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Dynamic Contrast-Enhanced MRI of the Breast: Quantitative Method for Kinetic Curve Type Assessment

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Abstract

OBJECTIVE—The type of contrast enhancement kinetic curve (i.e., persistently enhancing, plateau, or washout) seen on dynamic contrast-enhanced MRI (DCE-MRI) of the breast is predictive of malignancy. Qualitative estimates of the type of curve are most commonly used for interpretation of DCE-MRI. The purpose of this study was to compare qualitative and quantitative methods for determining the type of contrast enhancement kinetic curve on DCE-MRI.

MATERIALS AND METHODS—Ninety-six patients underwent breast DCE-MRI. The type of DCE-MRI kinetic curve was assessed qualitatively by three radiologists on two occasions. For quantitative assessment, the slope of the washout curve was calculated. Kappa statistics were used to determine inter- and intraobserver agreement for the qualitative method. Matched sample tables, the McNemar test, and receiver operating characteristic (ROC) curve statistics were used to compare quantitative versus qualitative methods for establishing or excluding malignancy.

RESULTS—Seventy-eight lesions (77.2%) were malignant and 23 (22.8%) were benign. For the qualitative assessment, the intra- and interobserver agreement was good ($\kappa = 0.76$ – 0.88), with an area under the ROC curve (AUC) of 0.73 – 0.77 . For the quantitative method, the highest AUC was 0.87 , reflecting significantly higher diagnostic accuracies compared with qualitative assessment ($p < 0.01$ for the difference between the two methods).

CONCLUSION—Quantitative assessment of the type of contrast enhancement kinetic curve on breast DCE-MRI resulted in significantly higher diagnostic performance for establishing or excluding malignancy compared with assessment based on the standard qualitative method.

Keywords

breast cancer; breast imaging; contrast-enhanced MRI; dynamic MRI; kinetic curve; washout

Contrast-enhanced MRI carries very high sensitivity but moderate specificity for the diagnosis of breast cancer [1,2]. Dynamic contrast-enhanced MRI (DCE-MRI) has been widely used to improve the specificity of MRI in characterizing breast lesions [3–7]. The

most widely used form of DCE-MRI analysis is the assessment of the type of time–signal intensity curve (i.e., kinetic curve) by categorizing the washout pattern of a gadolinium contrast agent. These patterns are classified as type I, persistently enhancing (progressive), which is suggestive of benignity; type II, plateau type, which has an intermediate probability for malignancy; and type III, washout type, which is indicative of malignancy. The washout patterns are typically assessed qualitatively, with intra- and interobserver variability reported to vary widely from 0.27 [8,9] to 0.80 [1].

The purpose of this study was to evaluate the reproducibility of qualitative assessment of the type of contrast enhancement kinetic curve on DCE-MRI for multiple observers and to compare the results with the results obtained using quantitative methods for determining the type of curve. Both qualitative and quantitative approaches were evaluated with respect to measures of overall accuracy of DCE-MRI for the prediction of malignancy.

Materials and Methods

Clinical Subjects

MRI scans of 300 consecutive patients who presented to our facility for bilateral breast MRI from January 2007 to February 2008 were retrospectively reviewed. Patients were included in the study if they had a breast lesion or lesions at least 1 cm in diameter that had a pathologically proven diagnosis or 2 years of imaging follow-up accepted as a proof of benignity. This study was approved by our institutional review board and was compliant with HIPAA.

Ninety-one patients met the inclusion criteria of the study. Patients were scanned on either a 1.5-T (48 patients) or a 3-T (48 patients) clinical MRI system (1.5-T Intera and 3-T Achieva, Philips Healthcare) using a bilateral dedicated phased-array breast coil (4-channel breast array coil, Invivo). The MRI protocol included 2 minutes of high-temporal-resolution imaging (15 seconds per acquisition) to capture the wash-in phase of contrast enhancement, high-spatial-resolution scanning for 2 minutes, and additional high-temporal-resolution imaging (15 seconds per acquisition) for an additional 2 minutes to characterize the slope of the washout curve. The high-temporal acquisition sequence (dynamic imaging) was a 3D gradient-echo sequence with fat suppression using a spectral selection attenuated inversion recovery (SPAIR) sequence acquired in the transverse plane (TR range/TE range, 3.38–3.8/1.7–1.97; flip angle, 10°; slice thickness, 5 mm; field of view, 35 × 35 cm; matrix, 256 × 254).

DCE-MRI Analysis

After contrast-enhanced high-spatial-resolution images and their subtraction images were used for lesion detection, time–intensity plots of dynamic images were generated using computer-assisted diagnosis (CAD) software (CADvue version 2.2.9, iCAD) as percentage enhancement (y-axis) versus time (x-axis) of a region of interest (ROI) placed in the detected lesion. Percentage enhancement was calculated as follows:

$$\frac{SI_{post} - SI_{pre}}{SI_{pre}} \times 100$$

where SI_{pre} is the signal intensity in the ROI on the unenhanced image and SI_{post} is the signal intensity in the ROI on the contrast-enhanced image. Signal intensities from the iCAD software were copied to an Excel spreadsheet (Microsoft) for calculation of slopes and signal intensity percentage differences.

Qualitative Assessment

Three radiologists, each with at least 10 years' experience in breast MRI, were involved in the qualitative assessment of kinetic curve type. Printed copies of the kinetic curves were given separately to each reader. Each reader independently classified each kinetic curve as persistently enhancing, plateau, or washout type according to the categories described by Kuhl et al. [3]. Readings were repeated by the same three readers after a period of at least 2 weeks. All readers were blinded to the morphologic features of the focal breast lesions and to clinical information regarding patients.

Quantitative Assessment

Two parameters were calculated from the kinetic curves: the average washout slope and the absolute washout percentage-enhancement difference. The average washout slope was calculated as the mean slope of the line from the peak enhancement, which was defined as peak enhancement within the first 2 minutes, until the last time point including all intermediate time points. The washout percentage-enhancement difference was calculated by subtracting the last time point percentage-enhancement from the peak percentage-enhancement (i.e., beginning and ending time points only).

The quantitative results were categorized into three categories analogous to the qualitative results. Both parameters were categorized as persistently enhancing, plateau, or washout on the basis of their values relative to cutoff points placed symmetrically above and below zero. An example of the categorization using one of the cutoff points ($\pm 5\%$ cutoff range) is shown in Figure 1. To optimize the diagnostic performance for each category, we tested multiple cutoff points for each parameter and selected the cutoff point that resulted in maximizing the area under the receiver operating characteristic (ROC) curve (AUC).

The sensitivity, specificity, likelihood ratios, and predictive values were calculated for two different diagnostic criteria for malignancy: malignancy defined as a washout curve (type III) and malignancy defined as a washout or plateau curve (type II and III curves).

Statistical Analysis

The study sample consisted of 101 breast lesions in 96 women who met the inclusion criteria. For qualitative readings, the percentage agreement and kappa statistics were used to assess intra- and interobserver variability. For interobserver variability, the second reading for each radiologist was used. Kappa values ≤ 0.20 indicate poor agreement between the two readers; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and > 0.80 , almost perfect agreement [10].

To assess the diagnostic accuracies of the qualitative and quantitative assessments, sensitivity, specificity, and ROC curves were calculated. The positive likelihood ratio and positive predictive value (PPV) for each kinetic curve type category (persistently enhancing, plateau, and washout) were calculated for both the qualitative and quantitative methods. A likelihood ratio of < 1 indicates the value in excluding malignancy, and a likelihood ratio of > 1 indicates its value in establishing malignancy.

To compare the qualitative and quantitative methods, we constructed a matched sample table [11] and used the McNemar test.

Finally, the AUC for the second reading of each radiologist was compared with the quantitative variable based on washout slope and washout percentage-enhancement difference data sets using the optimum cutoff point. Results were adjusted for magnetic field strength (1.5 vs 3 T) by adding the field strength as an independent variable in the

multivariate logistic regression model. A p value of < 0.05 was considered significant. Bonferroni adjustment was applied to account for the multiple comparisons. All analyses were performed using statistics software (Stata, version 9.0, Stata).

Results

There were 101 focal breast lesions in 96 women meeting the inclusion criteria. One lesion had 2 years of imaging follow-up confirming a benign diagnosis and all other lesions had histologic confirmation of the final diagnosis. In four cases, two concomitant lesions were detected but showed different pathology (the first lesion was malignant, and the second lesion was benign). The mean age of the patients was 50 ± 10.5 (SD) years (range, 24–73 years). Seventy-eight lesions (77.2%) were malignant: 38 infiltrating ductal carcinoma, 21 mixed in situ and infiltrating ductal carcinoma, seven pure DCIS, seven infiltrating lobular carcinoma, and five miscellaneous. Twenty-two patients (22%) had benign lesions: 12 fibroadenomas; two papillomas; three fibrocystic changes; one atypical ductal hyperplasia (ADH); and five benign breast tissue, fibrosis and adenosis.

The patients were scanned on either a 1.5- or 3-T scanner: 48 lesions were scanned at 1.5 T, of which 23% were benign (11/48), and 53 lesions were scanned at 3 T, of which 21% were benign (11/53). The indications for performing breast MRI examinations were screening of high-risk patients in 11.5% (11/96) of cases, evaluation of patients recently diagnosed with breast cancer in 74% (71/96) of cases, workup of mammographically suspicious lesions in 12.5% (12/96) of cases, and workup of patients with bloody nipple discharge in 2% (2/96) of cases. Breast density was fatty in 9.4% (9/96) of patients, mildly glandular in 12.5% (12/96), moderately glandular in 19.8% (19/96), and heterogeneously dense in 58.3% (56/96).

Among our patient population, 77.1% (74/96) had an average lifetime risk factor of developing breast cancer and 22.9% (22/96) had a high risk ($> 25\%$ lifetime risk) of developing breast cancer (7.3% with family history of breast cancer, 10.4% with personal history of breast cancer, 1% with personal history of ovarian cancer and positive *BRCA1* mutation, and 4.2% with ADH).

Kinetic Curve Type Assessment

Qualitative assessment—The intraobserver agreement for qualitative reads ranged from 91% to 92% with kappa coefficients ranging from 0.86 to 0.88. The interobserver agreements ranged from 84% to 89%, with kappa coefficients ranging from 0.76 to 0.83 (Table 1). The diagnostic performance of the three radiologists was similar after adjustment for the difference in field strength, with sensitivity ranging from 85.9% to 89.8%; specificity, 56.5–67.4%; and AUC, 0.73–0.77 ($p > 0.7$) (Table 2).

Quantitative assessment—The AUC value was maximized using cutoff values of $\pm 0.03\%/s$ average washout slope (AUC = 0.86) and $\pm 5\%$ absolute percentage-enhancement difference (AUC = 0.86). Based on these cutoffs, when a positive test result was defined as washout or plateau—that is, $> -5\%$ washout and > -0.03 slope—the sensitivities of the average washout slope and absolute percentage methods were 93.6% and 92.3%, and the specificities 73% and 64%, respectively, after adjustment for field strength difference ($p > 0.7$) (Table 3).

Comparing Quantitative Method Versus Qualitative Method

The AUCs of both quantitative methods were significantly greater than the AUCs of the qualitative method (for each reader) ($p < 0.01$, Fig. 2). With a positive test for malignancy defined as a washout or plateau pattern (type II or III), the qualitative method incorrectly

categorized five cases as benign, all of which the quantitative method (using $\geq -0.03\%/s$ slope as the cutoff for malignant diagnosis) correctly categorized as malignant (Table 4); examples are shown in Figure 3. No cases were incorrectly categorized as benign by the quantitative method.

At the same time, the qualitative method incorrectly categorized three cases as malignant, all of which the quantitative method correctly categorized as benign. Only one case was incorrectly categorized as malignant by the quantitative method, which was correctly categorized as benign by the qualitative method.

The differences in sensitivity and specificity between the qualitative and quantitative methods were not statistically significant ($p = 0.06$ for sensitivity, $p = 0.6$ for specificity, Mc-Nemar test). Using a malignancy pattern defined as the washout pattern (type III) and a benignity pattern defined as the persistently enhancing or plateau pattern (type I or II) showed statistical superiority for the quantitative analysis compared with qualitative assessment for sensitivity ($p > 0.001$) but not for specificity ($p = 1$).

The positive likelihood ratio and PPV for the washout category were higher for the quantitative methods (5.4 and 95% for average washout and 6.1 and 95% for the absolute percentage method, respectively) than for the qualitative method (2.7 and 90%, respectively) (Table 5). These results indicate more confident establishment of malignancy associated with the observation of washout with the quantitative methods. The positive likelihood ratio and PPV of the persistently enhancing category were lower for the quantitative methods (0.09–0.13 and 25–30%, respectively) than the qualitative method (0.20 and 40%, respectively), indicating more confident exclusion of malignancy associated with the observation of persistent enhancement with the quantitative method. For the plateau category, the positive likelihood ratios and PPVs were similar for the qualitative method (1.8 and 86%, respectively) and quantitative methods (1.8 and 0.6; 86% and 67%, respectively) (Table 5).

The matched sample table (Table 4) shows the better diagnostic performance of the quantitative method compared with the qualitative method. Eight cases were correctly diagnosed with the quantitative method but misdiagnosed with the qualitative method. In particular, identification of washout curve type was better with the quantitative method versus the qualitative method. On the other hand, the persistently enhancing curve type (type I) showed lower values for both the PPV and positive likelihood ratio when using the quantitative method compared with the qualitative method.

Discussion

DCE-MRI is routinely used to evaluate focal breast lesions. Adding information derived from kinetic curve type to architectural features of a lesion improves the specificity of breast MRI [3,5,6,8,12]. To our knowledge, prior studies have not compared quantitative kinetic curve type assessment with the standard qualitative method. In this study, intraobserver agreement and interobserver agreement were good for experienced readers at a single center, although the method is inherently subjective. By categorizing the type of the enhancement curve either as an absolute change in percentage enhancement (difference between peak enhancement and delayed enhancement at 5 minutes) or as an average slope (considering all points on the washout curve), significantly greater AUC values were seen compared with the qualitative method.

The performance of qualitative kinetic curve assessment was previously reported to be 0.66 (AUC) in a large multicenter study [5]. Our results showed somewhat higher AUC values (0.75–0.86) for both qualitative and quantitative methods. Kuhl et al. [3] reported a

sensitivity of 91%, specificity of 83%, and accuracy of 86% for DCE-MRI. Although our sensitivity values are similar to theirs, the specificity of DCE-MRI was lower in our study, ranging from 56% to 74%. It is likely that differences in reader procedures and differences in patient populations account for higher AUC values in the current study. No comparison studies are available that report quantitative results for kinetic curve assessment.

The quantitative methods for kinetic curve type assessment that we evaluated would be straightforward to implement in CAD software. Although the qualitative assessment was reproducible between trained readers, quantitative analysis would help standardize determination of the kinetic curve type. Establishment of specific cutoff criteria to define the washout pattern versus plateau pattern is essential for CAD diagnosis. Using either the average washout slope for all time points or simply the difference between peak and delayed enhancement at 5 minutes showed similar diagnostic performance in this analysis.

Limitations of this study include a high prevalence of malignant cases compared with benign cases in our sample. Most lesions included in this study (99%) had a histologically proven diagnosis. Lesions that were biopsied were likely to be malignant, indicating the bias of our patient population. This likely enriched the numbers of patients in the type II and type III categories. Also, the threshold values for kinetic curve categories that we determined are likely to be specific to the pulse sequence parameters and MRI scanners that were used in this study. We did not include the morphologic features of the lesions in this analysis; instead, our aim was to isolate the effect of quantitative versus qualitative interpretation of the kinetic curve. A limitation of our study was that scan acquisitions were performed at both 1.5 and 3 T, which could have confounded the results. However, field strength was not found to be a confounder in the multivariable logistic regression analysis ($p > 0.7$).

In conclusion, the reproducibility of qualitative assessment of kinetic curve type by experienced readers is good. However, quantitative measurement of kinetic curve type resulted in significantly higher overall diagnostic performance when compared with the qualitative assessment.

Acknowledgments

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Fig. 1.

Illustration of quantitative method for kinetic curve type assessment by categorizing washout parameters (percentage-enhancement difference in this figure). Any change from -5% to 5% was considered plateau (*gray*), more than 5% change was considered persistent, and less than -5% was considered washout.

Fig. 2.

Comparison between receiver operating characteristic (ROC) curves of quantitative method using 0.03%/s average washout slope as cutoff point and qualitative method assessed by each of three radiologists separately. Area under ROC curve (AUC) of quantitative method was significantly higher than that of qualitative method ($p < 0.01$).

Fig. 3.

Case examples of disagreement between qualitative method versus quantitative method in 39-year-old woman after lumpectomy undergoing breast MRI for 6-month follow-up (**A–C**) and 41-year-old woman undergoing breast MRI for assessment of recently diagnosed right breast cancer (**D–F**).

A and B, Axial (**A**) and sagittal (**B**) high-spatial-resolution T1-weighted images of right breast show irregular mildly enhancing lesion at upper outer quadrant (*arrow*, **B**).

C, Kinetic curve was categorized as persistent enhancement by three of three readers, whereas quantitative method categorized curve as plateau (i.e., suggestive of malignancy). Biopsy result showed mass to be in situ ductal carcinoma and infiltrating ductal carcinoma.

D and E, Axial (**D**) and sagittal (**E**) high-spatial-resolution T1-weighted images of right breast show retroareolar lobulated mass (*arrowhead*, **D**).

F, Kinetic curve was interpreted by three of three readers as persistently enhancing curve, whereas quantitative method categorized kinetic curve as plateau (i.e., suggestive of malignancy). Infiltrating ductal carcinoma was revealed by biopsy.

TABLE 1

Intra- and Interobserver Variability Tests

Reviewer	Agreement (%)	κ
Intraobserver		
Radiologist 1	91	0.86
Radiologist 2	92	0.88
Radiologist 3	91	0.86
Interobserver		
Radiologist 1B vs radiologist 2B	89	0.83
Radiologist 1B vs radiologist 3B	89	0.83
Radiologist 2B vs radiologist 3A	84	0.76

TABLE 2

Variation in Diagnostic Performance Between Radiologists

Reviewer	Sensitivity (%)	Specificity (%)	AUC	Positive Likelihood Ratio	Negative Likelihood Ratio	Odds Ratio	PPV (%)	NPV (%)
Radiologist 1 ^a	89.8	59.1	0.77	2.2	0.17	12.9	88.35	62.1
Radiologist 2 ^a	85.9	65.9	0.76	2.5	0.21	11.9	90.0	57.0
Radiologist 3 ^a	89.1	56.8	0.75	2.1	0.19	10.8	88.0	59.6

Note—AUC = area under the receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value.

^a Average value between the two readings for each radiologist is reported.

TABLE 3
Comparison of Diagnostic Performance of the Qualitative and Quantitative Methods

Method	Sensitivity (%)	Specificity (%)	AUC	Positive Likelihood Ratio	Negative Likelihood Ratio	Odds Ratio	PPV (%)	NPV (%)
Qualitative ^a	88.3	60.6	0.76	2.3	0.20	11.9	88.8	59.5
Quantitative 1 ^b	93.6	73.0	0.86	3.4	0.09	39	92.4	76.2
Quantitative 2 ^c	92.3	64.0	0.86	2.5	0.12	21	90.0	70.0

Note—AUC = area under the receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value.

^a Average value of the readings of the three radiologists.

^b Categorization using 0.03%/s slope cutoff.

^c Categorization using $\pm 5\%$ percentage-enhancement-difference cutoff.

TABLE 4

Matched Sample Table for Qualitative and Quantitative Methods

Quantitative Method ^a	Qualitative Method ^b			
	Malignant		Benign	
	True-Positive	False-Negative	False-Positive	True-Negative
Malignant				
True-positive	68	<u>5</u>	NA	NA
False-negative	<u>0</u>	5	NA	NA
Benign				
False-positive	NA	NA	5	<u>1</u>
True-negative	NA	NA	<u>3</u>	13

Note—Values set in **boldface** are tied values (i.e., the two methods agree). The underlined values are the untied values (i.e., the two methods disagree) that we used for our comparative analysis. NA = not applicable values.

^aUsing the data created with 0.03%/s slope as the cutoff.

^bUsing this data set resulted in the best accuracy, which was shown as the highest area under the receiver operating characteristic curve.

TABLE 5
Comparison in Diagnostic Performance of Different Kinetic Curve Type Categories Between Qualitative and Quantitative Methods

Method	Persistently Enhancing Curve		Plateau Curve		Washout Curve	
	Positive Likelihood Ratio	PPV (%)	Positive Likelihood Ratio	PPV (%)	Positive Likelihood Ratio	PPV (%)
Qualitative ^a	0.20	40	1.8	86	2.7	90
Quantitative 1 ^b	0.09	25	1.8	86	5.4	95
Quantitative 2 ^c	0.13	30	0.6	67	6.1	95

Note—PPV = positive predictive value.

^a Average value of the readings of the three radiologists.

^b Categorization using 0.03%/s slope cutoff.

^c Categorization using 5% percentage enhancement difference cutoff.