specific relaxivity of CA, $\Delta S(t)$ is the relative enhancement of SI at time t , $R_1(0)$ is the precontrast relaxation rate [$R_1(0) = 1/T_1(0)$], and TR and θ are repetition time (RT) and flip angle of the pulse sequence, respectively.

To obtain the CA concentration time course, the precontrast relaxation rate $R_1(0)$ [or $T_1(0)$] must be known first. Here we use a fixed baseline $T_1(0)$ value for muscle and tumor to avoid extending the clinical acquisition protocol and to remove the noise in estimating $T_1(0)$, and the detailed derivations are given in the Appendix.

II.B. Parameter estimation

In this study, we adopted the commonly used two-compartment RR model proposed by Yankeelov *et al.* for DCE-MRI data analysis, as shown in Fig. 1. Tumor and muscle are chosen as TOI and RR, respectively. Differential equations that describe the kinetic behavior of CA in the two tissues are given by

$$\frac{d}{dt} C_m(t) = K_m^{trans} \cdot C_p(t) - \frac{K_m^{trans}}{v_{e,m}} \cdot C_m(t), \quad (2)$$

$$\frac{d}{dt} C_t(t) = K_t^{trans} \cdot C_p(t) - \frac{K_t^{trans}}{v_{e,t}} \cdot C_t(t), \quad (3)$$

where C_m and C_t are CA concentrations (expressed in millimolar) in the muscle and the tumor, respectively; K_m^{trans} and

FIG. 1. The sketch of RR model. Contrast agent from the capillary diffuses bidirectionally from the intravascular space to the extravascular extracellular space (EES) of the reference tissue and to the EES of the tissue of interest.

K_t^{trans} are CA extravasation rate constants for the two tissues, respectively; and $v_{e,m}$ and $v_{e,t}$ are extravascular-extracellular volume fractions for RR and TOI, respectively.

Defining K_R^{trans} as the denotation of the ratio of K^{trans} values between TOI and RR (i.e., K_t^{trans}/K_m^{trans}), and then combining Eqs. (2) and (3), we can eliminate all C_p terms and derive

$$C_t(t) = K_R^{trans} \cdot C_m(t) + \frac{K_t^{trans}}{v_{e,m}} \cdot \int_0^t C_m(u) du - \frac{K_t^{trans}}{v_{e,t}} \cdot \int_0^t C_t(u) du. \quad (4)$$

Similarly, by replacing $v_{e,t}/v_{e,m}$ with $v_{e,R}$, we can easily get

$$\int_0^t C_t(u) du = v_{e,R} \cdot \int_0^t C_m(u) du + \frac{v_{e,t}}{K_m^{trans}} \cdot C_m(t) - \frac{v_{e,t}}{K_t^{trans}} \cdot C_t(t). \quad (5)$$

By applying Murase's linearization process,¹¹ we can estimate the relative values of K^{trans} and v_e from Eqs. (4) and (5) without knowing the AIF.

K_R^{trans} and $v_{e,R}$ are relative values, which have a close tie to the reference region we chose. This makes it impossible for an absolute comparison between patients. To overcome this issue, we chose a fixed muscle value reported by Walker-Samuel *et al.*¹⁸ to standardize the results. The muscle tissue is assumed to have $K_m^{trans} = 0.07 \text{ min}^{-1}$ and $v_{e,m} = 0.14$, respectively. Accordingly, the results can be standardized as follows: $K^{trans} = 0.07 * K_R^{trans}$ and $v_e = 0.14 * v_{e,R}$.

II.C. Data preprocessing

At present, most clinical breast DCE-MRI protocols acquire only 7–10 time frames after administration of CA, making it challenging to accurately estimate physiological parameters through NLS methods. Furthermore, image noise is usually at a high level, which makes it more difficult to estimate physiological parameters. FCM clustering can be applied to overcome the difficulties. Depending on the profile of the CA concentration time course, this 3D autoclustering processing can classify the concentration data into a few clusters. That is, FCM can automatically assemble pixels with proximate physiological function into one cluster and

then produce an average curve to represent all pixels in the same cluster, thus significantly reducing effects of noise in the data and computation time. The number of clusters (N_c) is determined empirically from the number of voxels in a lesion (N) as follows:¹⁷

$$N_c = \begin{cases} 2 & \text{if } N \leq 160 \\ \lceil N/80 \rceil & \text{if } N > 160 \end{cases}, \quad (6)$$

where $\lceil \cdot \rceil$ takes the nearest integer.

After replacing $C_t(t)$ in Eqs. (4) and (5) with the corresponding clustered data, $C_{t_cluster}(t)$, we get the following formulas to estimate the pharmacokinetic parameters:

$$C_t(t) = K_R^{trans} \cdot C_m(t) + \frac{K_t^{trans}}{v_{e,m}} \cdot \int_0^t C_m(u) du - \frac{K_t^{trans}}{v_{e,t}} \cdot \int_0^t C_{t_cluster}(u) du, \\ \int_0^t C_{t_cluster}(u) du = v_{e,R} \cdot \int_0^t C_m(u) du + \frac{v_{e,t}}{K_m^{trans}} \cdot C_m(t) - \frac{v_{e,t}}{K_t^{trans}} \cdot C_t(t). \quad (7)$$

To avoid the degradation of precision arising from the numerical integral with insufficient data points in Eq. (7), we fit the RR time course and clustered data to an empirical analytic formula,¹⁸ which has a simple triexponential form as follows:

$$C(t) = -(B_1 + B_2) \cdot e^{-k \cdot t} + B_1 \cdot e^{-m_1 \cdot t} + B_2 \cdot e^{-m_2 \cdot t}, \quad (8)$$

where B_1 , B_2 , k , m_1 , and m_2 are the five parameters to be fitted through Levenberg–Marquardt NLS curve fitting algorithm. The fitting process is to find a group of parameters to minimize the objective function: $F = \sum (C(t)_{\text{fit}} - C(t))^2$ through iterations. Convergence criterion is $|F_{\text{new}} - F_{\text{old}}| < 10^{-5}$. This way, the integral is analytic, thus offering a relatively high precision. In Eq. (7), we just need to calculate the integral terms of $C_t(t)$ and perform the NLS fitting process $N_c + 1$ times. Without these preprocessing steps, we would need to calculate the integral terms and perform the NLS fitting for each pixel. This is the reason why our method can dramatically reduce the computation time.

III. METHODS

III.A. Computer simulation

We directly simulated the AIF, RR, and TOI time courses using the following equation to generate the C_p time course (i.e., AIF):

$$C_p(t) = A \cdot e^{-t \cdot B} + C \cdot e^{-t \cdot D}. \quad (9)$$

The $C_p(t)$ adopted here uses the following typical values:¹⁹ $A = 2.55 \text{ mM}$, $B = 0.08 \text{ s}^{-1}$, $C = 1.2 \text{ mM}$, $D = 0.001 \text{ s}^{-1}$. Then, we converted $C_p(t)$ to the CA concentration curves of RR and TOI via the integral form of the Kety–Schmidt equation,

FIG. 2. Results of preprocessing steps for simulated data at different noise levels. The dashed line denote the simulated contrast agent curve in reference region; the crosses denote the simulated noisy data (we randomly picked one pixel for each group with different parameters); the stars denote the clustered data; and the solid curves are fitted from clustered data via Eq. (7). All the noisy data can be correctly classified into four clusters consistent with the assigned four groups. And all the fitted curves at all noise levels are consistent with that from noise free data in panel (a). The results illustrate that FCM and fitting to Eq. (7) reduce the effects of the noise.

$$C_i(t) = K^{\text{trans}} \int_0^t C_p(u) \cdot \exp(-(K^{\text{trans}}/v_e) \cdot (t-u)) du, \quad (10)$$

which can be easily derived from Eq. (2) or Eq. (3). To best simulate the clinical situation, the generated data from Eq. (10) had only eight time frames, with a temporal resolution of 88 s. In Eq. (10), we assigned $K^{\text{trans}}=0.07 \text{ min}^{-1}$ and $v_e=0.14$ for the CA concentration curve of muscle, and four groups of different values for CA concentration curves in TOI, which represented the heterogeneity in tumor, as shown in Fig. 2(a).

To test the precision of this method on the effects of noise, pseudorandom Gaussian noise was added to the CA

curves of TOI. The standard deviation of the noise is proportional to the maximum CA concentration according to the noise standard deviation formula,

$$\sigma = \alpha \max\{C_i(t)\}, \quad (11)$$

where σ is the standard deviation of one CA time course and α is the proportionality constant that determines the overall noise level in a CA concentration curve.

In this simulation study, α was set to 2%, 5%, and 10% to yield noisy CA concentration curves at various noise levels. We simulated 500 pixels for each of the four groups in Fig. 2(a) and repeated the process three times at each level of α . 2000 generated noisy CA concentration curves were classi-

FIG. 3. The flow chart of clinical data processing. It illustrates step by step how to process clinical DCE-MRI data through our method.

fied into four clusters via FCM clustering method. The clustered data were then fitted to Eq. (8), and the linear regression algorithm¹¹ was applied to calculate the parameters of each simulated pixel. The mean and relative standard deviation (RSD) of the estimated parameter values for each group were calculated and used as an index to evaluate the reliability and robustness of our method.

III.B. Clinical validation

To test the clinical feasibility, we applied our method to 39 routinely acquired clinical DCE-MRI data sets. All the 39 patients were confirmed by pathological results, including 4 benign fibroadenomas, 3 mammary hyperplasia, 24 invasive ductal carcinomas, 4 invasive lobular carcinomas, and 4 ductal carcinomas *in situ*. DCE-MRI were obtained by a T_1 -weighted fast 3D SPGR sequence with fat suppressed (repetition time=5.32 m, echo time (ET)=2.57 m, and flip angle=12°). Patients were scanned at prone position using a standard double-breast coil on a 1.5 T whole-body MRI system (Signa Excite; GE Medical Systems, USA). After the acquisition of precontrast series, Gd-DTPA contrast agent

was injected into the antecubital vein with a dose of 0.2 mmol/kg and flow rate of 2 ml/s. Administration of contrast agent was followed by a 20 ml saline flush with the same flow rate. Seven postcontrast time points were obtained with an interval of 88 s. Each time point contained 32 traverse slices with a matrix of 512×512 pixels, an in-plane resolution of 0.625×0.625 mm, and a slice thickness of 2.6 mm.

Guided by an experienced radiologist, we picked out all slices containing the lesion of interest in each patient. These image data were processed with the procedure shown in Fig. 3 to generate a pharmacokinetic parameter map at a pixel-by-pixel level. After obtaining the parametric maps, the areas with high K^{trans} values were chosen as ROIs for analysis, and the mean value of each ROI was considered as the patient's characteristic parameter for quantitative intercomparison. Among the 39 patients, 7 of them were benign lesions, 4 were grade I tumors, 18 were grade II tumors, and 10 were grade III tumors. Considering the limited samples for each group, we chose Kruskal–Wallis nonparametric test to check the statistical difference of parameters among groups via SPSS software. Also, to test the correctness of our method, we performed correlation comparison and Bland–Altman analysis between the results from our method and conventional NLS method.

IV. RESULTS

IV.A. Computer simulation

We first tested the accuracy of our method in a noise-free simulation and then added noise to simulated data to test the precision of the method on low, middle, and high noise levels. In all the simulations, we assumed an ideal condition as the one that the CA concentration curves of RR were noise-free, that is, all data of muscle tissue were uniquely generated from Eqs. (9) and (10) without any noise. Figure 2 shows the results of fitting the clusters to Eq.(8) for simulated data. We also performed the simulation with conven-

TABLE I. Summarized results of computer simulation at different noise levels. (N denotes that the returned result is illogical, and RSD denotes the relative standard deviation.)

Parameter	Actual	Estimated (mean $\pm$ RSD)							
		0% noise		2% noise		5% noise		10% noise	
		FCM+fitting	NLS	FCM+fitting	NLS	FCM+fitting	NLS	FCM+fitting	NLS
K_R^{trans}	1.286	1.286	1.280	$1.286 \pm 2.00\%$	$1.278 \pm 3.10\%$	$1.287 \pm 4.88\%$	$1.156 \pm 94.7\%$	$1.284 \pm 9.58\%$	N
	7.000	7.000	8.910	$7.002 \pm 1.40\%$	$8.807 \pm 20.1\%$	$7.006 \pm 3.12\%$	$9.511 \pm 40.4\%$	$6.976 \pm 6.57\%$	N
	1.429	1.429	1.440	$1.426 \pm 2.80\%$	$1.436 \pm 3.34\%$	$1.427 \pm 7.26\%$	$1.432 \pm 8.81\%$	$1.430 \pm 13.2\%$	$1.41 \pm 17.7\%$
	11.143	11.143	N	$11.148 \pm 1.4\%$	N	$11.123 \pm 3.44\%$	N	$11.201 \pm 6.8\%$	N
$v_{e,R}$	1.786	1.786	1.7761	$1.779 \pm 0.71\%$	$1.777 \pm 1.17\%$	$1.751 \pm 1.14\%$	$1.692 \pm 60.0\%$	$1.713 \pm 1.33\%$	N
	2.857	2.857	4.085	$2.857 \pm 0.14\%$	$4.010 \pm 30.4\%$	$2.858 \pm 0.32\%$	$4.481 \pm 52.1\%$	$2.866 \pm 0.63\%$	N
	3.571	3.571	3.564	$3.541 \pm 2\%$	$3.566 \pm 2.36\%$	$3.415 \pm 4.10\%$	$3.605 \pm 6.84\%$	$3.138 \pm 4.95\%$	$4.021 \pm 128\%$
	2.143	2.143	N	$2.143 \pm 0.06\%$	N	$2.144 \pm 0.15\%$	N	$2.146 \pm 0.28\%$	N

FIG. 4. (a) One slice of the used clinical images. The lesion is in the rectangle at the lower-left corner of panel A, and the area in the ellipse near the lesion is the reference region. (b) The segmented lesion in 3D space. All the lesion pixels will be analyzed to generate the parametric map. (c) The contrast agent concentration of RR and the lesion pixels after being clustered. The solid curves are fitted from clustered data via Eq. (7).

tional NLS method for comparison. The returned parameters from the simulated data at different noise levels of both methods are comparatively listed in Table I.

Figure 2(a) shows that all 2000 simulated pixels can be exactly classified into four clusters corresponding to the four groups of parameters that we had assigned before, and the data fitted from Eq. (7) are in a good agreement with the generated simulation data. At all tested noise levels, noise effects were significantly decreased through FCM clustering method, as shown in Fig. 2. Thus, the actual pharmacokinetic parameters could be recovered in the presence of all tested noise levels [panel (a)]. More importantly, the results also demonstrated that the four groups in the simulated data can be clustered correctly at all three tested levels of noise corruption.

Table I illustrates the results of the simulation study. The returned parameters from our method are identical to the values used to construct the simulation curves with no noise, which verifies the accuracy of our method. In contrast, results from NLS method have an obvious deviation due to the insufficiency of data points, as expected. At all three simulated noise levels, the returned values are consistent with the actual ones within a reasonable error range. Note that for both methods, the higher the noise level, the poorer the mean value, and the larger the RSD. In brief, our method offers more accurate and reliable results than NLS method does at

all noise levels. Moreover, the number of illogical values (negative or too large) generated by NLS method is dramatically reduced by our method (see Table I).

IV.B. Clinical validation

Figure 4(a) is one slice of DCE-MRI from a patient with invasive ductal carcinoma. The area in the rectangle is the TOI covering the lesion of interest, and the area in the ellipse is the thorax muscle chosen as the RR. The result of lesion segmentation and data preprocessing are displayed in Figs. 4(b) and 4(c). Figure 5 shows the distributions of K^{trans} and v_e in 3D space. The heterogeneity of the tumor can be easily observed from the distribution of both parameters. Both Figs. 5(a) and 5(b) have low parameter values in the tumor center, suggesting a necrotic core, while high parameter values in the rim suggest an active tumor. The results were consistent with biopsy findings: The existence of necrotic core and malignant rim for the lesion.

Figure 6 shows the relationship between pharmacokinetic parameters and clinical tumor grading for all the 39 patients. It illustrates distinctive K^{trans} values between benign and malignant tumors. Moreover, higher tumor grades tend to have higher K^{trans} , suggesting the potential of K^{trans} for tumor diagnosis and grading. But there is no such a trend for v_e . The result of independent sample nonparametric test for K^{trans} of different tumor groups is statistically significant ($\chi^2=27.636$, $P=0.000$). However, there is no obvious statistical significant difference for v_e ($\chi^2=4.770$, $P=0.092$).

To test our method in clinical application, we compared our results to those from the routine NLS method, the most commonly used method in pharmacokinetic parameter estimation. For quantitative comparison, we obtained the parametric maps using both the conventional NLS method and our method and then studied the correlation comparison of each method. The pharmacokinetic parameter K^{trans} and v_e generated from our method correlates well with that from the NLS method after eliminating pixels with obvious illogical values from the NLS method, as demonstrated in Fig. 7. Squared correlation coefficients (R^2) between parameters estimated by our method and routine NLS method are 0.941 for K^{trans} and 0.881 for v_e . By Bland–Altman analysis, the limits of agreement between the two methods are $0.005\,82 \pm 0.032\,57$ for K^{trans} and $0.000\,38 \pm 0.047\,76$ for v_e .

FIG. 5. An example of clinical results. (a) The 3D distribution map of K^{trans} . (b) The 3D distribution map of v_e .

FIG. 6. The summary of K^{trans} , v_e , and clinical breast tumor grading for all 39 patients.

Both verified the utility of our method in clinical data application. The computation time, however, is dramatically shortened by our method compared to NLS method. There is a linear relationship between computation time and voxel numbers for our method, but an exponential relationship for NLS method and our method can reduce the computation time by a factor of more than 30 times on average (Fig. 8).

V. DISCUSSION AND CONCLUSION

We presented a new method to obtain K^{trans} and v_e using routinely acquired clinical breast DCE-MRI data and is independent of obtaining AIF and $T_1(0)$ measurement. In this method, a more rigorous formula than that presented in Ref. 6 has been introduced to transform the signal intensity of SPGR data to CA concentration. Through fixed $T_1(0)$ and FCM clustering, effects of the noise in data sets are significantly reduced. By fitting the clustered data sets to an empirical expression of CA concentration, the error arising from inadequate data points is significantly decreased. Moreover,

this technique combined with linear regression for the estimation of pharmacokinetic parameters dramatically reduces the number of illogical values and the computation time compared to the NLS method. On average, illogical values were reduced from about 7% for K^{trans} and 10% for v_e by NLS method to only a few pixels by our method, and the computation time was reduced by more than a factor of 30. Preliminary results of both computer simulation and clinical study support the clinical utility of this improved method. It is worth noting that our method can be easily implemented for other human cancers. Several caveats should be recognized before routine implementation of this new method. When adopting the linear relationship between T_1 and CA concentration, we neglect water exchange effects (which can occur frequently) between separate compartments, and this can lead to errors in the analysis of dynamic MR data.⁶ In the CA concentration calculation, we assigned the T_1 of muscle to be 869 ms for all subjects. This does not consider the possible individual diversity among patients, which may introduce inaccuracy in the CA concentration. Furthermore, to obtain the proton density ratio between muscle and tumor, we assign tumor T_1 according to the value in literature,²⁰ which can affect the accuracy of parameter estimation. Although a fixed $T_1(0)$ can offer much more consistent results than absolute $T_1(0)$ due to errors associated with $T_1(0)$ estimation as demonstrated in literature,⁵ the situation could change in the future with the introduction of more powerful multichannel breast coils and the development of new MRI pulse sequences for accurate and fast 3D T_1 mapping. There are also some shortcomings in the RR model itself that can impact the results, such as the selection of reference region. As illustrated in Fig. 4, the muscle chosen as the RR is tens of millimeters away from the tumor. Thus, the heterogeneity of the magnetic field, including B_0 and RF field, could have a noticeable impact on the signal intensity and lead to errors in the CA concentration calculation. In the RR model, AIF of muscle and tumor are assumed the same. This assumption can be incorrect, particularly if the muscle is far from the tumor. In general, muscle close to the tumor with similar

FIG. 7. The correlation analysis of parameters estimated from our method and that from routine NLS method.

FIG. 8. Computation time with different tumor voxel numbers for our method and conventional NLS method.

surrounding tissue should be chosen as the reference region. Finally, all patients participating in this study were selected because they had a biopsy. We selected patients in this way because we use biopsy findings as our standard to help standardize the results from our methods.

In conclusion, we presented a new analytic method that combines several recent achievements in the area to improve speed and accuracy in estimating pharmacokinetic parameters K^{trans} and v_e from clinical DCE-MRI data. New adaptations include fixed $T_1(0)$, RR model, FCM clustering-based techniques, an improved formula to calculate CA concentration, an empirical formula of CA time course to fit the clustered data sets, and linear regression for the estimation of pharmacokinetic parameters. Computer simulation and clinical study of 39 patients have supported the accuracy, precision, robustness, and potential clinical usefulness of this new method.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Stuart Smith for his comments and proofread of the paper, the Department of Radiology, Beijing Cancer Hospital, and Peking University First Hospital for providing DCE-MRI images and related clinical data. This work was supported by the National Basic Research Program (973 Program, Grant No. 2006CB705705) from the Ministry of Science and Technology of China, National Natural Science Foundation of China (Grant Nos. 10527003; and 60672104), the Susan G. Komen Breast Cancer Foundation (Grant No. IMG0402881), and NIH (Grant No. R21 CA118569-01A1).

APPENDIX: CALCULATION OF $C(t)$

In a homogeneous tissue with fast water exchange, the CA concentration $[C(t)]$ can be derived as Eq. (A1) from the linear relationship between the tissue longitudinal relaxation time T_1 and $C(t)$,²¹

$$C(t) = \frac{1}{r_1} \left(\frac{1}{T_1(t)} - \frac{1}{T_1(0)} \right) = \frac{1}{r_1} (R_1(t) - R_1(0)), \quad (\text{A1})$$

where $T_1(0)$ and $T_1(t)$ denote the precontrast relaxation time and postcontrast longitudinal relaxation time at t seconds after the CA injection, respectively, and r_1 is the specific relaxivity of CA (typically $4.5 \text{ mM}^{-1} \text{ s}^{-1}$ at a magnetic field of 1.5 T).

The SI of SPGR (Ref. 22) can be simplified as follows:

$$S = G \cdot N(H) \cdot \frac{\text{TR} \cdot R_1 \sin \theta}{1 - (1 - \text{TR} \cdot R_1) \cdot \cos \theta}, \quad (\text{A2})$$

where $N(H)$ is the proton density, and G is the imager gain factor depending on the sequence parameters, TE, TR, and flip angle (θ).

To transform signal intensity to CA concentration, we construct a variable $\Delta S(t)$, which denotes the relative enhancement of SI at time t . That is,

$$\Delta S(t) = \frac{S(t) - S(0)}{S(0)}. \quad (\text{A3})$$

Substituting Eqs. (A1) and (A2) into Eq. (A3), we can derive the CA concentration as Eq. (1).

In Eq. (1), to obtain the CA concentration time course, we should first know the precontrast relaxation rate $R_1(0)$ [or $T_1(0)$]. Here we choose muscle as a reference tissue, with known T_1 value (869 ms) and compare the SI before contrast injection between TOI and muscle. Then we obtain

$$\frac{S(0)}{S_{\text{muscle}}} = \frac{N_{\text{tumor}}}{N_{\text{muscle}}} \cdot \frac{1 - \cos \theta + \text{TR} \cdot R_{1\text{muscle}} \cos \theta}{1 - \cos \theta + \text{TR} \cdot R_{1\text{tumor}} \cos \theta} \cdot \frac{R_{1\text{tumor}}}{R_{1\text{muscle}}}. \quad (\text{A4})$$

From Eq. (A4), we can derive the $R_1(0)$ of tumor in terms of the known $R_1(0)$ of muscle,

$$R_1(0) = \frac{R_{\text{pd}} \cdot \frac{S(0)}{S_{\text{muscle}}} \cdot R_{1\text{muscle}} \cdot (1 - \cos \theta)}{1 - \cos \theta + \text{TR} \cdot R_{1\text{muscle}} \cos \theta \cdot \left(1 - R_{\text{pd}} \cdot \frac{S(0)}{S_{\text{muscle}}} \right)}, \quad (\text{A5})$$

where R_{pd} is the proton density ratio between muscle and tumor ($R_{\text{pd}} = N_{\text{muscle}}/N_{\text{tumor}}$). In order to obtain the value of $R_1(0)$, we must know the value of R_{pd} . Here we used a fixed tumor $T_1(0)$ via Eq. (A4) to calculate an average R_{pd} . From Eq. (A4), we can get the values of $S(0)$ and S_{muscle} by averaging the SI from images, and T_1 of muscle is 869 ms. According to Bottomley,²⁰ the fixed tumor $T_1(0)$ value is determined by the type of breast lesions.

After getting the average R_{pd} , by combining Eqs. (1) and (A5) we can transform the SI to CA concentration in a TOI. Therefore, each SI data sets is calculated from the data obtained from routine clinical DCE-MRI protocol.

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