Improvement in Breast Lesion Characterization With Dynamic Contrast-Enhanced MRI Using Pharmacokinetic Modeling and Bookend T_1 Measurements

Greg O. Cron,^{1*} Frederick Kelcz,² and Giles E. Santyr¹

Dynamic contrast-enhanced breast MR imaging was performed on 14 patients (five cancerous lesions, nine benign) with slice-selective spoiled gradient-recalled echo (2D SPGR) imaging. Adiabatic saturation recovery T_1 measurements were performed before ($T_{1\text{pre}}$) and after ($T_{1\text{post}}$) 2D SPGR imaging. These two “bookend” T_1 measurements were used to calibrate the equations which were employed to convert the time course of the 2D SPGR signal strength to T_1 -vs.-time, which in turn was used to compute the gadolinium concentration-vs.-time ($[C](t)$) in the lesion. The extraction-flow product (EF) was computed for each lesion by pharmacokinetic modeling of $[C](t)$. For this study, EF provided a sensitivity and specificity for cancer of 100% and 78%, respectively. When only $T_{1\text{pre}}$ was used to estimate $[C](t)$ (which assumes a priori knowledge of the shape and amplitude of the slice profile), the sensitivity and specificity fell to 80% and 56%, respectively. This is presumably due to unexpected variations in the shape and/or amplitude of the slice profile, which could be caused by factors such as patient-to-patient variations in breast geometry or inconsistently set transmit gains. Therefore, both $T_{1\text{pre}}$ and $T_{1\text{post}}$ measurements are necessary for optimum sensitivity and specificity using pharmacokinetic analysis. Magn Reson Med 51: 1066–1070, 2004. © 2004 Wiley-Liss, Inc.

Key words: magnetic resonance imaging (MRI); breast cancer; gadolinium contrast agent

Quantitative T_1 -weighted dynamic contrast-enhanced MRI (T_1 -w DCE-MRI) is used by many researchers for detecting and evaluating breast disease (1–6). This technique involves intravenous injection of a gadolinium (Gd) contrast agent during rapid (~sec), repeated T_1 -weighted imaging. From these images, the Gd concentration-vs.-time ($[C](t)$) of a lesion of interest can be estimated (1–4,6,7). Pharmacokinetic modeling can then be applied to $[C](t)$ to extract parameters such as the extraction-flow product (EF, which is equivalent to K^{trans}) (1,4,5,8). These parameters are useful for lesion diagnosis and tracking of treatment progress.

A broad class of pulse sequences frequently used for T_1 -w DCE-MRI is slice-selective (i.e., two-dimensional) spoiled gradient-recalled echo (2D SPGR) imaging (2,3,6,7,9,10). Such pulse sequences are often used for

T_1 -w DCE-MRI because they provide relatively artifact-free images with the high temporal resolution ($< \sim 15$ sec), which is useful for differentiating benign from malignant breast lesions (11).

The signal-vs.-time ($S(t)$) of a pixel or region of interest (ROI) in a lesion can be measured directly from the 2D SPGR images. The goal is then to convert $S(t)$ to $T_1(t)$, which can subsequently be used to compute $[C](t)$ for pharmacokinetic modeling (1,4,9,12). The $T_1(t)$ can be estimated from $S(t)$ by utilizing a 2D SPGR signal strength equation which gives the relationship between S and T_1 . The signal strength equation has an overall scaling factor which must be determined either by measuring T_1 before injection of the Gd contrast agent ($T_{1\text{pre}}$) or by measuring one or more values of S obtained with special flip angles and TR settings (4,6,7,9,13).

Unfortunately, the 2D SPGR signal strength is very sensitive to even modest variations in the transmit magnetic field (B_1), which can cause the signal strength equation to become more and more inaccurate as the T_1 shortens (and $[C]$ increases) postinjection (7). This can lead to significant errors ($> 50\%$) in the estimated $[C](t)$ (7). Inaccuracies in $[C](t)$ are undesirable because they lead to errors in the estimated pharmacokinetic parameters, reducing sensitivity and specificity and making the method less consistent for tracking treatment progress.

We have demonstrated that a second measurement of T_1 (denoted $T_{1\text{post}}$), performed after the dynamic contrast-enhanced 2D SPGR imaging, can minimize the errors in the estimated $T_1(t)$ (7). This second T_1 measurement is an important part of the “Bookend Method” that we have developed, which allows $T_1(t)$ to be estimated accurately ($< \sim 10\%$ error) from 2D SPGR image data, even in the presence of variations in B_1 or the slice-select profile shape (7). For the Bookend Method, $T_{1\text{pre}}$ and $T_{1\text{post}}$ are employed to calibrate and correct the 2D SPGR signal strength equation used to estimate $T_1(t)$.

The purpose of this work was to validate the clinical usefulness of the Bookend Method for quantitative T_1 -w DCE-MRI of the breast. In order to do this, it was first necessary to develop a reasonably fast (~min) clinical T_1 measurement imaging pulse sequence which would be insensitive to variations in B_1 . The Bookend Method was then performed on a group of 14 patients (five cancerous lesions, nine benign lesions). For each lesion, EF was calculated from the estimated $[C](t)$ data and compared to pathological diagnosis. In order to compare the Bookend Method with a more conventional approach of estimating $[C](t)$, the entire analysis was repeated using $T_{1\text{pre}}$ but ignoring $T_{1\text{post}}$.

¹Department of Physics, Carleton University, Ottawa, Ontario, Canada.

²Department of Radiology, University of Wisconsin, Madison, Wisconsin.

This work was presented in part at the Eleventh Meeting of the ISMRM, Toronto, 2003.

Grant sponsor: U.S. National Cancer Institute; Grant number: R29 CA59840-05; Grant sponsor: Canadian Breast Cancer Research Initiative.

*Present address and correspondence to: Greg O. Cron, c/o Prof. Bernard Gallez, Lab. of Biomed. MR, Catholic Univ. of Louvain, CMFA/REMA, Avenue Mounier 73.40, B-1200 Brussels, Belgium.
E-mail: Gregory.Cron@rema.ucl.ac.be

Received 21 February 2003; revised 1 December 2003; accepted 1 December 2003.

DOI 10.1002/mrm.20042

Published online in Wiley InterScience (www.interscience.wiley.com).

© 2004 Wiley-Liss, Inc.

MATERIALS AND METHODS

This study was approved by the Kingston General Hospital and Ottawa Hospital Human Research Ethics Boards. Fourteen patients with either palpable lumps or mammographically or sonographically suspicious lesions were recruited who were scheduled for surgical biopsy. Informed written consent was obtained from each patient prior to each MR imaging exam. Imaging was performed with 1.5 T Signa Imaging Systems (General Electric, Milwaukee, WI) and a transmit/receive breast coil (MRI Devices, Milwaukee, WI).

For each patient, the lesion was first localized with conventional MRI pulse sequences (20). Subsequently, the following protocol was used:

1. ($T_{1\text{pre}}$ measurement) adiabatic saturation recovery (ASR) 8 slices, recovery times (τ) = 230, 635, 1329, then 2920 ms. This T_1 measurement technique is described in more detail below. The total imaging time for this step was ~ 10 min. For this and subsequent pulse sequences, coronal 5-mm-thick contiguous slices, 256×128 matrix size, and 16 cm FOV were used.
2. (2D SPGR imaging) T_1 -weighted dynamic contrast-enhanced fast spoiled gradient echo (2D FSPGR) TR = 10 ms, TE = 3 ms, flip angle = 20° , 2 NEX, 5–8 slices, temporal resolution = ~ 12 –19 sec, 0.1 mmol/kg Omniscan (Nycomed, Brampton ON, Canada) injected as a bolus after the fourth complete image set (i.e., fourth time point), total duration of dynamic imaging = ~ 10 min.
3. ($T_{1\text{post}}$ measurement) Same as 1 except that the recovery times (τ) were 230, 432, 775, then 2920 ms.

Postprocessing was performed off-line with Matlab (MathWorks, Natick MA). For each 2D SPGR imaging slice which contained part of the lesion, an ROI was manually drawn on the area of the lesion which demonstrated the greatest signal enhancement, defined as $\Delta S = S(t=2 \text{ min}) - S(t=0 \text{ min})$. Each ROI covered a group of contiguous pixels for which ΔS was at least 80% of the maximum ΔS for that slice.

Each ROI was propagated through the saturation recovery and 2D SPGR images. $T_{1\text{pre}}$ and $T_{1\text{post}}$ were each determined with a three-parameter fit to the four recovery points. For each ROI, $T_1(t)$ was estimated from $S(t)$ using the Bookend Method analysis (Method 4 in Ref. 7). For this analysis, $T_{1\text{pre}}$ and $T_{1\text{post}}$ were used to correct a lookup table that relates S and T_1 (7). The change in $1/T_1$ as a function of time was converted to $[C](t)$ by dividing by $4.5 \text{ mM}^{-1}\text{s}^{-1}$ (12). The conversion of $T_1(t)$ to $[C](t)$ assumed that the intravascular component was insignificant and that there was slow exchange of water between the plasma and the extravascular space (14). Under these assumptions, $[C](t)$ represents the time course of the average concentration of Gd in the extravascular space (14).

The $[C](t)$ data were fit to a well-known pharmacokinetic model:

$$\frac{d[C](t)}{dt} = \text{EF} \left[C_a(t) - \frac{[C](t)}{\nu} \right]. \quad [1]$$

For this equation, $C_a(t)$ is the arterial input function (AIF), defined as the concentration-vs.-time of Gd in the plasma

of the arterial blood supply. For this study, $C_a(t)$ was not measured for each patient. Instead, an approximate average of published data was used (15,16). The peak amplitude (2.7 mM) of the initial bolus phase ($t = 0$ to ~ 25 s) of this average AIF was calculated by averaging the peak amplitudes of the six AIF measurements shown in fig. 8 of Fritz-Hansen et al. (15). The initial, rapid washout of the average AIF from that peak value ($t = \sim 25$ to 50 sec) was modeled as a simple monoexponential decay with no recirculation. The rate constant for this decay (0.12 s^{-1}) was calculated by fitting a monoexponential decay to the initial washout phase of each of the Fritz-Hansen curves, then averaging the resultant rate constants. The longer, slower washout phase of the average AIF ($t = \sim 50$ –600 sec) was calculated similarly from data published by Weinmann et al. (16).

The unitless quantity ν , a free-floating parameter for the curve fit of Eq. 1, is the volume fraction of extravascular space occupied by the extracellular interstitial space (i.e., the space outside the cells and capillaries). The term EF (the other free-floating parameter) is known as the extraction-flow product. EF was expressed in units of ml/(min 100 g), under the assumption of unit density of tissue, to facilitate comparison to other studies (4,5,8). To further facilitate such comparison, the value of EF extracted from the curve fit was subsequently divided by one minus the hematocrit ($H_c = 40\%$ assumed). This adjustment made the EF values more consistent with those of many other investigators who use whole blood concentrations for $C_a(t)$ instead of plasma concentrations (4).

For each lesion, a set of EF values was therefore obtained which corresponded to the set of ROIs which had been drawn. The maximum EF value in that set was defined as the one which was representative of the lesion. As a comparison, the entire analysis was repeated using the ROI which corresponded to that maximum EF value, this time assuming that there were no imperfections in the 2D SPGR signal strength equation (e.g., no variations in B_1 or slice profile shape). Under this assumption, $[C](t)$ could be estimated accurately using only the $T_{1\text{pre}}$ measurement (4,7,13). This alternative analysis method is known as the “Single- $T_{1\text{pre}}$ Method” (Method 2 in Ref. 7), in contrast to the Bookend Method, which utilizes both $T_{1\text{pre}}$ and $T_{1\text{post}}$.

The $T_{1\text{pre}}$ and $T_{1\text{post}}$ measurements were obtained with an ASR pulse sequence. For the acquisition of each line of k -space, a nonselective sin/cos adiabatic saturation pulse was applied, followed by a recovery time τ , followed by readout pulses and data acquisition for all slices (17). An adiabatic saturation pulse was used in order to make the T_1 measurement less sensitive to B_1 inhomogeneities. The nonselective sin/cos pulse was applied for 102 ms. This pulse started 233 Hz off-resonance and ended with a maximum B_1 amplitude of ~ 0.073 Gauss. The pulse sequence had conventional, sequential phase encode ordering and interleaved slice ordering. Thus, after the recovery time τ , slices 1, 3, 5, then 7 were read out, followed immediately by slices 2, 4, 6, then 8. The pulse sequence was repeated with the same τ until an entire image had been acquired. One image was acquired for each of four values of τ as described above.

The peak specific absorption rate (SAR) generated in the breast by the ASR pulse sequence was calculated to be under 8 W/kg, which is the limit recommended by the

FIG. 1. Representative ASR and 2D SPGR images (cropped) for a single slice of one patient who had a fibroadenoma (round mass near the top of the images).

United States Food and Drug Administration for a local transmitter coil. This calculation was done using manufacturer-supplied information and was based on the assumption that the transmit/receive breast coil and the transmit/receive head coil behave similarly in terms of RF heating.

Numerical simulations were performed in order to determine the theoretical accuracy of this ASR T_1 measurement technique. T_1 was fit to simulated, noiseless, recovery data for τ values of 230, 470, 877, and 3000 ms. Recovery data were generated for all combinations of the following parameters: T_1 (400, 1200 ms); T_2 (50, 300 ms); B_1 inhomogeneity (i.e., the actual B_1 divided by the expected B_1) (0.5, 0.75, 1.0, 1.25, 2.0); and resonant offset (–25, 0, 25 Hz). For each case of T_1 , T_2 , B_1 inhomogeneity, and resonant offset, the effect of the adiabatic pulse was calculated by solving the Bloch equations numerically. The readout pulses were assumed to be single-lobed sinc pulses which are typically used in 2D SPGR imaging.

Phantom experiments were also performed to test the accuracy of the ASR technique: 12 mm- and 5 mm-wide plastic tube phantoms were filled with different aqueous concentrations of Gd contrast agent providing T_1 ranging from 1290 ± 10 ms down to 450 ± 5 ms as measured by inversion recovery (IR). This range of T_1 was used because it is approximately the range expected in vivo. The IR measurements were performed with a single-slice IR technique with 12 inversion time (TI) values ranging from 50–8000 ms, and $TR = TI + 9000$ ms. For this work, the IR measurements were considered the “Gold Standard” measurements of T_1 .

For ASR imaging, the tubes were placed upright at 8 to 9 different positions in a 9-cm high plastic container of water. The transmit/receive breast coil was used to obtain coronal images of this container with a slice thickness of 5 mm, 8 contiguous slices, matrix = 256×128 , and field of view = 16 cm. T_1 measurements with ASR were repeated six times for different locations in the water container and different arrangements of the phantom tubes. A total of 816 ASR T_1 measurements were performed, covering a volume of 830 cm^3 , which is nearly all the useful imaging volume of the coil. τ values of 230, 635, 1329, and

2920 ms were used to measure the T_1 of the tubes with $T_1 > 650$ ms, while τ values of 230, 432, 775, and 2920 ms were used to measure the T_1 of the tubes with $T_1 < 650$ ms. These sampling schemes were the same as those which were used for the patients to measure $T_{1\text{pre}}$ (which was expected to be >650 ms) and $T_{1\text{post}}$ (which was expected to be <650 ms).

RESULTS

For the simulations, the ASR technique maintained reasonably small errors ($<10\%$) even down to B_1 inhomogeneities of 0.5. In phantoms, the ASR technique measured T_1 accurately (5%) for all experiments. Figure 1 shows representative ASR and 2D SPGR images. Figure 2 shows the correction that had to be applied to the 2D SPGR signal strength equation for the Bookend Method, as a function of $1/T_1$ for all 14 patients. The ordinate may also be described as the ratio of the actual 2D SPGR signal strength to the

FIG. 2. The correction that had to be applied to the 2D SPGR signal strength equation for the Bookend Method, as a function of $1/T_1$ for all 14 patients. A value greater than 1 indicates that the measured signal was greater than that predicted by the theoretical 2D SPGR signal strength equation.

FIG. 3. The concentration of Gd in tissue as a function of time ($[C](t)$) for two different lesions (benign proliferative dysplasia and infiltrating moderately differentiated ductal carcinoma). The solid and dotted lines show the curve fits for the pharmacokinetic model. **a**: $[C](t)$ calculated with the Single- T_{1pre} Method. For this data, the EF of the benign lesion was 44.4, compared to 26.8 for the cancerous lesion. **b**: $[C](t)$ calculated with the Bookend Method. This time, the EF of the cancerous lesion was much higher than that of the benign lesion (EF = 43.1 compared to 9.8).

theoretical value predicted by the signal strength equation. Although this ratio is linear with T_1 (7), the plot was displayed as a function of $1/T_1$ to give a sense of how it can vary wildly from patient to patient with increasing Gd concentration. This figure shows that the actual 2D SPGR signal strength may differ from the theoretical value by factors ranging from ~ 0.8 – 1.5 and underlines the value of the second T_1 bookend measurement (T_{1post}).

Figure 3 shows example tissue $[C](t)$ data for two lesions from two different patients. One of the lesions was benign (proliferative dysplasia) and the other was cancerous (infiltrating moderately differentiated ductal carcinoma). Both lesions were ~ 5 mm in size. Figure 3a shows $[C](t)$ for the lesions as calculated by the Single- T_{1pre} method, whereas Fig. 3b shows $[C](t)$ as calculated by the Bookend Method. Figure 3a gives the false impression that the benign lesion absorbed a higher concentration of Gd than the cancerous lesion. In fact, as shown in Fig. 3b, the cancerous lesion had a much more aggressive enhancement than the benign lesion.

Figure 4 shows EF values for all the lesions for (4a) the Single- T_{1pre} Method and (4b) the Bookend Method. For each of the two methods, an EF threshold between cancerous and benign lesions was chosen which would maximize sensitivity and specificity. For the Single- T_{1pre} Method, the sensitivity and specificity were 80% and

56%, respectively. For the Bookend Method, the sensitivity and specificity were 100% and 78%, respectively.

For the Bookend Method analysis, the average value of ν was found to be 0.59 ± 0.31 for malignant lesions and 0.70 ± 0.26 for benign lesions. The average uncertainty in the curve fits for EF was 7% (range 1–10%), whereas that for ν was 6% (range 1–15%). The average measured value of T_{1pre} was 1256 ± 142 ms for the cancerous lesions and 1537 ± 265 ms for the benign lesions. For T_{1post} , these numbers were 446 ± 151 ms and 508 ± 148 ms, respectively.

DISCUSSION

The results of this study show that a single preinjection T_1 measurement is not sufficient for estimating $[C](t)$ reliably from rapid 2D SPGR imaging for pharmacokinetic modeling. This is because the discrepancy between the measured 2D SPGR signal strength and its theoretical value is not consistent from lesion to lesion (Fig. 2). This inconsistency is presumably due to unexpected variations in the B_1 or slice-select profile, which could be caused by factors such as patient-to-patient variations in breast geometry or inconsistently set transmit gains. The Bookend Method, however, circumvents these problems by obtaining a case-by-case empirical calibration of 2D SPGR signal strength vs. T_1 . The $[C](t)$ as estimated by the Bookend Method should therefore be much more accurate than $[C](t)$ estimated by the Single- T_{1pre} Method. This is consistent with the fact that the Bookend Method provided higher sensitivity and specificity for this study than the Single- T_{1pre} Method, given the assumption that there should be a significant separation in EF values between cancerous and benign lesions.

For the Bookend Method, it is important that the accuracy of the T_{1pre} and T_{1post} measurements not be adversely affected by the same variations in the B_1 or slice-select profile which render the Single- T_{1pre} Method unreliable. For this reason, we chose a T_1 measurement method (ASR) which would be relatively unaffected by B_1 inhomogeneities. The ASR method demonstrated low systematic errors ($<5\%$) for both the simulations and phantom experiments.

The principal drawback of the Bookend Method is that the exam time must be lengthened to accommodate the T_{1post} measurement. If limiting the total exam time is crucial, both bookend T_1 measurements could be performed with a faster, more efficient method such as one of the Look-Locker techniques (18). Whatever fast T_1 measurement method is chosen, it must maintain the same spatial resolution as the 2D

FIG. 4. EF vs. lesion type for the Single- T_{1pre} Method (**a**) and the Bookend Method (**b**). The EF thresholds chosen were (**a**) 44.4 and (**b**) 32.7.

SPGR imaging and not suffer problems from B_1 inhomogeneities or multislice interference.

One of the weaknesses of this study, and most other studies which have been published on breast MR, is the lack of a true arterial input function (19). The assumed input function used was based on the approximate average of some input function data obtained from a small group of subjects (15,16). However, changes in the input function from one individual to another could cause significant changes in the $[C](t)$ data, leading to unwanted variations in the measured pharmacokinetic parameters (19). Based on the work by Port et al. (fig. 7 of Ref. 19), it can be estimated that using the same input function for all patients will cause unwanted errors in the pharmacokinetic parameters of about 25% on average. However, a certain fraction of patients (~15% in Port et al.) will have input functions which deviate very significantly from the average, leading to very large (>40%) errors. Therefore, there is a need to develop rapid, accurate methods for measuring the arterial input function while simultaneously acquiring the Gd concentration-vs.-time in the breast tissue ($[C](t)$).

CONCLUSIONS

For dynamic contrast-enhanced MR imaging of the breast, when estimating $[C](t)$ for a lesion from T_1 -weighted 2D SPGR imaging, it is not sufficient to use a single preinjection T_1 measurement (T_{1pre}) to calibrate the signal strength equations used to convert signal strength to T_1 . This is because the discrepancy between the measured signal strength and its theoretical value is not consistent from lesion to lesion. A second T_1 measurement, performed after the dynamic contrast-enhanced imaging (T_{1post}), must be done to obtain a case-by-case empirical calibration of signal strength vs. T_1 . This improves the accuracy of the estimated $[C](t)$ and ultimately improves sensitivity and specificity for the pharmacokinetic parameter(s) used to differentiate benign from malignant tumors (e.g., the extraction-flow product which was used in this work). For this particular patient study ($n = 14$), using the two T_1 measurements (the "Bookend Method"), gave a sensitivity and specificity of 100% and 78%, respectively, compared to use of the preinjection T_1 measurement alone, which had a poorer performance (80% and 56%, respectively). The power of the Bookend Method is that, as long as T_{1pre} and T_{1post} are measured accurately, $[C](t)$ can be estimated reliably from 2D SPGR signal strengths without any a priori knowledge of system imperfections.

ACKNOWLEDGMENTS

The authors thank the Children's Hospital of Eastern Ontario and the Kingston General Hospital for assistance and cooperation with this research. We also thank Peggy Florack and Lisa Johnston of the Women's Breast Health Centre of the Ottawa Hospital for assistance with patient recruitment and follow-up, and Rick L'Heroux for clinical assistance with the patient studies performed in Ottawa. We thank Dr. Brian Pearse for help with the patient studies in Kingston, and Dr. Albert Cross for help with maintenance of the breast RF coil, and Dr. Julia Wallace, Cyndi Little, Dr. Peter Shragge, and Jennifer Mallalieu for help with the Adiabatic Saturation Recovery work.

REFERENCES

1. Padhani AR. Dynamic contrast-enhanced MRI in clinical oncology: current status and future directions. *J Magn Reson Imag* 2002;16:407-422.
2. Warner E, Plewes DB, Shumak RS, Catzavelos GC, Di Prospero LS, Yaffe MJ, Goel V, Ramsay E, Chart PL, Cole DEC, Taylor GA, Cutrara M, Samuels TH, Murphy JP, Murphy JM, Narod SA. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. *J Clin Oncol* 2001;19:3524-3531.
3. Brown J, Buckley D, Coulthard A, Dixon AK, Dixon JM, Easton DF, Eeles RA, Evans DGR, Gilbert FG, Graves M, Hayes C, Jenkins JPR, Jones AP, Keevil SF, Leach MO, Liney GP, Moss SM, Padhani AR, Parker GJM, Pointon LJ, Ponder BAJ, Redpath TW, Sloane JP, Turnbull LW, Walker LG, Warren RML. Magnetic resonance imaging screening in women at genetic risk of breast cancer: imaging and analysis protocol for the UK Multicentre Study. *Magn Reson Imag* 2000;18:765-776.
4. Hulka CA, Smith BL, Sgroi DC, Tan L, Edmister WB, Semple JP, Campbell T, Kopans DB, Brady TJ, Weisskoff RM. Benign and malignant breast lesions: differentiation with echo-planar MR imaging. *Radiology* 1995;197:33-38.
5. Hulka CA, Edmister WB, Smith BL, Tan L, Sgroi DC, Campbell T, Kopans DB, Weisskoff RM. Dynamic echo-planar imaging of the breast: experience in diagnosing breast carcinoma and correlation with tumor angiogenesis. *Radiology* 1997;205:837-842.
6. Brookes JA, Redpath TW, Gilbert FJ, Needham G, Murray AD. Measurement of spin-lattice relaxation times with FLASH for dynamic MRI of the breast. *Br J Radiol* 1996;69:206-214.
7. Cron GO, Santyr G, Kelcz F. Accurate and rapid quantitative dynamic contrast-enhanced breast MR imaging using spoiled gradient-recalled echoes and bookend T_1 measurements. *Magn Reson Med* 1999;42:746-753.
8. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HBW, Lee TY, Mayr NA, Parker GJM, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced T_1 -weighted MRI of a diffusible tracer: standardized quantities and symbols. *J Magn Reson Imag* 1999;10:223-232.
9. Parker GJM, Suckling J, Tanner SF, Padhani AR, Revell PB, Husband JE, Leach MO. Probing tumor microvascularity by measurement, analysis and display of contrast agent uptake kinetics. *J Magn Reson Imag* 1997;7:564-574.
10. Rijpkema M, Kaanders JHAM, Joosten FBM, van der Kogel AJ, Heerschap A. Method for quantitative mapping of dynamic MRI contrast agent uptake in human tumors. *J Magn Reson Imag* 2001;14:457-463.
11. Henderson E, Rutt BK, Lee TY. Temporal sampling requirements for the tracer kinetics modeling of breast disease. *Magn Reson Imag* 1998;16:1057-1074.
12. Donahue K, Burstein D, Manning W, Gray M. Studies of gadopentetate dimeglumine relaxivity and proton exchange rates in tissue. *Magn Reson Med* 1994;32:66-76.
13. Tofts PS, Berkowitz B, Schnall MD. Quantitative analysis of dynamic Gd-DTPA enhancement in breast tumors using a permeability model. *Magn Reson Med* 1995;33:564-568.
14. Donahue KM, Weisskoff RM, Burstein D. Water diffusion and exchange as they influence contrast enhancement. *J Magn Reson Imag* 1997;7:102-110.
15. Fritz-Hansen T, Rostrup E, Larsson HBW, Sndergaard L, Ring P, Henriksen O. Measurement of the arterial concentration of Gd-DTPA using MRI: a step toward quantitative perfusion imaging. *Magn Reson Med* 1996;36:225-231.
16. Weinmann HJ, Laniado M, Mutzel W. Pharmacokinetics of GdDTPA dimeglumine after intravenous injection into healthy volunteers. *Physiol Chem Phys Med NMR* 1984;16:167-172.
17. Bendall MR, Pegg DT. Uniform sample excitation with surface coils for in vivo spectroscopy by adiabatic rapid half passage. *J Magn Reson* 1986;67:376-381.
18. Hendersen E, McKinnon G, Lee TY, Rutt B. A fast 3D Look-Locker method for volumetric T_1 mapping. *Magn Reson Imag* 1999;17:1163-1171.
19. Port RE, Knopp MV, Brix G. Dynamic contrast-enhanced MRI using Gd-DTPA: interindividual variability of the arterial input function and consequences for the assessment of kinetics in tumors. *Magn Reson Med* 2001;45:1030-1038.
20. Kelcz F, Santyr GE, Cron GO, Mongin SJ. Application of a quantitative model to differentiate benign from malignant breast lesions detected by Gd-enhanced MRI. *J Magn Reson Imag* 1996;6:743-752.