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FULL PAPER

The feasibility of synthetic MRI in breast cancer patients: comparison of T_2 relaxation time with multiecho spin echo T_2 mapping method

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Objective: To compare the T_2 relaxation times acquired with synthetic MRI to those of multi-echo spin-echo sequences and to evaluate the usefulness of synthetic MRI in the clinical setting.
Methods: From January 2017 to May 2017, we included 51 patients with newly diagnosed breast cancer, who underwent additional synthetic MRI and multiecho spin echo (MESE) T_2 mapping sequences. Synthetic MRI technique uses a multiecho and multidelay acquisition method for the simultaneous quantification of physical properties such as T_1 and T_2 relaxation times and proton density image map. A radiologist with 9 years of experience in breast imaging drew region of interests manually along the tumor margins on two consecutive axial sections including the center of tumor mass and in the fat tissue of contralateral breast on both synthetic T_2 map and MESE T_2 map images.
Results: The mean T_2 relaxation time of the cancer was 84.75 ms (± 15.54) by synthetic MRI and 90.35 ms (± 19.22) by MESE T_2 mapping. The mean T_2 relaxation time of the fat was 129.22 ms (± 9.53) and 102.11 ms (± 13.9), respectively. Bland–Altman analysis showed mean difference of 8.4 ms for the breast cancer and a larger mean difference of 27.8 ms for the fat tissue. Spearman's correlation test showed that there was significant positive correlation between synthetic MRI and MESE sequences for the cancer (r = 0.713, p < 0.001) and for the fat (r = 0.551, p < 0.001). The positive estrogen receptor and low histologic grade were associated with little differences between two methods (p = 0.02 and = 0.043, respectively).
Conclusion: T_2 relaxation times of breast cancer acquired with synthetic MRI showed positive correlation with those of MESE T_2 mapping. Synthetic MRI could be useful for the evaluation of tissue characteristics by simultaneous acquisition of several quantitative physical properties.
Advances in knowledge: Synthetic MRI is useful for the evaluation of T_2 relaxation times of the breast cancers.

INTRODUCTION

Breast MRI has a high sensitivity for breast cancer and it has been used as a preoperative staging method in patients with newly diagnosed breast cancer,[1–3] as a screening method in high-risk patients,[4–6] and a screening method in patients with personal history of breast cancer.[7–10]

Recently introduced SyMRI is a synthetic MRI technique which can acquire the quantitative physical properties including the longitudinal relaxation rate, transverse relaxation rate and the proton density (PD).[11,12] This technique uses a multiecho and multidelay acquisition method for the simultaneous quantification of these properties.

Several studies have reported the clinical application of synthetic MRI, especially in the brain imaging. Synthetic T_1- and T_2 weighted images and PD images were acceptable for the diagnosis of multiple sclerosis and for the differentiation of gray/white matter in pediatric patients.[13,14] Krauss et al reported that the synthetic MRI was sufficiently accurate for use in clinical practice showing slight underestimation of T_1 and T_2 relaxation times and slightly overestimation of PD values.[15]

T_2 relaxation time is dependent on the chemical component of tissue itself and we can detect the change in tissue component or any pathologic changes using the T_2 relaxation time. There are several studies reporting the clinical

implication of T_2 values in breast cancer patients. The T_2 value was significant lower in malignant breast lesions than benign lesions.[16] After neoadjuvant chemotherapy, T_2 value was significantly reduced in responders compared to non-responders.[17,18] Intratumoral T_2 high signal intensity has been reported as characteristic finding of triple negative breast cancer[19] and it was associated with the poor response to neoadjuvant chemotherapy.[20] A recent study reported that T_2* relaxation time of invasive breast cancer was significantly longer than that of ductal carcinoma *in situ*. Among invasive breast cancers, T_2* relaxation time was significantly longer in the cancers having higher histologic grades and high signal intensity on T_2 weighted image.[21]

As far as we know, there has been no research about the application of synthetic MRI to the breast imaging. The purposes of our study were to compare the T_2 relaxation times acquired with synthetic MRI to those of multiecho spin echo (MESE) sequences and to evaluate the usefulness of synthetic MRI in the clinical setting.

METHODS AND MATERIALS

Case selection

This retrospective study received Institutional Review Board approval and the requirement for informed consent was waived. From January 2017 to May 2017, 196 patients underwent pre-operative breast MRI for the newly diagnosed breast cancer. The inclusion criteria were MR images of breast cancer patients who were diagnosed as invasive ductal carcinoma, not otherwise specified and who were examined using 3 T MRI with routine protocol sequences, additional synthetic sequences and two-dimensional (2D) fast spin echo MESE sequences for T_2 mapping. We excluded 82 patients who were not scanned on 3 T MRI or not scanned with additional synthetic sequences, 24 patients who were diagnosed as other histologic types of breast cancer, 18 patients who had underwent surgical excision or vacuum-assisted breast biopsy before the breast MRI and 21 patients who had small cancers which were not visualized on both synthetic MR images and MESE T_2 mapping images. Finally, a total of 51 patients were included and evaluated in this retrospective study. Mean age of 51 patients was 52.11 years old (52.11 ± 9.78 years old).

MRI acquisition

MRI was performed using a 3 T MRI system (Discovery MR750w, GE Healthcare, Milwaukee, WI) using a 8-channel phased-array breast surface coil. Axial synthetic MR sequences and 2D MESE sequences for T_2 mapping were added to the routine clinical MR sequences. The imaging parameters of additional sequences are summarized in Table 1.

Synthetic MRI data were acquired using MAGiC (MAGnetic resonance image Compilation) multi contrast MRI technique. The MAGiC sequence is a 2D spin echo multidynamic, multiecho sequence, which is performed using an interleaved slice-selective 120 degrees saturation and multiecho acquisition. This sequence includes two echo times and four automatically calculated saturation delays. With different combinations of echo time and saturation delay, each acquisition produced eight real images and eight imaginary images per section for the quantification of tissue physical properties, like longitudinal T_1, transverse T_2 relaxation times and PD.

T_2 quantification was performed by using axial MESE sequence, with 16 echo times (TEs) from 9 to 147 ms. The T_2 map from MESE was obtained using dedicated software (Discovery 750w, T2 Map; GE Healthcare). SyMRI software could automatically calculate the T_2 values and make a T_2 map in the GE 3 T scanner console. Figure 1 shows examples of synthetic MR images and T_2 map.

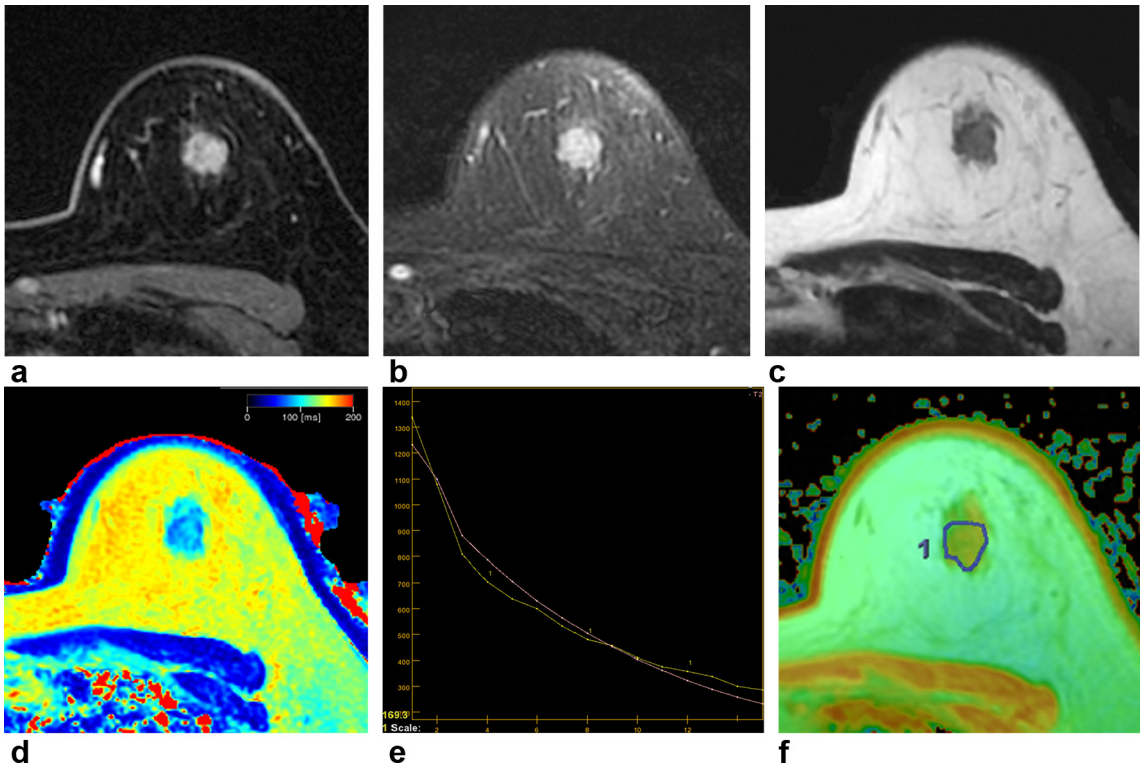
Conventional MRI protocols included axial T_2 weighted iterative decomposition of water and fat with echo asymmetry and

Table 1. MRI acquisition parameters

	Synthetic MRI	MESE T_2 mapping
TR (ms)	4000	1083
TE (ms)	2290	9,18,28,37,46,55,64,73,83,92,101,110,119,129,138,147
TI (ms)	130, 500, 1370, 2970[a]	–
Flip angle	120	90
Field of view	34	30
Matrix	320 × 256	320 × 224
Section thickness (mm)	5	5
Interslice gap (mm)	5	5
Number of sections	26	14
Echo-train length	12	1
Acceleration factor	2	1
Acquisition time (min)	5 min 32 s	8 min 2 s

TE, echo time; TI, inversion time; TR, repetition time;MESE, multiecho spin echo;
[a]Four saturation delays, automatically calculated.

Figure 1. A 47-year-old female with invasive ductal carcinoma in the left breast. Contrast-enhanced axial image (a) shows an enhancing mass with irregular shape and margin in her left breast 12 o'clock direction. T_2 weighted IDEAL fast spin echo image (b) shows an irregular mass showing high signal intensity in the same location. On synthetic T_2 weighted image (c) and synthetic T_2 map image (d), the T_2 relaxation time was 87 ms. On MESE T_2 mapping, T_2 relaxation time can be measured using 16 different TEs (e). The *x*-axis indicates TEs and *y*-axis indicates the signal intensity (e). On MESE T_2 mapping (f), the T_2 relaxation time was 77.9 ms showing difference of 9.1 ms compared to synthetic T_2 mapping. IDEAL, iterative decomposition of water and fat with echo asymmetry and least squares estimation; MESE, multi echo spin echo; TE, echo time.



least squares estimation fast spin echo image, axial short-time inversion recovery combination diffusion-weighted image and axial three-dimensional dynamic contrast enhanced T_2 weighted images.

Image analysis

Synthetic T_2- and T_2 weighted images were generated from multidynamic, multiecho data using a MAGiC, which is a customized version of synthetic MR's SyMRI software. Using both T_1 and T_2 maps, one radiologist with 9 years of experience in breast imaging drew region of interests (ROIs) manually along the tumor margins on two consecutive axial sections including the center of tumor mass. In each ROI, T_2 relaxation time was automatically calculated and we used the mean value of two ROIs. For the measurement of T_2 value of fat tissue, the radiologist drew an ROI in the subcutaneous fat of contralateral breast.

The longitudinal T_2 relaxation time from MESE data was calculated using Functool software on Advantage Workstation (v. 4.5; General Electric Healthcare, Milwaukee, WI). The same radiologist drew ROIs manually with same manner and T_2 relaxation time was automatically obtained.

Data analysis

Patients' medical records were reviewed to collect clinical and pathological data. Hormone receptor positivity was defined as estrogen receptor and/or progesterone receptor positivity (≥10% nuclear staining) according to immunohistochemistry (IHC). Human epidermal growth factor receptor-2 (HER2) positivity was defined as an IHC HER2 score of 3 + or gene amplification by fluorescence *in situ* hybridization in tumors with an IHC HER2 score of 2+.

Black nuclear grade (nuclear Grade 1, poorly differentiated; Grade 2, moderately differentiated; and Grade 3, well differentiated) and modified Bloom–Richardson histological grade (histological Grade 1, well differentiated; Grade 2, moderately differentiated; and Grade 3, poorly differentiated) were also reviewed. For dichotomous-dependent variables, nuclear grade was classified as high (Grade 1) *vs* low (Grades 2 and 3) and histological grade as low (Grades 1 and 2) *vs* high (Grade 3).

Ki-67 expression was estimated as the percentage of tumor cells positively stained by the antibody. Ki-67 <14% was considered low and negative and Ki-67 ≥14% was considered high and positive.

Table 2. Comparison of T_2 relaxation time acquired by synthetic MRI and MESE T_2 mapping in the breast cancer and fat tissue

	T_2 relaxation time acquired with synthetic MRI (ms)	T_2 relaxation time acquired with MESE T_2 mapping (ms)	Difference between synthetic MRI and MESE T_2 mapping (ms)
Cancer (n = 51)			
Mean ± SD	84.75 ± 15.54	90.35 ± 19.22	8.41 ± 5.8
Min ~ Max	56 ~ 134	46.4 ~ 136.1	0.2 ~ 23.2
Fat (n = 51)			
Mean ± SD	129.22 ± 9.53	102.11 ± 13.9	27.84 ± 12.96
Min ~ Max	107 ~ 146	70.2 ~ 142.5	4 ~ 54.1

MESE, multiecho spin echo; SD, standard deviation;

Statistical analysis

To evaluate the difference of T_2 values between synthetic MRI and MESE T_2 mapping, we generated Bland–Altman plots. Spearman's correlation test was performed for the evaluation of correlations between T_2 values obtained with synthetic MRI and MESE T_2 mapping. Patients with lower differences than mean difference value were classified as little difference group and patients with higher differences than mean difference value were as large difference group. χ^2 test was used for the evaluation of relationships between the histopathologic factors and these two groups.

We used the SPSS 19.0 statistical software package (IBM, Armonk), with a value of $p < 0.05$ considered to be significant.

RESULTS

The mean T_2 relaxation time of the cancer was 84.75 ms (±15.54) by synthetic MRI and 90.35 ms (±19.22) by MESE T_2 mapping (Table 2). The mean T_2 relaxation time of the fat was 129.22 (±9.53) and 102.11 ms (±13.9), respectively. Bland–Altman analysis showed mean difference of 8.4 ms and 95% limits of agreement (−3.0 and 19.8 ms) for the breast cancer and a larger mean difference of 27.8 ms and 95% limits of agreement (2.4 and 53.2 ms) for the fat tissue of breast (Figure 2).

Spearman's correlation test showed that there was significant positive correlation between synthetic MRI and MESE sequences for the cancer (r = 0.713, $p < 0.001$) and for the fat (r = 0.551, $p < 0.001$).

We analyzed which histopathological factors were associated with the differences in T_2 relaxation time of the cancer between synthetic MRI and MESE T_2 mapping. The status of estrogen receptor was significantly correlated with the degree of differences (p = 0.02) and the presence of estrogen receptor was more frequently observed in the group with little difference than the group with large difference. The histologic grade was also associated with the degree of differences (p = 0.043) and the low histologic grade was more frequently observed in the group with little difference. Other histologic factors including nuclear grade, the progesterone receptor, HER2 and Ki-67 were not associated with the degree of difference (Table 3). Representative case is shown in Figure 1.

DISCUSSION

Synthetic MRI is a promising acceleration MRI technique and radiologists can review multi-contrast images including T_1-, T_2-, PD-weighted images and inversion recovery images with one acquisition. Recently, the feasibility of synthetic MRI has been reported in the neuroimaging and musculoskeletal imaging.[13–15,22–24] In the study of Lee et al[14] the quality of T_1- and T_2 weighted images were within the diagnostically acceptable range. The lesion conspicuity and differentiation of gray/white matter was comparable or better in synthetic T_1-and T_2 weighted images. In the study of Yi et al[24] the diagnostic accuracy of synthetic MRI was similar to the conventional MRI for the diagnosis of cartilage lesions and tears of the cruciate ligament or meniscus.

Figure 2. Bland–Altman plots of T_2 relaxation times of breast cancer (a) and fat (b). The y- and x-axes indicate the difference and average between synthetic MR and MESE sequences, respectively. The blue lines show the means of differences, while the 95% confidence intervals are denoted by the pairs of dotted red lines. MESE, multi echo spin echo.

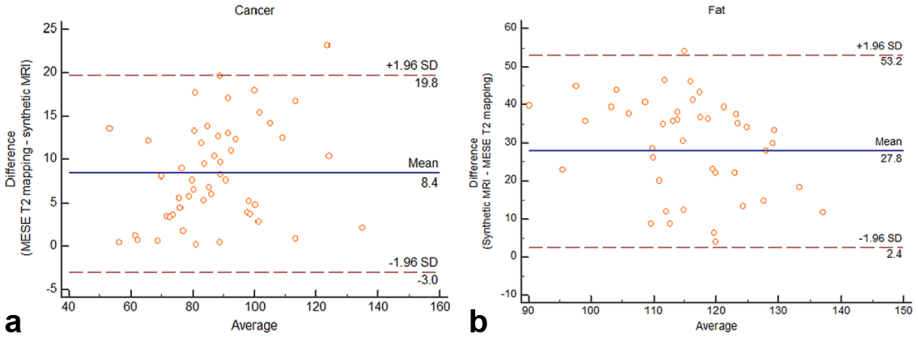


Table 3. Histopathologic factors associated with the differences between synthetic MRI and MESE T_2 mapping

	Little difference between synthetic MRI and MESE T_2 mapping (n = 28)	Large difference between synthetic MRI and MESE T_2 mapping (n = 23)	p-value
Histologic grade			0.043[a]
Low (n = 38)	24 (85.7%)	14 (60.9%)	
High (n = 13)	4 (14.3%)	9 (39.1%)	
Nuclear grade			0.288
Low (n = 37)	22 (78.6%)	15 (65.2%)	
High (n = 14)	6 (21.4%)	8 (34.8%)	
Estrogen receptor			0.02[a]
Positive (n = 37)	24 (85.7%)	13 (56.5%)	
Negative (n = 14)	4 (14.3%)	10 (43.5%)	
Progesterone receptor			0.603
Positive (n = 33)	19 (67.9%)	14 (60.9%)	
Negative (n = 18)	9 (32.1%)	9 (39.1%)	
HER2			0.577
Positive (n = 13)	8 (28.6%)	5 (21.7%)	
Negative (n = 38)	20 (71.4%)	18 (78.3%)	
Ki-67[b]			0.292
Low (n = 13)	10 (43.5%)	3 (23.1%)	
High (n = 23)	13 (56.5%)	10 (76.9%)	

MESE, multiecho spin echo;
[a]Statistically significant
[b]The result of Ki-67 index was available in 36 patients.

In the current study, we applied synthetic MRI to the breast imaging and as far as we know, this is the first report in the breast imaging. Our results revealed that mean T_2 value of breast cancer was 84.75 ms by synthetic MRI and 90.35 ms by MESE T_2 mapping. Previous studies also reported similar T_2 values to ours and it ranged from 75 to 82.7 ms.[16–18]

There are several studies reporting the clinical implication of T_2 and T_2* values of the breast cancer. In the study of Liu et al, the mean T_2 relaxation time of malignant breast lesion was lower than that of benign lesions, 82.7 *vs* 95.5 ms.[16] They speculated that large size of cancer cells with abundant cytoplasm, lymphocyte/plasma cell infiltrations and necrotic materials in the intercellular space might cause reduced extracellular space and reduced free water content. This could account for the shorter T_2 relaxation time in malignant breast lesions. Several studies reported the T_2 and T_2* values of breast cancer. Previous studies revealed that the mean T_2 relaxation time of breast cancer had significantly decreased after neoadjuvant chemotherapy and T_2 value of responders was significantly shorter than that of non-responders.[17,18] In the study of Seo et al,[21] the T_2* relaxation time of invasive breast cancer was significantly longer than that of ductal carcinoma *in situ*. Among invasive breast cancers, T_2* relaxation time was significantly longer in the cancers with higher histologic grades and high signal intensity on T_2 weighted imaging.

As shown in Table 3, the relatively larger discrepancy above the mean difference was frequently observed in breast cancers with negative estrogen receptor and high histologic grade. We speculate that negative estrogen receptor and high histologic grade are associated with more aggressive form and more aggressive cancer might have more heterogeneous texture in its internal components. Thus, heterogeneous tissue characteristics could cause larger discrepancies in T_2 values between synthetic MRI and MESE T_2 mapping. Further research should be performed which tissue characteristics are associated with different T_2 values and discrepancies between two sequences.

In our results, the mean T_2 relaxation time of the fat was 129.22 ms with synthetic MRI and 102.11 ms with MESE T_2 mapping showing a large mean difference of 27.8 ms. Many studies have reported the T_2 relaxation time of the fat at 3 T with various measurement methods. There is a big dispersion of the reported T_2 relaxation times of the fat ranging from 41 to 371 ms.[25–29] In the study of Rakow-Penner et al, T_2 relaxation time of the fat was 52.96 ms at 3 T with TEs of 20 and 100 ms.[26] However, in the study of Edden et al,[25] T_2 value of the fat was 154 ms showing higher T_2 value compared to a previous study. They proposed that one likely reason of the higher T_2 relaxation time was the use of a 32-echo readout compared with the single spin echo with TEs of 20 and 100 ms. Our synthetic MRI used similar TR and TE with the study by Rakow-Penner et al,[26] but the T_2 values of

our study were much higer. The mechanism of synthetic MRI is very different from the MESE T_2 mapping method for the acquisition of T_2 values. In synthetic MRI, it used two different TEs and four different TI and it could make eight different kinds of images with different combination of each TE and TI. Thus, using eight images, SyMRI software automatically calculate the T_2 values by the Bloch equation. Therefore, we speculate that this different mechanism of T_2 value acquisition could be the main cause of the different T_2 values.

Several factors including noise, partial volume effect and B1 effects could cause systematic errors and compromise the accuracy of the T_2 relaxation times.[30] Furthermore, the MAGiC sequences are highly optimized for the brain tissue and the TEs are chosen automatically (22 and 90 ms). Therefore, the signal intensity of the fat with very long T_2 values could be measured as inaccurate values.

There are many limitations in our study. First, we measured the T_2 relaxation time of the cancer in two consecutive axial planes showing the largest diameter not in the whole tumor. Therefore, the T_2 value in our study did not represent the value of whole tumor. Second, some patients were excluded for the analysis because the cancer size was small and was not visualized on synthetic T_1- and T_2 weighted images. This could cause a selection bias. Third, the sample size was relatively small to draw a solid conclusion. A larger study is needed to validate these results. Fourth, we did not evaluate the clinical implication of T_2 relaxation time of the cancer, because the purpose of this study was only to compare the T_2 values of synthetic MRI and MESE sequences. Further study should be performed about the effect of T_2 relaxation time on the patients' prognosis.

In conclusion, T_2 relaxation times of the breast cancer acquired with synthetic MRI showed positive correlation with those of MESE T_2 mapping with acceptable difference range. However, the difference of T_2 relaxation times in the fat was large in several cases and the adjustment of acquisition parameters could decrease the difference between two methods. Synthetic MRI could be useful for the evaluation of tissue characteristics by simultaneous acquisition of several quantitative physical properties.

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