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3 Tesla Dynamic Contrast Enhanced Magnetic Resonance Imaging of the Breast: Pharmacokinetic Parameters versus Conventional Kinetic Curve Analysis

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Abstract

Purpose—To evaluate the incremental value of pharmacokinetic analysis of dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) compared to conventional breast MRI (morphology plus kinetic curve type analysis) in characterizing breast lesions as malignant or benign.

Patients and Methods—The study was approved by our institutional review board. Patients underwent 3D high resolution T1 (3DT1) contrast enhanced MRI and dynamic contrast enhancement (DCE) MRI at 3T, and had pathology proven diagnosis (95%) or more than 2 years follow up confirming lesion stability (5%). Lesions were identified using the high-spatial resolution post-contrast MRI. Morphologic features (margin, enhancement pattern) and conventional DCE-MRI results (kinetic curve types I, II or III) or pharmacokinetic parameters (wash-in rate K^{trans} , washout rate K_{ep} , and leakage space volume V_e), were included in multivariate models for prediction of benign versus malignant diagnosis.

Results—95 patients with 101 lesions were included: 52% of patients were pre-menopausal and 48% post-menopausal. Sixty eight lesions (67.3%) were malignant and 33 (32.7%) were benign. There was a significant association between K^{trans} and K_{ep} and the diagnosis of benign versus malignant ($p < 0.001$). The AUC for morphologic features (lesion margin and enhancement pattern) was 0.85, while inclusion of K^{trans} or K_{ep} in the model showed similar modest improvement in performance (AUC, 0.88–0.89).

Conclusion—The use of kinetic curve type assessment or pharmacokinetic modeling in conjunction with high resolution 3D breast MRI appears to offer similar improvement in diagnostic performance..

Introduction

Conventional breast MRI protocols implement the dynamic contrast enhanced (DCE) MRI together with high spatial resolution gadolinium enhanced MRI. Use of such protocols results in high sensitivity and somewhat lower specificity for identification and characterization of focal breast lesions (1–9). DCE MRI yields a time intensity curve (kinetic curve) that is commonly used in clinical settings. A key characteristic of the time

intensity curve is the shape of the washout portion of the curve. The shape of DCE MRI curve is usually categorized as persistently enhancing (type I), plateau (type II), or washout (type III) (4). Categorization of the kinetic curve shape contributes to characterization of focal lesions as benign or malignant (5, 10, 11).

Pharmacokinetic modeling offers a quantitative approach to analyzing the distribution of gadolinium contrast agent in relation to the vascularity of focal breast lesions (12–21). These models describe the exchange of contrast agent between different body compartments. The simplest of these models describes two compartments: the tissue of interest as one compartment and the plasma as the other compartment. The model accuracy is increased using a greater number of compartments to describe the biodistribution of the gadolinium contrast agent within the vascular bed and tumor region (18, 22, 23). Three main pharmacokinetic parameters are usually used for pharmacokinetic modeling in breast imaging: 1) the volume transfer constant (washin rate), K^{trans} (min^{-1}), 2) the extravascular extracellular space (EES) volume per unit volume of tissue, V_e , and 3) the washout rate constant, K_{ep} (min^{-1}) (2, 18, 22, 23).

The value of these pharmacokinetic parameters in characterizing breast lesions as benign or malignant has shown that high permeability and low extravascular fraction is a signature of malignancy (24–28). Yet, it remains unclear if pharmacokinetic analysis improves the diagnostic performance of conventional breast MRI that includes DCE MRI to characterize the shape of the washout curve. The aim of this study was to evaluate the incremental value of pharmacokinetic analysis compared to conventional breast MRI in characterizing breast lesions as malignant or benign at 3T MRI.

Methods and Materials

Clinical Subjects

This HIPPA compliant study was approved by our institutional review board. Informed consent was waived by IRB. Inclusion criteria included 1) MRI scan on a 3T magnet, 2) DCE sequences with 15 sec/acquisition temporal resolution, 3) pathology proven diagnosis or at least 2 years follow-up confirming benign diagnosis, 4) technically adequate MRI. Out of the 550 patients referred to our facility for bilateral breast MRI between February and November 2008, 280 patients were excluded for not having a suspicious abnormality on DCE MRI, 150 patients for having lesions without sufficient follow up period, 10 patients for being scanned at 1.5 T instead of 3T, and 15 patients for failure of fat suppression. MRI examinations for 95 patients met the inclusion criteria. Two primary breast pathologists with more than 10 years experience were responsible for supervision of histo-pathologic diagnosis.

MRI acquisition

Patients were imaged on a 3T clinical MRI system (3T Achieva, Philips Medical Systems, Best, The Netherlands) using a bilateral dedicated 4 channel phased array breast coil (in-Vivo, Orlando, FL) in prone position.

We used a hybrid protocol combining high temporal resolution with high spatial resolution T1-weighted gradient echo imaging before and after contrast injection. High spatial-resolution images were obtained with fat suppression using spectral selective attenuated inversion recovery (SPAIR) sequence and the following parameters (TR/TE 7.08/3.56; FA= 10; ST= 2.5 mm; FOV: 35 × 35 cm; and matrix: 512 × 512, acquisition time, 2 minutes, 30 seconds). DCE MRI images were then obtained with no fat suppression and a temporal resolution of 15 seconds/acquisition and the following parameters (TR/TE: 3.8/1.7; FA= 10; ST= 5 mm; FOV: 35 × 35 cm; and matrix: 256 × 254). Intravenous administration of

gadobenate dimeglumine (Gd-BOPTA, Multihance; Bracco Imaging SpA, Milan, Italy) at a dose of 0.1 mMol/Kg was injected at a rate of 2 ml/sec using a power injector (Spectris Solaris MR injection system, Medard Inc., PA, USA). DCE MRI for a total 1:45 minute duration (7 acquisitions) was acquired beginning at 10 sec (delay) from the start of the contrast injection. These sequences were used to define the wash-in tissue characteristics. Then, high spatial resolution T1 images were obtained (as specified above) in a single sequence over 2:30 minutes, followed by additional DCE MRI series (7 acquisitions) using the same pulse sequence as used to characterize the wash-in kinetics to obtain the delayed enhancement kinetics. Subtraction images were obtained for high resolution and DCE MRI.

MRI Analysis

High-spatial resolution image analysis—Focal masses or suspicious areas of enhancement were identified by a reader (with 4 years experience in breast MRI) blinded to the clinical history and pathology results and classified into mass or non-mass like enhancement (NMLE). Morphologic assessment was done according to BI-RADS lexicon (29). For mass lesions, margin (smooth, lobulated, irregular or spiculated), internal enhancement pattern (homogenous, heterogeneous or rim), and presence or absence of non-enhancing septations were evaluated. For NMLE, distribution (diffuse, regional, ductal or segmental) and enhancement pattern (homogenous, heterogeneous, stippled, reticular or clumped) were evaluated. For both, T2 signal (bright, intermediate, or dark) was also evaluated.

Quantitative evaluation of DCE MRI

Different methods for tissue perfusion analysis from DCE MRI were performed and compared in subsequent analysis: conventional classification of the kinetic curve (types I, II or III), and pharmacokinetic analysis using a modified Tofts model (18, 23, 30). In addition, an empiric classification of the pharmacokinetic parameters was performed based on a commercially available software tool. These methods are described below:

Conventional DCE MRI analysis—Breast lesion localization was done using the post-contrast high spatial-resolution images. Regions of interest (ROI) were drawn to include the whole lesion in three dimensions by a single observer blinded to the clinical history and pathology results (figure 1). Time-intensity plots of dynamic images were generated using a computer aided detection (CAD) software (iCAD, Nashua, NH) as percentage enhancement (Y-axis) versus time (X-axis) for an ROI placed within the detected lesion, excluding necrotic areas of the lesion if present. Percentage enhancement was calculated as $(SI_{\text{post}} - SI_{\text{pre}})/SI_{\text{pre}} \times 100$, where SI_{pre} is the signal intensity in the pre-contrast image and SI_{post} is the signal intensity in the post-contrast image.

For DCE MRI, peak percentage enhancement within the first 2 minutes, the time to peak enhancement (categorized as ≤ 2 minutes or > 2 minutes), and kinetic curve type were assessed. Kinetic curve type assessment was done using a semi-quantitative method that was validated in a prior study (31). Kinetic curve shape was categorized as persistently enhancing (type I), plateau (type II) or washout (type III) using 5% as a cutoff value (signal intensity percentage change $>5\%$ was considered persistent, between -5% and 5% considered plateau and $<-5\%$ was considered washout).

Pharmacokinetic analysis—Post-processing of the high temporal resolution images was done using CAD software (iCAD, Nashua, NH). CAD software performs full time point (FTP) analysis using a pharmacokinetic analysis model that was modified from the basic Toft's model (15, 23, 30). This model describes the exchange of contrast material between four main compartments; the plasma, the whole body extra-cellular space, tumor leakage

space, and the elimination of contrast from blood through the kidneys, as previously described (12, 15, 17, 18, 22, 23).

Breast lesion localization was done using the post-contrast high spatial-resolution images, as above. For each lesion, the mean and median values of transfer constant (K^{trans}) representing permeability, extra-cellular volume fraction - EVF (V_e), and the rate constant (K_{ep}) were recorded.

Empirical categorization of pharmacokinetic parameters—Using permeability and EVF, a two dimensional lookup table was constructed by iCAD software combining both parameters (K^{trans} and EVF) based on empirical analysis by the software manufacturer. This was described by the manufacturer as validation of 100 breast MRI cases with known diagnosis and known vascular profile of tumors (30, 32)(Figure 2). Three regions on the look-up table were identified; Region 1 (blue color in Figure 2) corresponded to K^{trans} and V_e pairs observed in benign lesions, region 2 (green color) corresponded to areas of overlap between benign and malignant lesions, and region 3 (red color) corresponded to K^{trans} and V_e pairs observed in malignant lesions. Within the 3D ROI, the percentage of pixels classified as region 1, 2 or 3 was recorded.

Statistical Analysis

Morphologic features were classified as either 1) definitely malignant (spiculated irregular margin, rim enhancement, ductal or segmental distribution of clumped enhancement), 2) definitely benign (smooth border or diffuse distribution with homogenous enhancement), or 3) indeterminate morphology (all other morphologic features).

Univariate logistic regression analysis was used to find associations between the independent parameters (morphology, conventional kinetic, and pharmacokinetic parameters) and the final diagnosis (benign vs. malignant) for focal breast lesions. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of each parameter in characterizing benign versus malignant lesions.

Forward step-wise multivariate logistic regression analysis was performed to determine the combination of parameters that best predicted the final diagnosis of benign or malignant. Four multivariate models were developed; 1) Model 1: morphologic features (lesion margins and pattern of internal enhancement), 2) Model 2A: model 1 parameters plus kinetic curve type (Type I, II, or III), 3) Model 2B: model 1 parameters plus pharmacokinetic parameters (K^{trans} , V_e , K_{ep}) 4) Model 3: model 1 parameters plus empirical CAD regions (percentage distribution of CAD region 1, 2 or 3). Median values resulted in similar results as the mean value for pharmacokinetic parameters, so median values are presented since the distributions were not normal. For model selection, Akaike information criterion (AIC) was used (33); smaller AIC is indicative of better model performance. ROC curve analysis was used to assess diagnostic performance of the tested models. P-values <0.05 were considered significant. Multivariate analysis and model selection were also repeated for lesions categorized indeterminate by morphologic criterion. All analyses were performed using STATA statistical software (Version 9.0, College Station, TX).

Results

Ninety five women with 101 lesions met our inclusion criteria (Table 1). The mean age of the patients was 52 ± 11 (range= 24–80) years. Sixty eight lesions (67.3%) were malignant (23 infiltrating ductal carcinoma, 26 mixed insitu and infiltrating ductal carcinoma, 9 pure DCIS, 6 infiltrating lobular carcinoma and 4 miscellaneous) and 33 (32.7%) were benign (9

fibroadenomas, 3 intra-ductal papillomas, 4 fibrocystic changes, 4 sclerosing adenosis, 2 atypical ductal hyperplasia and 11 benign breast tissue).

As shown in Table 1, malignant lesions were more likely than benign lesions to have spiculated margins (63% versus 18%, respectively, $p < 0.001$) and heterogeneous enhancement (60% versus 21%, $p < 0.001$). Regarding DCE MRI, malignant lesions were more likely than benign lesions to show washout curves (53% versus 18%, respectively, $p < 0.001$), while benign lesions were more likely to show persistent enhancement (67% versus 26%, $p < 0.001$). Mean K^{trans} and K_{ep} were higher in malignant than benign lesions (0.5 ± 0.5 versus 0.22 ± 0.19 and 1.5 ± 1.2 versus 0.9 ± 0.7 , respectively, $p < 0.005$ for both). CAD region 1 was more common in benign than malignant lesions (40.7% versus 10.7%, respectively, $p < 0.001$), while region 3 was more common in malignant lesions (41.8% versus 13.4%, $p < 0.001$).

Odds ratios and AUC values are shown in Table 2 for MRI parameters. Lesion margin, enhancement pattern, T2 signal, and the presence of non-enhancing septations were significant predictors of malignant versus benign diagnosis ($p \leq 0.05$ for all parameters). Of the morphologic parameters, the highest AUC value was for lesion margin (AUC, 0.81).

For kinetic parameters, time to peak enhancement and kinetic curve type were significant predictors of malignant versus benign diagnosis ($p = 0.006$ and $p < 0.001$, respectively), while percent peak enhancement was not. K^{trans} , K_{ep} as well as the empiric CAD regions 1 and 3 were also significant discriminators for malignant versus benign diagnosis ($p < 0.05$ for all). For region 3, the AUC was maximized when $>16\%$ of the pixels in a lesion were red (considered as malignant). For region 1, the AUC was maximized at $>20\%$ of pixels as blue (considered as benign). Of the kinetic parameters, the highest AUC value was obtained for K_{ep} (AUC, 0.92).

Multivariate logistic regression models

Model 1 included the morphologic features of lesion margin and enhancement pattern. The AUC for this model was 0.85 (AIC 93.6) (Table 3). Addition of kinetic curve type (model 2a) to model 1 was significant (O.R. 2.5 for curve type, $p = 0.004$) with a small improvement in the AUC value (0.88) (AIC 86.7).

K^{trans} added significantly to model 1 (O.R. 15.3, $p = 0.05$) while K_{ep} did not. Addition of both K^{trans} and K_{ep} to model 1 was nonsignificant suggesting the parameters had opposing effects. The AUC for the combination of morphologic parameters and K^{trans} (0.88, AIC 88.7) were similar to that of model 2a (Table 3).

Adding either the percentage distribution of region 1 (blue) or region 3 (red) to the morphologic model 1 parameters showed very slight improvement in the overall model performance (e.g., AUC 0.9, AIC 83 for region 3, Table 3) (Figure 3) compared to models 1 and 2. Colinearity of regions 1 and 3 was noted if both parameters were added to the model.

Analyses were repeated for 37 lesions that were indeterminate by morphologic analysis alone. Addition of kinetic curve type to model 1 for indeterminate lesions improved the AUC from 0.88 to 0.94. Adding pharmacokinetic parameters or empiric CAD regions resulted in similar AUC values (0.96 and 0.95, respectively). Case examples are shown in Figures 4, 5 and 6

Analyses were repeated for 90 lesions that represent the whole sample excluding the DCIS cases. Addition of kinetic curve type to model 1 for lesions other than DCIS improved the

AUC from 0.86 to 0.91. Adding pharmacokinetic parameters or empiric CAD regions resulted in similar AUC values (ranging between 0.9 and 0.93).

Discussion

In this study, we demonstrated that addition of semi-quantitative kinetic curve type analysis (i.e. Types I, II or III) and/or pharmacokinetic parameters to high spatial resolution 3D breast MRI at 3T improves diagnostic performance of MRI. The pharmacokinetic analysis produced nearly equivalent results to the kinetic curve analysis. A convenient method for expressing functional pharmacokinetic results is via a look-up table overlaid onto an anatomical image provides additional diagnostic information to the radiologist. Using that approach produced similar AUC results compared to using kinetic curve type albeit slightly better performance based on AIC evaluation criteria for the look-up table. Thus, the performance of any of the DCE MRI analytic methods was shown to be nearly equal in distinguishing malignant from benign breast lesions.

Our results regarding the contribution of DCE MRI to analysis of lesion morphology builds on the results of prior studies. In a multi-center study, Schnall et al 2006 (6) reported the best predictive parameters for malignancy to be lesion margin (AUC=0.76), T2 intensity (AUC=0.7), enhancement pattern (AUC = 0.62), and kinetic curve type (I, II or III) (AUC=0.66). In the current study, the same parameters plus pharmacokinetic parameters were found to have the best predictive value for malignancy. On the other hand, Szabo et al. 2003 (34) concluded that the lesion margin and time to peak enhancement are the strongest independent predictive value for breast cancer.

The kinetic curve type assessment originally proposed by Kuhl (4) is subjective. A prior study has found this approach to be highly reproducible amongst experienced readers (31). Nevertheless, a more quantitative approach was shown to be useful if automated software analysis could be used, where cut-off values of $\pm 5\%$ increase or decrease in enhancement over two minutes performed well in categorizing curve type as I, II or III (31)

The attractiveness of using the pharmacokinetic model to characterize breast lesions is that it attempts to simulate the physiology of the MRI contrast agent distribution in relationship to the breast tissue. Multiple parameters describe the contrast delivery, accumulation and washout, rather than using a single observational parameter such as percentage of contrast washout. Unfortunately, multiple complex parameters become difficult to interpret in a clinical setting. CAD software implements categorization of lesions through mapping of parameters into one of three colors representing a probability range from benign to indeterminate to malignant, an approach that converts pharmacokinetic parameters to easily visualized data distributions. However, within a single lesion, pixels that have both malignant and benign parameters pixels may be present, therefore in this study the percentage of pixels was assessed and, region 3 pixels (red) of more than approximately 16% of the lesion volume showed the best performance in predicting malignancy. These results are similar to both preclinical and clinical studies using only one model (14, 16, 17, 19, 20, 35, 36)

Despite the theoretical advantages of a pharmacokinetic approach, there is little information comparing that method to a simpler kinetic curve type analysis as an adjunct to high spatial resolution 3D MRI. Veltman et al. (2008) attempted to compare the pharmacokinetic modeling to kinetic curve assessment. They evaluated the value of pharmacokinetic parameters derived from high temporal resolution (4.1 sec/acquisition) dynamic imaging compared to diagnostic performance of morphologic features plus kinetic curve type derived from low temporal resolution dynamic imaging (86 sec/acquisition). In that study,

morphology and low temporal resolution (86 sec/acquisition) kinetic curve type resulted in AUC value of 0.84. Hauth et al. (28) used similar software as in the current study for determination of pharmacokinetic parameters. In that study, K^{trans} was shown to correlate with the final diagnosis, while V_e did not.

The current study shows that either kinetic curve type classification or more sophisticated pharmacokinetic modeling is likely to produce similar overall performance compared to morphologic features alone. There are several possible reasons for this. First, the morphologic features alone are powerful predictors, since the AUC for morphologic features alone was 0.85. Thus, a larger sample size may show more benefit of one of the two methods. Second, the pharmacokinetic model may be inaccurate or oversimplified. Finally, there is substantial heterogeneity in the perfusion of breast lesions. Our analysis assumes a binary categorization of tumors as either benign or malignant without gradation in either category. However, pharmacokinetic parameters are continuous variables and cut-off values that match a binary classification of malignant versus benign is unlikely.

There are several limitations of this study. We required that all lesions had a “proven” diagnosis. As a result, we had a high percentage of malignant lesions in this study since patients with benign appearing lesions on mammography were unlikely to undergo MRI. The sample size (101 lesions) may be too small to reveal subtle differences that may exist between the various methods used for DCE MRI analysis. Even if differences in diagnostic performance do exist, it seems unlikely that small improvements in performance will be clinically significant for breast lesion evaluation. For breast cancer, clinical standards currently demand negative predictive values for noninvasive imaging to be close to 100%; thus, most of the indeterminate lesions will be biopsied. Finally, some of our pharmacokinetic results apply specifically to software from one manufacturer. However, we also modeled pharmacokinetic parameters as continuous variables and obtained results very similar to empiric categorization models used for validation by the software manufacturer.

In conclusion, the use of kinetic curve type assessment or pharmacokinetic modeling on DCE breast MRI appears to offer similar improvement in diagnostic performance when used in conjunction with morphologic assessment of breast lesions on high spatial resolution 3D MRI.

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Advances in knowledge

1. For dynamic contrast enhanced (DCE) MRI, both pharmacokinetic modeling and kinetic curve type analysis improve characterization of malignant and benign breast lesions.
2. A diagnostic model including lesion morphology plus either pharmacokinetic parameters or kinetic curve assessment showed similar diagnostic performance in characterizing breast lesions.

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Implications for patient care

1. While morphologic analysis alone provides good characterization of breast lesions on MRI, as benign or malignant, analysis of the lesion perfusion on DCE MRI using either kinetic curve shape assessment or a pharmacokinetic modeling approach improves diagnostic accuracy.

Figure 1.

Demonstration of the automated method of plotting the region of interest (ROI). The lesion is identified on the color map images (A) by correlating with the subtraction images. Then we determine the colors that the lesion exhibiting and select a seed point by clicking in part of the lesion and then the software start growing the seed to include all the adjacent pixels exhibiting the color we chose (blue in this example) till it reach a pixel with different color or no color, it stops growing the seed (B). The areas of blue the represent vascularity was not included in the ROI because it was not connected to the blue pixels of the lesion.

Figure 2.

CAD lookup table constructed by combining two pharmacokinetic parameters, permeability (K^{trans}) and EVF (V_e) on the y and x-axis, respectively. Independently of the current study, three regions were identified based on 100 test cases from the software manufacturer (iCAD); Region 1 (blue color) corresponds to areas of K^{trans} and V_e pairs that are more common in benign lesions, region 2 (green color) corresponds to areas of overlap between benign and malignant lesions, and region 3 (red color) corresponds to areas of K^{trans} and V_e pairs that are more common in malignant lesions.

Figure 3.

Graph showing ROC curve comparison between model 1 (lesion morphology only) and model 3 (model 1 plus CAD region 3 (red) percentage) (AUC 0.85 and 0.90, $p = 0.057$).

Figure 4.

Magnetic resonance imaging of the breast in 60 year old female patient referred to MRI for evaluation of a suspicious lesion in mammography. A) Maximum intensity projection (MIP) image of the axial subtraction of post-contrast 3DT1 high spatial resolution image (TR/TE/FA 7.08/3.56/10) showing a clumped regional enhancement in the upper central left breast indicating suspicious morphology. B) Kinetic curve extracted from the DCE MRI series (TR/TE/FA: 3.8/1.7/10). The curve is type I (persistently enhancing), which is suggestive of benign nature of the lesion. C) Maximum intensity projection (MIP) image of the axial computer aided detection color map constructed from pharmacokinetic parameters extracted from the DCE MRI series (TR/TE/FA: 3.8/1.7/10). About 87% of the lesion exhibits blue color (empirical CAD region 1) suggestive of benign nature of the lesion. D) The corresponding CAD look up table demonstrating the number of pixels corresponding to each permeability (K^{trans}) and extracellular volume fraction (V_e) combination and corresponding color. Most of the pixels lie in the low permeability and low to intermediate EVF range. Histo-pathologic examination of the lesion revealed the diagnosis of fibrocystic changes.

Figure 5.

Magnetic resonance imaging of the breast in 57 year old female patient referred to MRI for evaluation of a mass in the upper outer quadrant of the right breast. A) Axial subtraction of post-contrast 3DT1 high spatial resolution image (TR/TE/FA 7.08/3.56/10) showing an enhancing spiculated mass lesion in the right upper outer quadrant with rim enhancement indicating suspicious morphology. B) Kinetic curve extracted from the DCE MRI series (TR/TE/FA: 3.8/1.7/10). The curve is type 2 (Plateau), which is suggestive of suspicious nature of the lesion. C) Maximum intensity projection (MIP) image of the axial computer aided detection color map constructed from pharmacokinetic parameters extracted from the DCE MRI series (TR/TE/FA: 3.8/1.7/10). 48% of the lesion exhibited red color (empirical CAD region 3) suggestive of malignant nature of the lesion. D) The corresponding CAD look up table demonstrating the number of pixels corresponding to each permeability (K^{trans}) and extracellular volume fraction (V_e) combination and corresponding color. Most of the pixels lie in the low permeability and low to intermediate EVF range. Histopathologic examination of the lesion revealed the diagnosis of infiltrating ductal carcinoma.

Figure 6.

Magnetic resonance imaging of the breast in 49 year old female patient with strong family history referred to MRI for evaluation of a suspicious lesion in ultrasound. A) Axial subtraction of post-contrast 3DT1 high spatial resolution image (TR/TE/FA 7.08/3.56/10) showing a round, well defined enhancing mass lesion at 9 O'clock position of the right breast with non enhancing septations indicating benign morphology. B) Kinetic curve extracted from the DCE MRI series (TR/TE/FA: 3.8/1.7/10). The curve is type III (washout), which is indicative of malignant nature of the lesion. C) Axial computer aided detection color map constructed from pharmacokinetic parameters extracted from the DCE MRI series (TR/TE/FA: 3.8/1.7/10). About 33% of the lesion exhibits red color (empirical CAD region 3) suggestive of malignant nature of the lesion. D) The corresponding CAD look up table demonstrating the number of pixels corresponding to each permeability (K^{trans}) and extracellular volume fraction (V_e) combination and corresponding color. Most of the pixels lie in the low permeability and low to intermediate EVF range. Histopathologic examination of the lesion revealed the diagnosis of fibro-adenoma.

Table 1

Characteristics of subjects and breast masses

Characteristics	Benign N=33	Malignant N = 68	p-value
^a Age, years	50 (1.7)	53.5 (11)	0.13
^b Pre-menopausal (n=41/93)	17/41 (41.5%)	24/41 (58.5%)	0.29
^b Post-menopausal(n=52/93)	16/52 (30.8%)	36/52 (69.2%)	0.29
Morphology			
^a Size	1.7 (2.3)	2.6 (1.6)	0.49
^b Mass	24/33 (72.7%)	51/68 (75%)	0.8
^b NMLE	8/33 (24.2%)	17/68 (25%)	0.9
Margin			
^b Smooth	12/33 (36.4%)	3/68 (4.4%)	< 0.001
^b Lobulated	15/33 (45.5%)	12/68 (17.7%)	0.003
^b Irregular	0/33 (0%)	10/68 (14.7%)	0.02
^b Spiculated	6/33 (18.1%)	43/68 (63.2%)	< 0.001
Enhancement			
^b Homogenous	22/33 (66.7%)	12/68 (17.7%)	< 0.001
^b Heterogeneous	7/33 (21.2%)	41/68 (60.3%)	< 0.001
^b Rim	4/33 (12.1%)	15/68 (22%)	0.23
DCE			
Kinetic curve type			
^b Persistently enhancing	22/33 (66.7%)	18/68 (26.5%)	< 0.001
^b Plateau	5/33 (15.2%)	14/68 (20.6%)	0.5
^b Washout	6/33 (18.1%)	36/68 (52.9%)	0.001
Pharmacokinetic parameters			
^a K ^{trans}	0.22 (0.19)	0.5 (0.5)	< 0.001
^a V _e	0.25 (0.1)	0.8 (4.5)	0.3
^a K _{ep}	0.9 (0.7)	1.5 (1.2)	<0.005
Empirical CAD regions			
% Region 1 (Blue)	40.7 (28.7)	10.7 (22.9)	< 0.001
% Region 2 (Green)	46.8 (28.7)	47.5 (25.8)	0.9
% Region 3 (Red)	13.4 (22.4)	41.8 (29.6)	< 0.001

^aData are presented as mean (standard deviation)^bData are presented as number of cases (%)p-value are either of t-test (for mean values comparison ^a) or pf chi square test (for percentage comparison ^b)

Table 2

Univariate logistic regression.

	OR (95% CI)	P-value	AUC
Morphology			
Margin	3.3 (2–5.2)	<0.001	0.81
Enhancement pattern	4 (1.9–8.3)	<0.001	0.73
T2 signal	1.9 (0.99–3.6)	0.05	0.59
Non-enhancing septations	5.9 (1.1–32.2)	0.04	0.56
Time to peak enhancement	3.4 (1.4–8.2)	0.006	0.65
Conventional kinetic			
% initial enhancement	1 (0.99–1.02)	0.28	0.67
Kinetic curve type	2.8 (1.6–4.7)	<0.001	0.72
Pharmacokinetic parameters			
Permeability (K^{trans}) [*]	63.8 (4–1026)	0.003	0.76
EVF (V_e) [*]	15.9 (0.3–949)	0.19	0.58
K_{ep} [*]	3.4 (1.4–8.4)	0.008	0.92
Empirical CAD regions			
Region 1 (blue)	1 (0.96–0.98)	<0.001	0.74
Region 2 (green)	1 (0.98–1)	0.9	0.5
Region 3 (red)	1 (0.99–1)	<0.001	0.8

OR = Odds Ratio, **AUC** = Area under receiver operating characteristic (ROC) curve **% initial enhancement**= the highest percentage enhancement within the first two minutes

^{*} Median values are tested.

Table 3

Multivariate logistic regression

	OR	95% CI	P-value	AUC/AIC
M1. Morphology				
Margin	2.9	1.8–4.8	<0.001	0.85/93.6
Enhancement pattern	2.86	1.3–6.4	0.01	
M2A. Morphology + kinetic curve type				
Margin	2.9	1.7–4.8	<0.001	0.88/86.7
Enhancement pattern	2.6	1.1–5.8	0.022	
Kinetic curve type	2.5	1.3–4.7	0.004	
M2B. Morphology + Pharmacokinetic parameters (K^{trans})				
Margin	2.7	1.6–4.6	<0.001	0.88/88.7
Enhancement pattern	2.8	1.2–6.3	0.014	
Median permeability (K^{trans})	15.3	1–234	0.05	
M2B. Morphology + Pharmacokinetic parameters (K_{ep})				
Margin	2.9	1.7–4.9	<0.001	0.89/87.2
Enhancement pattern	3	1.3–6.9	0.012	
Median rate constant (K_{ep})	2.2	0.9–5.2	0.068	
M3. Morphology + Empirical CAD regions (region 1, blue)				
Margin	2.4	1.6–4.6	0.001	0.89/83
Enhancement pattern	4.2	1.2–6.8	0.002	
Region 1 (blue)	1	1–1.1	0.001	
M3. Morphology + Empirical CAD regions (region 3, red)				
Margin	2.7	1.4–4.2	<0.001	0.90/83
Enhancement pattern	3	1.7–10.4	0.014	
Region 3 (red)	1	0.9–0.99	0.002	

OR = Odds Ratio, AUC = Area under receiver operating characteristic (ROC) curve, AIC= Akaike information criterion, DCE= Dynamic contrast enhanced MRI; DWI= Diffusion weighted imaging using normalized ADC value.