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Ultrafast Dynamic Contrast-Enhanced Breast MRI: Kinetic Curve Assessment Using Empirical Mathematical Model Validated with Histological Microvessel Density

Naoko Mori, MD, Hiroyuki Abe, MD, Shunji Mugikura, MD, Chiaki Takasawa, MD, Satoko Sato, MD, Minoru Miyashita, MD, Yu Mori, MD, Federico D. Pineda, PhD, Gregory S.

Karczmar, PhD, Hajime Tamura, MD, Shoki Takahashi, MD, and Kei Takase, MD

Department of Diagnostic Radiology, Tohoku University Graduate School of Medicine, Seiryō 1-1, Sendai 980-8574, Japan (N.M., S.M., C.T., S.T., K.T.); Department of Radiology, University of Chicago, Chicago, Illinois (H.A., F.D.P., G.S.K.); Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan (S.S.); Department of Surgical Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan (M.M.); Department of Orthopedic Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan (Y.M.); Department of Medical Physics, Tohoku University Graduate School of Medicine, Sendai, Japan (H.T.)

Abstract

Rationale and Objectives: To evaluate whether parameters from empirical mathematical model (EMM) for ultrafast dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) correlate with histological microvessel density (MVD) in invasive breast cancer.

Materials and Methods: Ninety-eight consecutive patients with invasive breast cancer underwent an institutional review board-approved ultrafast DCE-MRI including a pre- and 18 postcontrast whole breast ultrafast scans (3 seconds) followed by four standard scans (60 seconds) using a 3T system. Region of interest was placed within each lesion where the highest signal increase was observed on ultrafast DCE-MRI, and the increase rate of enhancement was calculated as follows: $S = (SI_{\text{post}} - SI_{\text{pre}})/SI_{\text{pre}}$. The kinetic curve obtained from ultrafast DCE-MRI was analyzed using a truncated EMM: $S(t) = A(1 - e^{-\alpha t})$, where A is the upper limit of the signal intensity, α (min^{-1}) is the rate of signal increase. The initial slope of the kinetic curve is given by

Address correspondence to: N.M. naokomori7127@gmail.com.

CONFLICTS OF INTEREST

We wish to draw the attention of the Editor to the following facts that may be considered as potential conflicts of interest and to significant financial contributions to this work.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing, we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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$A\alpha$. Initial area under curve (AUC30) and time of initial enhancement was calculated. From the standard DCE-MRI, the initial enhancement rate (IER) and the signal enhancement ratio (SER) were calculated as follows: $IER = (SI_{early} - SI_{pre})/SI_{pre}$, $SER = (SI_{early} - SI_{pre})/(SI_{delayed} - SI_{pre})$. The parameters were compared to MVD obtained from surgical specimens.

Results: A , α , $A\alpha$, AUC30, and time of initial enhancement significantly correlated with MVD ($r=0.29, 0.40, 0.51, 0.43$, and -0.32 with $p=0.0027, p<0.0001, p<0.0001, p<0.0001$, and $p=0.0012$, respectively), whereas IER and SER from standard DCE-MRI did not.

Conclusion: The parameters of the EMM, especially the initial slope or $A\alpha$, for ultrafast DCE-MRI correlated with MVD in invasive breast cancer.

Keywords

Magnetic resonance imaging; Breast cancer; Dynamic contrast-enhanced MRI; Microvessels

INTRODUCTION

Kinetic analysis of dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) covering the whole breast with high-spatial-resolution images (generally 60—90 seconds) has been found useful in distinguishing between benign and malignant lesions, and this method has been employed in the breast imaging reporting and data system (BI-RADS) MRI lexicon (1–3). Recently, an approach using high-temporal-resolution (3 — 10 seconds) that relies on conventional uniform k-space sampling with modest spatial resolution has been developed as an ultrafast DCE-MRI (4). It uses higher sensitivity encoding (SENSE) acceleration factors and generates images that are of high temporal resolution covering the whole breast. This method is considered more reliable for quantitative analysis of the enhancement rate or increasing rate of signal intensity in whole tumoral area in very early postcontrast phases of DCE-MRI. The kinetic assessment of the ultrafast DCE-MRI was shown to be comparable to the standard kinetic assessment obtained from the combination of early and delayed phases of standard DCE-MRI for distinguishing between benign and malignant lesions (5,6).

Regarding parameters to analyze ultrafast DCE-MRI, Mann et al. used the maximum slope (6), while Abe et al. used the enhancement rate or increasing rate of signal intensity (5) as nonfitting approach for differentiating between benign and malignant tumors. To our knowledge, however, no study has ensured whether the maximum slope or enhancement rate of the kinetic curve is the most reliable parameters to evaluate the vascularity of breast tumors in ultrafast DCE-MRI. Fan et al. reported an advantage of using an empirical mathematical model (EMM) to fit the uptake and washout of contrast media on DCE-MRI (7,8). Pineda et al. showed the feasibility of using a truncated EMM to fit ultrafast DCE-MRI data during only the early uptake phase (4). With the truncated EMM, a few simple parameters will be obtained and they will represent the uptake behavior of kinetic data from multiple time points acquired with ultrafast DCE-MRI (4,9).

While microvessel density (MVD) is a measure of new blood vessel formation or vascularity, several reports showed a significant relationship between MVD and risk of

metastasis of breast cancer (10–13). High MVD is associated with shorter relapse-free survival and decreased overall survival (14,15). Furthermore, evaluation of MVD during neoadjuvant chemotherapy is considered to be an important marker of treatment effectiveness (16), because solid tumor growth might be arrested by inhibiting angiogenesis, and treatment efficacy can be monitored by measuring MVD (17,18). MVD has been used to verify the parameters of contrast enhancement of tumors or normal tissue (19–25). MVD has been shown to relate to the enhancement effect of DCE-MRI in breast, brain, and prostate tumors (22,26,27). Therefore, we selected the MVD as a standard parameter to verify the efficacy of truncated EMM for ultrafast DCE-MRI.

In this study, we evaluated whether parameters from truncated EMM for enhancement in very early postcontrast phases of ultrafast DCE-MRI correlated with histological MVD or vascularity in invasive breast cancer.

MATERIALS AND METHODS

Patients

Our institutional review board approved this retrospective study and waived the informed consent requirement. All 155 patients diagnosed histologically by core needle biopsy with breast carcinoma during December 2015 through June 2017 underwent preoperative MR examination followed by mastectomy or lumpectomy. Excluding patients treated with neoadjuvant therapy ($n = 30$), which likely caused some changes in MVD, patients with ductal carcinoma in situ ($n = 26$), and atypical ductal hyperplasia ($n = 1$) for which clinical significance of MVD is unknown (28), consecutive 98 patients with 98 lesions of invasive breast cancer who underwent preoperative MR examination were included in this study. In one patient with multiple lesions unilaterally and four patients with multiple lesions in both breasts, we evaluated only one of the lesions with largest diameter. All patients were female; their median age was 59 years (range 30–87).

MRI Acquisition

A 3T system (Intera Achieva dStream, Philips Healthcare, Best, the Netherlands) with single-source radiofrequency transmission was used for all scans. All patients were imaged in the prone position with both breasts placed in a 16-channel bilateral breast coil. Protocols included ultrafast and standard DCE-MRI using a 3D fat-suppressed T1-weighted gradient-echo sequence: ultrafast DCE-MRI (repetition time/echo time [milliseconds], 2.8/1.5; voxel size, $1.09 \times 1.66 \times 4.0$; SENSE acceleration factor [RL], 3.2; SENSE acceleration factor [FH], 2.2; half scan factor, 0.7 [ky], 0.7 [kz]; temporal resolution, 3 seconds; number of sections, 80; flip angle, 10° ; field of view, 350 mm; fat suppression method, SPAIR), and standard DCE-MRI (repetition time/echo time [milliseconds], 5.2/2.6; voxel size, $0.73 \times 1.24 \times 1.8$; SENSE acceleration factor [RL], 1.6; SENSE acceleration factor [FH], 1; half scan factor, 0.75 [ky], 0.8 [kz]; temporal resolution, 60 seconds; number of sections, 170; flip angle, 10° ; field of view, 350 mm; fat suppression method, SPAIR) with intravenous infusion of 0.1 mmol/kg gadobenate dimeglumine (Guerbet, Japan), followed by a 20-mL saline flush at a rate of 2 mL/s. The DCE series included a precontrast acquisition for standard DCE-MRI (standard-pre) and ultrafast DCE-MRI (ultrafast-pre). The postcontrast

ultrafast DCE-MRI acquisition (scan time of 3 seconds) started 10 seconds after the beginning of contrast injection (Fig 1): 18 postcontrast series of ultrafast DCE-MRI were repeatedly acquired until 64 seconds after the beginning of contrast injection, followed immediately by the standard DCE-MRI (each scan time of 60 seconds) for four postcontrast acquisitions (Fig 1).

Image Interpretation

The extent of lesions, longest tumor diameter, and lesion type (mass or nonmass) were initially evaluated using standard DCE-MRI by two readers (9 and 6 years of experience in breast MR imaging, respectively), blinded to the clinical and pathological information according to the BI-RADS MRI criteria (3).

We standardized a time of arrival of contrast agent in the ultrafast DCE-MRI according to the initial enhancement in the descending aorta at the level of the nipple. We labeled the ultrafast scan phase when the aorta started to enhance as “F1,” and labeled the subsequent 3-second phases as “F2,” “F3,” etc. successively. The largest oval or round region of interest (ROI) was placed inside the enhancing lumen of the aorta. The “F1” was defined as when the signal intensity within a ROI measured twice the mean signal intensity within the same ROI in the precontrast scans. The “F2” was defined as the phase occurring 3 seconds after F1.

Analysis of Lesion Enhancement Using Ultrafast and Standard DCE-MRI

Pre- and postcontrast ultrafast and standard DCE images were transferred to clinical image viewer (Natural Report and NV-1000 viewer, Hitachi Medical Systems, Japan) for ROI placement and analysis of signal intensity changes using the subtraction images. The two readers visually identified the 98 lesions and placed a ROI where the highest signal increase was observed within each lesion on ultrafast DCE images (Fig 2c). The last phase of ultrafast DCE images was used to place ROIs in the same manner as our prior studies (5,29). Care was taken for the ROI to be at least 5 mm² in size. The ROIs were copied to all the ultrafast (Fig 2c) and standard DCE images (Fig 2a), and the increase rate of enhancement (ΔS) was calculated as follows:

$$\Delta S = (SI_{\text{post}} - SI_{\text{pre}})/SI_{\text{pre}} \quad (1)$$

where SI_{pre} and SI_{post} indicate the signal intensity of each ROI obtained before and after the injection of contrast agent, respectively.

The kinetic curve obtained from ultrafast images was analyzed quantitatively using the truncated EMM as follows (4,9,29,30):

$$\Delta S(t) = A(1 - e^{-\alpha t}) \quad (2)$$

where A is the upper limit of the signal intensity, α (min⁻¹) is the rate of signal increase. The goodness of fit of parameter R^2 was calculated for each lesion. We obtained the

following derivations for diagnostic parameters: (a) Initial area under curve (AUC_{γ}): The AUC_{γ} can be calculated by integrating the kinetic curve (2) from the time 0 to γ :

$$AUC_{\gamma} = A(\gamma - [1 - e^{-\gamma\alpha}]/\alpha) \quad (3)$$

In this study, we used $\gamma = 30$ seconds following the study of Jansen et al. (9). (b) Initial slope of enhancement ($Slope_{ini}$): The initial slope of the kinetic curve can be calculated as the product of the uptake rate α and the amplitude of enhancement A :

$$Slope_{ini} = A\alpha \quad (4)$$

(c) Time of initial enhancement (TIE): TIE was calculated from F1 to the time at which a lesion demonstrated 20% increase in signal intensity on the precontrast images. The parameters were compared to MVD obtained from surgical specimens.

From the same ROI (Fig 2a), the initial enhancement rate (IER) and the signal enhancement ratio (SER) of standard DCE-MRI were also calculated (Fig 2b). IER and SER were defined as:

$$IER = S_{early}/S_{pre} \quad (5)$$

$$SER = (S_{early} - S_{pre})/(S_{delayed} - S_{pre}) \quad (6)$$

where SI is the signal intensity of the ROI on the precontrast, early (phase standard 1), and delayed (phase standard 4) contrast-enhanced standard images. The parameters from standard images were also compared to MVD obtained from surgical specimens. Reproducibility of the parameters measured by each reader was evaluated using the interclass correlation coefficient (ICC) (31).

PATHOLOGICAL EVALUATION

All patients underwent mastectomy or lumpectomy; surgical specimens were prepared for histological evaluation. Specimens were fixed in 10% formaldehyde solution, and 2- μ m-thick sections were taken every 5 mm. An experienced pathologist evaluated the specimens based on the World Health Organization histological classification of breast tumors. For MVD immunostaining, mouse antihuman CD31 monoclonal antibody (Dako Cytomation, Glostrup, Denmark) was used. Microvessels labeled with the CD31 antibody were quantified by the counting procedure of Simpson et al. (32,33). Each slide was examined at a low magnification (40 $\times$) to identify five separate areas containing the greatest number of microvessels or hot spots. MVD was calculated by dividing these CD31 + hot-spot areas by the total area on a 200 $\times$ field. The mean counts in these five areas were then recorded as the MVD.

STATISTICAL ANALYSIS

Relationships between the parameters obtained from ultrafast and standard DCE-MR images and MVD were analyzed using Pearson's correlation analysis. Interobserver reliability of results of A , α , $A\alpha$, AUC30, and TIE of EMM and IER and SER of standard DCE-MRI was assessed using ICCs. An r of 1.0 was deemed to indicate perfect agreement; 0.81–0.99, almost perfect agreement; 0.61–0.80, substantial agreement; 0.41–0.60, moderate agreement; 0.21–0.40, fair agreement; and 0.20 or less, slight agreement (31). Statistical analyses were performed using commercial software (JMP Pro 13, SAS Institute, Cary, NC). The $p < 0.05$ was considered significant. After Bonferroni correction of seven multiple comparisons, the critical value became <0.0071 ($0.05/7$).

RESULTS

Of 98 lesions, 17 were treated with mastectomy and other 81 were treated with lumpectomy. Patients' characteristics, diameter, findings of distribution type according to BI-RADS, and histopathological results obtained from surgical specimen are shown in Table 1. Pathological evaluation revealed invasive ductal carcinoma not otherwise specified ($n = 88$), invasive lobular carcinoma ($n = 6$), mucinous carcinoma ($n = 2$), and invasive micropapillary carcinoma ($n = 2$). Immunohistochemical staining revealed that 89 lesions were estrogen receptor positive and nine were negative; 80 lesions were progesterone receptor (PR) positive and 18 were negative; 14 lesions were human epidermal growth factor receptor 2 (HER2) positive and 84 were negative. Immunohistochemical subtype was luminal type ($n = 87$), HER2 type ($n = 9$), and triple negative type ($n = 2$). Median Ki-67 labeling index was 15.6 (range 1–78.1). Median histopathological MVD of the 98 lesions was 1.6% (range 0.5–4.6).

The truncated EMM was able to accurately fit the curves of ultrafast DCE-MRI, with a goodness of fit parameter $R^2 > 0.90$ for all cases studied here. Of the parameters of ultrafast DCE-MRI, $A\alpha$ or the initial slope of the kinetic curve significantly correlated with MVD ($r = 0.51$; $p < 0.0001$; Table 2). A , α , AUC 30, and TIE also significantly correlated with MVD with a lesser degree ($r = 0.29, 0.40, 0.43$, and -0.32 ; $p = 0.0027, <0.0001, <0.0001$, and 0.0012 , respectively; Table 2). In standard DCE-MRI, either IER or SER did not correlate with MVD ($r = 0.11$ and -0.03 ; $p = 0.29$ and 0.74 , respectively). In evaluating the agreement between readers, ICCs for A , α , $A\alpha$, AUC30, and TIE from ultrafast DCE-MRI and IER and SER from standard DCE-MRI were >0.8 , indicating almost perfect agreement.

DISCUSSION

In our results, the A , α , $A\alpha$, AUC30, and TIE in the truncated EMM of ultrafast DCE-MRI showed almost perfect interobserver reliability and significant correlation with histopathological MVD, whereas IER and SER of standard DCE-MRI did not.

DCE-MRI signal enhancement depends not only on MVD, but also on blood flow, vascular permeability, interstitial volume and pressure, and lymphatic drainage (34). Among them, MVD assessment is the most commonly used technique to quantify intratumoral angiogenesis in breast cancer (26, 27, 34). Several studies have compared the correlation

between signal enhancement on DCE-MRI and MVD in breast cancer. However, the results were variable. Buadu et al. reported a significant correlation between the steepest slope of contrast medium uptake and MVD using MR acquisition of 15-second single-section technique (22). Teifke et al. reported a positive association of peripheral-to-central MVD ratio and peripheral-to-central IER, while MVD and enhancement ratio did not correlate with each other using MR acquisition of 93-second multiple-section technique (25). Stomper et al. reported no significant correlation between MVD and MR parameters using a 30-second multiple-section technique (24). Such inconsistency in correlation between MR parameters and MVD may be ascribed to the MR acquisition with lower temporal resolution or single-section technique that could not allow the whole lesion analysis. In this respect, our method to detect signal changes from whole breast every 3 seconds after the contrast injection allows more accurate quantitative analysis of signal change of DCE-MRI than standard DCE-MRI with low temporal resolution (Fig 2). Thus, it was unsurprising that A , α , $A\alpha$, AUC30, and TIE calculated from ultrafast DCE-MRI data fitted with the truncated EMM showed significant correlation with MVD in our study.

There have been several studies correlating pharmacokinetic compartment modeling of 3D DCE-MRI data with MVD in cancers (34, 35). The results were inconsistent: van Niekerk et al. reported a significant correlation between a pharmacokinetic parameter such as K_{ep} (the rate of constant between the extracellular extravascular space and the plasma space) and MVD in prostate cancer (34), while Shen reported no significant correlation between pharmacokinetic parameters such as K_{trans} (the volume transfer constant) and K_{ep} and MVD in breast cancer (35). These models required an arterial input function, calculating the change of T1 values by placing a ROI in thin afferent vessels, which might have made accurate estimation difficult and therefore caused inconsistent results. As an alternative to these approaches, a five-parameter mathematical model was developed to describe contrast uptake and washout behavior without an arterial input function by Fan et al. (7,8), and this model successfully distinguished between benign and malignant breast lesions. The original mathematical model in their equation had been made by Tofts et al. as generalized kinetic model on the basis of physiology (the Appendix) (36). In the present study, we used a modified or truncated EMM to fit the ultrafast DCE-MRI data similar to previous work by Pineda et al. (4). This was appropriate because there was no washout in the very early phase after the contrast injection. Only two parameters (A and α) for describing contrast uptake behavior was used to analyze data of 3D breast DCE-MRI. Because we revealed a significant correlation of the parameters of the equation with MVD, we believe that this study could demonstrate their correlation with the underlying pathophysiology of breast tumors.

MVD is known to be correlated to the risk of metastasis (10–12), prognosis (14, 37), and effectiveness of neoadjuvant chemotherapy (16–18). Therefore, prediction of MVD using ultrafast DCE-MRI with the truncated EMM would be potentially of help for predicting a prognosis, deciding a treatment strategy and monitoring an effectiveness of neoadjuvant chemotherapy.

Regarding feasibility in discriminating between benign and malignant diseases, Mann et al. reported that the maximum slope manually obtained from kinetic curve of ultrafast DCE-

MRI provided high diagnostic accuracy (6). Abe et al. reported that the enhancement rate measured immediately after the injection of contrast agent in ultrafast DCE-MRI showed significant differences between benign and malignant lesions (5). Although these studies did not evaluate histological MVD, the differential enhancement between benign and malignant lesions likely represents the difference in MVD between benign and malignant lesions (23). By examining parameters of the truncated EMM fits to ultrafast DCE-MRI data, our study confirmed their significant correlation with MVD on histology. Especially, $A\alpha$ or the initial slope in our study showed the highest correlation coefficient with MVD. As $A\alpha$ represents the initial slope of the kinetic curve, it is similar to parameters for enhancement rate (5) and maximum slope (6) used in previous studies. Thus, we believe our results support the utility of maximum slope or the enhancement rate in nonmodel analysis in discriminating between benign and malignant lesions, although the present study was conducted only with malignant lesions.

This study has several limitations. First, the sample size was small. Second, selection of ROI with the strongest enhancement was subjective, although the ICC for the parameters in this study was very high. Furthermore, we used the last phase of ultrafast DCE-MRI to visually place ROIs. We did not evaluate which phase of ultrafast DCE-MRI was effective to place the ROIs; however, we showed in our previous study that visually identified strongest enhancement obtained by placing cursor in the last phase of ultrafast DCE-MRI was acceptable for differentiating benign from malignant lesions (29). Third, the concentration of contrast agent in cancerous tissue depends not only on MVD but also on perfusion, leakage from capillaries, back-flux from tissue to efferent vessels, and the volume of the interstitial space. Nevertheless, our study showed a significant correlation between MVD and parameters from the truncated EMM of kinetic curve from ultrafast DCE-MRI. Fourth, a majority of patients in our study had luminal-type breast cancer (87 out of 98 patients). In addition, they were treated with surgery without neoadjuvant chemotherapy, which is generally applied to patients with advanced breast cancer. Thus, most of the patients had non-advanced, luminal-type cancer in this study. Further study is needed to determine if our results could be applied to patients with advanced breast cancer and HER2/triple negative subtypes. Finally, temporal resolution of our method was 3 seconds, while it was variable in a range of 4.5 — 10 seconds in other ultrafast DCE-MRI studies reported (5,6). Appropriate temporal resolution to obtain the signal change most accurately remains to be studied.

In conclusion, parameters from truncated EMM fits to ultrafast DCE-MRI data (especially $A\alpha$ or the initial slope) were significantly correlated with histological MVD in invasive breast cancer.

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APPENDIX

Interpretation of the Parameters A and α

A general kinetic model has been described by Tofts et al. for analyzing dynamic contrast-enhanced T₁-weighted data (36). The two-compartment model (Fig A1) consists of blood pool and extravascular extracellular space (EES).

The concentration of tracer in tissue per unit volume (C_t , ignoring the contribution of intravascular tracer to the total tissue concentration) will change at the rate of:

$$\frac{dC_t}{dt} = K^{\text{trans}}(C_p - C_e) = K^{\text{trans}}\left(C_p - \frac{C_t}{v_e}\right)$$

where K^{trans} is the transfer constant, C_p denotes tracer concentration in arterial blood plasma, C_e denotes tracer concentration in EES, and v_e is the fractional volume of EES.

The solution of this differential equation for an abrupt step change in C_p from 0 to C_{p0} , at time $t = 0$, is

$$C_t(t) = v_e C_{p0} \left(1 - e^{-\frac{K^{\text{trans}}}{v_e} t} \right)$$

On the other hand, we used the expression in this study for enhancement rate of signal intensity, S :

$$\Delta S(t) = A(1 - e^{-\alpha t})$$

space (EES).

Figure A1.

A two-compartment model consisting of blood vessels and extravascular extracellular space (EES). A diffusible tracer in arterial blood plasma (concentration of C_p) moves into EES at the rate of $C_p K^{\text{trans}}$, where K^{trans} is the transfer constant. It flows back at the rate of $C_e K^{\text{trans}}$, where C_e denotes tracer concentration in EES.

If the repetition time (TR) of MRI sequence is short enough, S will be approximately proportional to C_t . By comparing this equation for $S(t)$ with above equation for $C_t(t)$, we see the following relationships under the condition of short TR: the parameter A would be proportional to $v_e C_{p0}$ and a corresponds to K^{trans}/v_e . Thus, Aa would be proportional to $C_{p0} K^{\text{trans}}$, which equals to the slope of time—concentration curve of $C_t(t)$ at $t = 0$.

Abbreviations

DCE-MRI	dynamic contrast-enhanced MRI
EMM	empirical mathematical model
MVD	microvessel density
AUC	area under curve
TIE	time of initial enhancement
IER	initial enhancement rate
SER	signal enhancement ratio
ROI	region of interest

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Figure 1.

Protocols for ultrafast scanning. The dynamic contrast-enhanced (DCE) MRI series include precontrast acquisitions for standard DCE-MRI (standard-pre) and ultrafast DCE-MRI (ultrafast-pre) scans. The postcontrast ultrafast DCE-MRI starts 10 seconds after the beginning of contrast injection, and 18 ultrafast DCE-MRI scans (each scan time of 3 seconds) and four standard DCE-MRI scans (each scan time of 60 seconds) follow. MRI, magnetic resonance imaging.

Figure 2.

Methods for placing a region of interest (ROI) and acquiring kinetic curves for ultrafast and standard DCE-MRI in a 64-year-old woman diagnosed with invasive ductal carcinoma preoperatively. (a, c) A ROI is placed at a place within a lesion where the highest signal increase was found on ultrafast DCE-MRI. The last phase of ultrafast DCE images was used to place the ROI. The ROI was copied to all the ultrafast (c) and standard images (a) to generate kinetic curves. (b, d) Kinetic curves of standard (b) and ultrafast (d) DCE-MRI, which are plotted with time on the x-axis and enhancement or signal increase on the y-axis. In the kinetic curve of ultrafast DCE-MRI (d), the real values are plotted with *blue squares*, while the fitted values are plotted with *orange circles*. The *light-blue squares* enclosed by the *dashed line* on both standard and ultrafast DCE-MRI kinetic curves indicate an identical time interval immediately after the contrast injection. When the first 30 seconds immediately after the contrast injection of standard and ultrafast DCE-MRI are compared, it would be

obvious that temporally sequential signal change is more accurately analyzed with ultrafast DCE-MRI. (Color version of figure is available online.)

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TABLE 1.**Patients' and Lesions' Characteristics**

Variables	Value (n = 98)
Age (years)	
Median (range)	59 (30–87)
Menopausal status (n [%])	
Pre	40 (41)
Post	58 (59)
Diameter (mm)	
Median (range)	16 (6–65)
The lesion type (n [%])	
Mass	87 (89)
Nonmass	11 (11)
Histology (n [%])	
Invasive ductal carcinoma not otherwise specified	88 (90)
Invasive lobular carcinoma	6 (6)
Mucinous carcinoma	2 (2)
Invasive micropapillary carcinoma	2 (2)
ER (n [%])	
Positive	89 (91)
Negative	9 (9)
PR (n [%])	
Positive	80 (82)
Negative	18 (18)
HER2 (n [%])	
Positive	14 (14)
Negative	84 (86)
Ki-67 labeling index (%)	
Median (range)	15.6 (1–78.1)
MVD (%)	
Median (range)	1.6 (0.5–4.6)

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MVD, microvessel density; PR, progesterone receptor.

TABLE 2.
Interclass Correlation Coefficients (ICC) and Pearson's Correlation Coefficient Between Parameters' Microvessel Density

	Values (Mean $\pm$ SD)	ICC	<i>r</i>	<i>p</i>
Ultrafast DCE-MRI				
A	183 $\pm$ 60	0.96 (0.89, 0.95)	0.29	0.0027
α	0.12 $\pm$ 0.05	0.80 (0.67, 0.87)	0.40	<0.0001
<i>A</i> α	24 $\pm$ 13	0.92 (0.86, 0.92)	0.51	<0.0001
AUC30	3983 $\pm$ 1513	0.97 (0.95, 0.98)	0.43	<0.0001
TIE	6.5 $\pm$ 4.0	0.94 (0.92, 0.97)	-0.32	0.0012
Standard DCE-MRI				
IER	160 $\pm$ 52	0.91 (0.86, 0.95)	0.11	0.29
SER	1.06 $\pm$ 1.03	0.96 (0.93, 0.97)	-0.03	0.74

A, the upper limit of the signal intensity; α , the rate of signal increase; *A* α , the initial slope of the kinetic curve; AUC30, integration of the kinetic curve; DCE, dynamic contrast enhanced; IER, initial enhancement rate; MRI, magnetic resonance imaging; SD, standard deviation; SER, signal enhancement ratio; TIE, time of initial enhancement.