A Prospective Evaluation of T2-Weighted First-Pass Perfusion MR Imaging In Diagnosing Breast Neoplasms

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OBJECTIVE To compare the results from breast cancer patients who undergo T2-weighted first-pass perfusion imaging after dynamic contrast-enhanced T1-weighted imaging during the same examination, and to evaluate if T2-weighted imaging can provide additional diagnostic information over that obtained with T1-weighted imaging.

METHODS Twenty-nine patients with breast lesions verified by pathology (benign 12, malignant 17) underwent MR imaging with dynamic contrast-enhanced T1-weighted imaging of the entire breasts, immediately followed by 6-sections of T2-weighted first-pass perfusion imaging of the lesions. The diagnostic indices were acquired by individual 3D T1-weighted enhancement rate criterion and the T2 signal-intensity loss rate criterion. The sensitivity and specificity were calculated and the 2 methods were compared.

RESULTS With the dynamic contrast-enhanced T1-weighted imaging, there was a significant differences between the benign and malignant breast lesions (t=2.563, P=0.016). However we found a considerable overlap between the signal intensity increase in the carcinomas and that in the benign lesions, for a sensitivity of 94% and a specificity of 25%. With T2-weighted first-pass perfusion imaging, there was a very significant difference between the benign and malignant breast lesions(t=4.777, P<0.001), and the overlap between the signal intensity decrease in the carcinomas and that of the benign lesions on the T2-weighted images was less pronounced than the overlap in the T1-weighted images, for a sensitivity of 88% and a specificity of 75%.

CONCLUSION T2-weighted first-pass perfusion imaging may help differentiate between benign and malignant breast lesions with a higher level of specificity. The combination of T1-weighted and T2-weighted imaging is feasible in a single patient examination and may improve breast MR imaging.

KEYWORDS: breast neoplasm, magnetic resonance imaging, diagnosis, differential.

The detection sensitivity of contrast-enhanced MR imaging of the breast is high, but its specificity for differencing benign from malignant lesions is variable, the main reason being that some benign lesions can also show significant contrast.[1,2] Recently, several articles[1,3,4] have suggested that using T2-weighted first-pass perfusion imaging can differentiate benign from malignant lesions. The

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objective of this article is to evaluate the diagnostic value of T2-weighted first-pass perfusion imaging.

MATERIALS AND METHODS

General materials

Patients

From March, 2001 to February, 2003, 127 patients in our hospital underwent a breast MR examination, of whom 29 patients in this study underwent both dynamic T1-weighted MR imaging and T2-weighted first-pass perfusion imaging during the same examinations, and whose pathology was confirmed by histologic examination. The patients all were females, ranging in age from 17 to 70 years (mean, 45 years). For pre-menopausal patients there were no restrictions on performing the examinations with regard to the time period within the patients' menstrual cycle.

Surgical histology

All 29 patient pathology was verified by histologic examination. There were 17 patients with carcinomas (7 with multiple lesions), 13 duct (5 with multiple lesions), 1 medullar (multiple lesions), 1 mucinous, and 2 lobular (1 with multiple lesions). The diameters of the carcinomas ranged from 0.4 to 6.5 cm (the diameter of only the biggest lesion was measured when there were multiple lesions), the mean was 2.8 cm. There were 12 patients with benign pathology, 9 fibroadenomas, 2 papillomas, and 1 chronic mastitis. The diameters of the benign lesions were 0.8~3.7 cm with an average of 1.7 cm. The ages of patients with carcinomas ranged from 31~72 with an average of 50. The patient's ages with benign lesions ranged from 17~53, and with an average of 37.

MR Imaging

All images were acquired using a 1.5 T Signa Horizon LX GE Medical Systems by employing a commercially available, dedicated, receive-only double breast coil. The patients were examined while in a prone position. Before dynamic contrast-enhanced imaging, two-dimensional sagittal T1-weighted imaging, T2-weighted imaging and axial T2-weighted imaging with fat-saturation were routinely acquired. Dynamic contrast-enhanced T1-weighted images in a sagittal plane were obtained by using a 3-dimensional fast radio-frequency spoiled gradient-echo sequence with a repetition time of 8.1 ms, an echo time of 2.1 ms, a flip angle of 60^0, a field of view of 18~20 cm, a signal acquired of 0.75, and an acquired matrix of 256 × 192. The 3-dimensional volume covered the whole breast and was obtained with 32 partitions, with corresponded to an effective section thickness of 2.7~3.0 mm. The 3-dimensional sequence was repeated continuously 16 times, with a temporal resolution of 37.8 s; during the last 10 s of the acquisition of the fifth set of images, a bolus injection of 0.1 mmol/kg body weight gadolinium-DPTA was administered through a vein in the back of the hand and was followed with a 15~20 ml flushing bolus of isotonic saline solution.

Immediately after acquisition of the image, the dynamic contrast-enhanced T1-weighted images were reviewed and 6 sections in the most contrast-enhancing part of the tumor were chosen for T2-weighted first-pass perfusion imaging. If no contrast-enhanced lesion was detected, the 6 sections were positioned in the center of the lesion according to native MR imaging or the clinical examination.

For T2-weighted first-pass perfusion imaging, a SE echo-planner sequence (2000/60, one signal acquired, 180 mm field of view, 160 × 192 acquisition matrix, 3 mm section thickness with no spaces, in the sagittal plane, with a temporal resolution of 2 s) was used. The sequence was repeated 50 times. After the first 10 repetitions, a rapid injection (3 ml/second) of 0.1 mmol/kg gadodiamide was administered immediately and was followed with 15~20 ml flushing bolus of isotonic saline. The time between the contrast agent injection for T1-weighted imaging and the contrast agent injection for T2-weighted imaging was approximately 15 minutes.

Image analysis

Quantity analysis of the images in 3-dimensional dynamic contrast-enhanced T1-weighted imaging: The

lesions' signal-intensity of the images in the dynamic contrast-enhanced T1-weighted sequence were measured using Functool function protocol of GE on the Sun-Spark ADW 4.0 work-station, and developed corresponding time-signal intensity curves (Fig.1). [3,5] The interesting areas were placed on the most enhanced parts of the lesions, and the dimensions of the interesting areas were determined according the size of lesions, but must be bigger than the images' space resolution of 1.58-mm. The early enhancement velocity of the lesions was calculated according the formula as follows: (SIC- SI) /SI × 100%. SI and SIC respectively represent the signal intensity of lesions before and after contrast material enhancement.[6]

In our study, the criteria for malignancy was the maximum signal-intensity increase rate being equal or higher than 90% within the first 75 s after the first contrast material enhancement. The following diagnosis parameters such as sensitivity, specificity, positive predictive value, and negative predictive value were calculated according to the quantity analysis of the images in the 3-dimensional dynamic contrast-enhanced T1-weighted imaging.

Quantity analysis of the images in T2- weighted first-pass perfusion imaging: Regions of interest were positioned in the different parts of the tumor and corresponding time-signal intensity curves and values were acquired by using the Functool functional-protocol on the Sun-Spark ADW 4.0 work-station (Fig.2). The maximum signal intensity loss within the first 30 s after a bolus injection was calculated according to the formula: (SI -SIC) /SI × 100% . SI and SIC respectively represent the signal-intensity of lesions before and after the second contrast material enhancement.

In our study, the criteria for malignancy was the maximum signal-intensity decrease rate being equal or bigger than 20% within the first 30 s after the second contrast material enhancement. [1,3,4] The following diagnosis parameters such as sensitivity, specificity, positive predictive value, and negative predictive value were calculated according to the quantity analysis of the images in the T2-weighted first-pass perfusion imaging.

Statistical analysis

Statistical analysis was performed by using SPSS software version 10.0. The two-different sample Student *t* test was performed for the statistical comparison of the signal-intensity increases in the group of carcinomas and in the group of benign lesions during the first post-contrast image acquisition with T1-weighted imaging ,and the second post-contrast image acquisition with T2-weighted first-pass perfusion imaging. A *P* value of 0.05 for two sides was considered to indicate a significant difference.

RESULTS

The 3-dimensional dynamic contrast-enhanced T1-weighted sequence

The mean maximum early enhancement velocities of the benign and malignant lesions on the 3-dimensional dynamic contrast-enhanced T1-weighted sequence are shown in Table 1. A mean signal intensity increase during the acquisition of the first 75 s post-contrast images of (243±101) % (95% CI:195%~291%) in the carcinomas and of (151±87)% (95% CI:102~200%) in the benign lesions. There was a significant difference of the signal-intensity increase between benign and malignant lesions (t=2.563, P=0.016), but a considerable overlap between the signal intensity increase in the benign and that in the malignant lesions was found (Fig.3).

Table 1. The mean maximum early enhancement velocity of the benign and malignant lesions on the 3-dimensional dynamic contrast-enhanced T1-weighted sequence

Histology	Cases	Increase range (%)	Mean value (%)	SD (%)
Benign	12	64-238	150.67	87.26
Malignant	17	142-344	242.82	100.57

If a threshold of a 90% signal-intensity increase during the acquisition of the first 75 s post-contrast images was chosen for the differentiation between benign and malignant lesions, 16 of 17 malignant and 3 of 12 benign lesions were classified correctly. Although the sensitivity was 94%, the specificity was

only 25%, the positive predictive value was 64%, and the negative value was 75%.

T2-weighted first-pass perfusion sequence

The mean maximum signal-intensity loss of the benign and malignant lesions is shown in Table 2. The difference in signal intensity decrease between the carcinomas and the benign lesions was highly significant (t=4.777, P<0.001). A mean maximum signal intensity loss in carcinomas was (35 ±13)% during the first 30 s after the bolus contrast agent injection (95% CI:29% -41%). The time-signal intensity loss curves present as a rapid and strong initial signal intensity loss and recovery slowly later, but can't recover to the baseline within 81 s after the contrast material is administrated (Fig.2,4). On average, the decrease in signal intensity usually occurred 22~28 s after the contrast material injection (Fig.4). A rapid and strong signal intensity loss began at 2~8 s in only 3 patients with malignant lesions, as bulky vessels were observed in these lesions (Fig.5,6). A mean maximum signal intensity loss in benign lesions was of (13±11)% during the first 30 s after the bolus contrast agent injection (95% CI: 7%, 19%). Very little overlap between the signal-intensity decrease in the benign and that in the malignant lesions was found (Fig.7).

Table 2. The mean maximum signal intensity loss of the benign and malignant lesions on the T2-weighted first-pass perfusion sequence

Histology	Cases	Increase range (%)	Mean value (%)	SD (%)
Benign	12	2-24	12.50	10.93
Malignant	17	22-48	34.53	13.05

If a threshold of a 20% signal-intensity loss during the first 30 s after the bolus contrast agent injection was chosen for the differentiation between benign and malignant lesions, 15 of 17 malignant and 9 of 12 benign lesions were classified correctly. The sensitivity was 88%, the specificity was 75%, the positive predictive value was 83%, and the negative value was 82%.

The 3 patients with benign lesions with a signal-intensity loss greater than 20% in the T2-weighted first pass perfusion sequence were 2 fibroadenoma and 1 chronic mastitis. The time-signal intensity loss curves were shown as sustained dropping, and the mean maximum signal intensity loss occurred later than 22~28 s (Fig.8).

DISCUSSION

The initial signal-intensity increase velocity in 3-dimensional dynamic contrast -enhancement sequence

As it is well known, some morphologic characteristics such as non-enhancing internal separations, spiculated borders, initial peripheral rim enhancement, and ductal enhancement are useful criteria for differentiating benign from malignant lesions,[6] but their sensitivities are not high. In addition, the shape of the time-signal intensity curves of the dynamic contrast enhancement sequence are also useful in differentiating benign from malignant lesions (Fig.1).[6-8] For example, the type of washout time-signal intensity curve correlates highly with malignant, whereas mono-phasic type clues suggest benign lesions. But the time-signal intensity curve and the related initial contrast enhancement extent is a complex reflection of several factors with perfusion and washout of the lesion vessels, such as the pre-contrast T1 value of the tumor tissue, the tumor perfusion, the tumor interstitial matrix, the capillary density and permeability of the tumor, and so on.[1,5-7] As a result, the specificity of diagnosis is low. Our study results show that there is a significant difference in the initial contrast-enhancement rate of the benign and malignant lesions (t=2.56, P=0.016). But a considerable overlap between the signal-intensity increase in the carcinomas and that in the benign lesions was found. The specificity was only 25%. In addition, menstrual cycle also influences the T1 initial enhancement.[8,9]

T2-weighted first pass perfusion imaging

On the T2-weighted first-pass perfusion imaging, a rapid and strong signal intensity loss was observed

after a bolus injection of gadolinium-based contrast agent for most breast carcinomas, which indicated high capillary perfusion. The decrease in signal intensity usually occurred 15-20 s after the contrast material injection, which corresponded to the time it takes for the contrast agent bolus to reach the mammary capillary bed.[5] In our study, the decrease in signal intensity usually occurred 22-28 s after the contrast material injection, which took place latter than that of the preliminary studies 1 and 3 (Fig.4). In our opinion, it was related to the injection position because in the preliminary studies, the injection position was the ante-cubital vein and in our study, the injection position was the superficial vein on the back of the hand. In addition, there were 3 malignant tumors in which the maximal signal intensity loss began at 2-8 s after contrast material injection (Fig.5). This phenomenon could not be explained by the capillary perfusion of the tumor and in the absence of related reports, we hypothesize that it was related to the antidromic opening of the branch vein valve, but this idea needs further investigation.

Conventional dynamic post-contrast T1-weighted images of the breast display changes in signal intensity that have a nonlinear dependence on the gadolinium concentration.[3,10] There was a great extent of overlap between the signal intensity increase in the carcinomas and that in the enhanced fibro-adenomas (Fig.3). But the changes in the relaxation rate R2* (R2* = 1/T2) are linearly proportional to the concentration of contrast agent in the tissue; therefore, changes in the T2 may be greater than changes in intensity for characterizing the contrast agent uptake by the tissue.[11] The signal-intensity loss in fast T2-weighted first-pass perfusion is specifically dependent on the changes in the micro-vascular perfusion.[12] When a paramagnetic contrast agent passed through the capillary network, the magnetic susceptibility difference between the capillaries filled with the paramagnetic agent and the surrounding tissues results in steep local gradients that extend well beyond the capillary wall. These gradients destroy phase coherence of the spins located and diffusing in their vicinity, so that a dramatic loss of a signal is seen when sequences are sensitive to magnetic coefficients. T2-weighted first-pass perfusion imaging has been shown to be suitable for evaluating cerebral micro-vascular perfusion,[13] and others have reported that it can help differentiate between benign and malignant breast lesions with a high level of specificity.[1,3,4] In the breast carcinomas, the observable perfusion effect was restricted to or most pronounced in several separate foci within the tumor, and this is consistent with the inhomogeneous tumor vascularization, as described in the "hot spot" vascularity concept.[1] No detectable-perfusion effect is present in the healthy breast parenchyma, irrespective of the phase of the menstrual cycle.[1] The results of our study showed that there was a highly significant difference in signal intensity losses between the benign and malignant lesions in the T2-weighted first-pass perfusion imaging (t=4.77, P<0.001), and the overlap between the signal-intensity decrease in the benign lesions and that in the carcinomas was very little (Fig. 7).

Investigators[10] in studies of the micro-vascular architecture of breast carcinomas have demonstrated that compared with capillaries in normal tissue, the number of capillaries and the mean capillary diameter in carcinomas increased, and their endothelium is thinner and lacking of pericytes. Furthermore the biochemical constitution of carcinomatous basal membrane causes increased permeability, and the vascular network is typified by the presence of arteriovenous shunts.[10] Compared with other tissues, increased capillary number and capillary diameter enhance the fractional volume of the intravascular space in carcinomas, and thus provide a biologic explanation for the high susceptibility effect observed at T2-weighted imaging of breast carcinomas.[4,5] Gadolinium leaks rapidly through the capillary endothelium,[3] and this leakage causes the diminution of the concentration gradient between the vessels and the surrounding tissues and also the T1 shortening effects by the paramagnet contrast agent in the extra-cellular space.[3] Therefore, this leakage counteracts the desired signal-intensity losses, and the signal -intensity did not recover to the pre-contrast

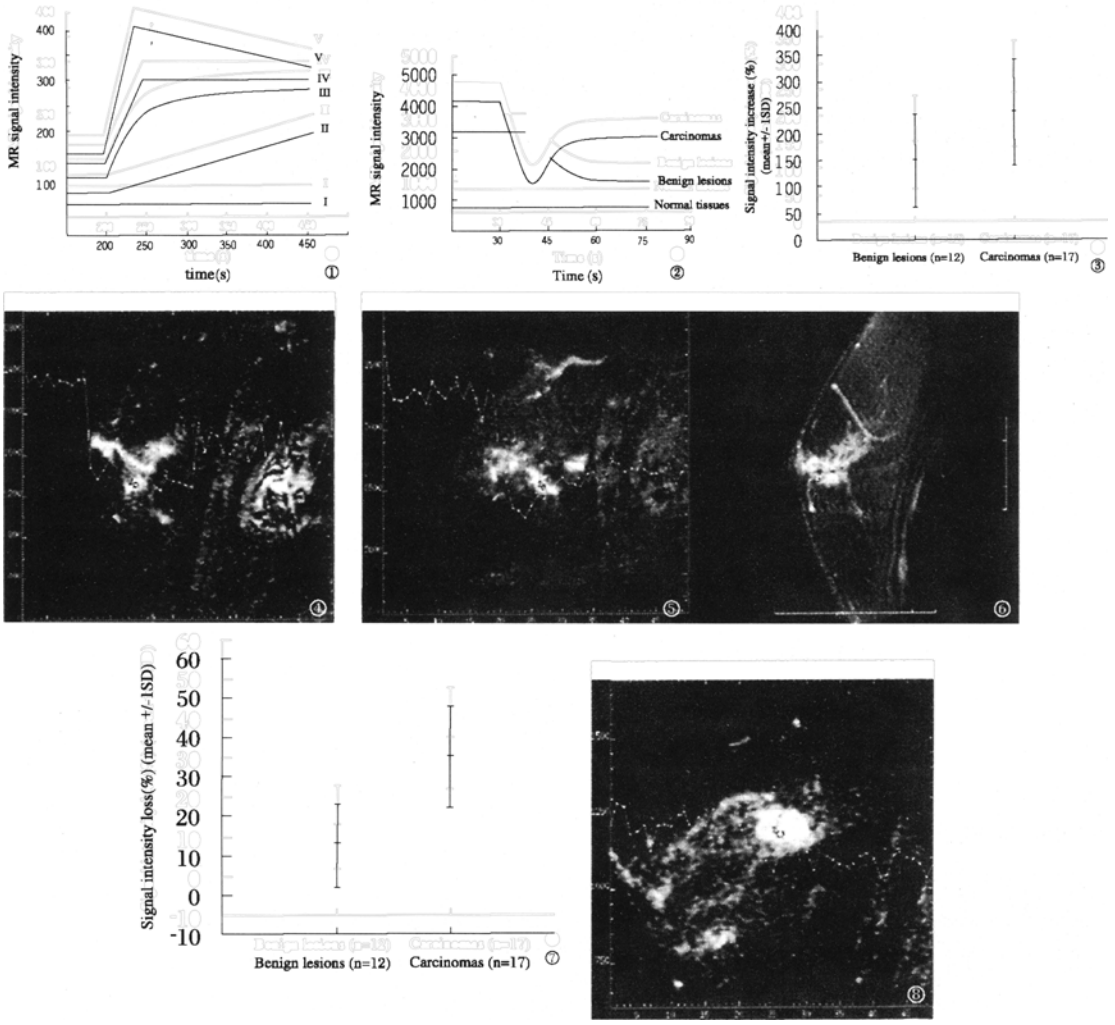

Fig.1. The classification system for the subjective evaluation of the time-signal intensity curves in three-dimensional dynamic T1-weighted contrast enhancement imaging: Type Ⅰ has essentially no enhancement; Type Ⅱ, slows sustained enhancement; type Ⅲ, rapid initial and sustained late enhancement; type Ⅳ, rapid initial and stable late enhancement (plateau); and type Ⅴ, rapid initial and decreasing late enhancement (washout). Type Ⅰ~Ⅲ (mono-phase) suggests benign lesions; type Ⅳ is suspicious of malignancy; and type Ⅴ is highly suggests malignancy.

Fig.2. The classification system for the subjective evaluation of the time-signal intensity curves in T2-weighted first-pass perfusion imaging.

Fig.3. Dynamic contrast enhanced T1-weighted imaging, with mean values ± 1SD (error bars) of the maximal signal intensity increase during the acquisition of the first post-contrast 75 s images as a percentage of the pre-contrast value. There was a considerable overlap between the benign and malignant lesions.

Fig.4. Invasive ductal carcinoma. Sagittal T2-weighted first-pass perfusion imaging shows the time signal-intensity curve with an initial signal intensity loss reaching to 45%. The time-signal intensity loss curves present as a rapid and strong initial signal intensity loss and recover slowly later, but can not recover to the precontrast baseline value.

Fig.5. Invasive ductal carcinoma. Sagittal T2-weighted first-pass perfusion imaging, the time signal intensity loss curve presented as type 2-peak, a rapid signal-intensity loss was observed early to just 2 s after contrast agent injection, reached the first peak value at 6 s after contrast agent injection, and reached the second peak value at 24 s after contrast agent injection.

Fig.6. The same patient as Fig 5. Sagittal FSE T2-weighted imaging with fat saturation, a thick vessel flow-out phenomenon was observed in the lesion (arrow).

Fig.7. T2-weighted first-pass perfusion imaging, with mean values ± 1SD (error bars) of the signal intensity loss during the first 30 s after contrast material injection as a percentage of baseline value. There was little overlap between the benign and malignant lesions.

Fig.8. Fibroadenoma. Sagittal T2-weighted first-pass perfusion imaging, a signal intensity loss was observed during the first 30 s after contrast material injection in the lesion (30 s), and the time-signal intensity curve presented as a sustained decrease.

baseline signal intensity. Sometimes the signal intensity even reverses to increase above the baseline.

A significant signal intensity loss (≥ 20%) within the first 30 s in the T2-weighted first-pass imaging was observed in carcinomas. This phenomenon was absent or small in most breast benign lesions. [1,3,4] In our study, the signal-intensity loss beyond the threshold was found only in 2 fibro-adenomas and 1 chronic mastitis. Previous study [1] suggests that the slow signal-intensity decrease in fibro-adenomas corresponds not to a true perfusion effect, but rather to a gradual diffusion of contrast agent from the intravascular compartment into the interstitial space.

Improved sensitivity of T2-weighted first-pass imaging can possibly be reached by increasing the measured T2 effects. One way of doing this is to increase the dosage of the gadolinium-based contrast agent. [11] Another way of increasing T2 effects is by prolonging the echo time in the gradient-echo sequence. [1] The recommended best scanning parameters from the previous studies [1,3,4] were as follows: TR 54 ms, TE 35 ms, and flip angle 10^0. The SE EPI sequence used in our study is more sensitive to T2 effects because it used a series of gradient-echo.

In previous studies, [1,3,4] the specificity of T2-weighted first-pass imaging was high, but its sensitivity was not optimal. In our study, the sensitivity of T2-weighted first-pass imaging was 88%, but its specificity was relatively low (75%). The resulting difference may be influenced by the following facts: (1) In our study, we used the SE EPI sequence for T2-weighted first-pass imaging, and the scanning parameters were absolutely different from that in previous studies; [1,3,4] (2) The temporal resolution of T2-weighted first-pass imaging in our study was improved down to 2 s per dynamic image, and we can acquire 6 sections of images at the same time in this sequence (in the previous study, temporal resolution was 4.8 s and only one slice of an image is obtainable); (3) The smaller number of patients in our study may be another factor resulting in much different sensitivity and specificity compared with that in previous studies.

The results of previous studies [1,3,4] as well as our present study have shown the following. In T2-weighted first-pass imaging, strong signal intensity losses still could be observed in carcinomas even though contrast medium was present in the tumor from the T1-weighted sequence performed 15 min prior to the perfusion sequence. T2-weighted first-pass perfusion imaging can be performed with good results immediately after dynamic contrast-enhanced T1-weighted imaging.

The specificity of T2-weighted first-pass perfusion imaging to differentiate between benign and malignant breast tumors was high, but its sensitivity was not optimal, and still it was limited by the small coverage and poor special resolution, so it can not be performed alone in MR diagnosis of breast diseases; T1-weighted dynamic contrast-enhanced MR imaging can diagnose breast tumors with a high sensitivity, wide area, and high special resolution, but its specificity is not optimal, and it has a higher false positive rates, which may result in unnecessary surgeries. The combination of T1-weighted dynamic contrast-enhanced MR imaging and T2-weighted first-pass perfusion imaging in our study can improve the tumor diagnosis veracity, and decrease unnecessary invasive therapy.

In conclusion, the combination of T1-weighted and T2-weighted imaging is feasible in a single patient examination and may improve breast MR imaging.

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