Feasibility study of 2D Dixon-Magnetic Resonance Fingerprinting (MRF) of breast cancer

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ABSTRACT

Purpose: Application of MRF to evaluate the feasibility of 2D Dixon blurring-corrected MRF (2Ddb-cMRF) to differentiate breast cancer (BC) from normal fibroglandular tissue (FGT).

Methods: Prospective study on 14 patients with unilateral BC on 1.5 T system/axial T2w-TSE sequence, 2Ddb-cMRF, B1 map, dynamic contrast-enhanced (DCE) T1-w GE-series. Mean T1 and T2 values and standard deviations were computed in the BC-/FGT-ROI on pre-/post-contrast MRF-maps and their differences were tested by two-tailed student t-test.

Accuracy and repeatability of MRF were evaluated in a phantom experiment with gelatin with Primovist surrounded by fat.

The T1 reduction between pre-/post-contrast MRF-maps was correlated to DCE signal enhancement in the last image post-contrast through the Pearson’s correlation coefficient (r) and for the phantom validation experiment through the Lin’s concordance correlation coefficient (CCC).

Visual evaluation of cancers on MRF-Maps was performed by rating each MRF-Map by 3 radiologists.

Results: T1- and T2-MRF values of BC vs. FGT were for T1 and T2 pre-contrast respectively: 1147 ± 1 ms vs. 1052 ± 9 ms (p = 0.007) and 83 ± 1 ms vs. 73 ± 1 ms (p = 0.03); post-contrast respectively: 367.3 ± 121.5 ms vs. 690.3 ± 200.3 ms (p = 0.0005) and 76.9 ± 11.5 ms vs. 69.8 ± 15.2 ms (p = 0.12). r was positive (FGT r = 0.7; BC r = 0.6). CCC was 0.999 for T1 and 0.994 for T2. In the T1- and T2-MRF-Maps before contrast respectively (7,7,8)/14 and (5,9,8)/14 cancers were visible to the readers; afterwards, (11,12,12)/14 and (5,6,11)/14.

Conclusions: MRF is promising for distinction between BC and FGT as well as for analyzing pre-/post-contrast T1 changes. However, its potential for differential diagnosis warrants further studies.

1. Introduction

Dynamic contrast enhanced (DCE)-MRI is currently the most sensitive diagnostic tool for the detection of breast cancer [1–6]. However its cost, the use of a contrast agent and the difficulties in interpreting the images for non-experienced radiologists limit the use of breast MRI.

A tool which promises to solve some these problems is quantitative MRI (qMRI). qMRI allows the reconstruction of parametric maps, assigning to every voxel a quantitative tissue property. These intrinsic tissue properties accessible by MRI are the tissue relaxation times T1 and T2, the proton density, the diffusion coefficient and many more. These data are unique because they provide an absolute, quantitative value.
independently form the subjective interpretation of the image, which inevitably relies on the experience of the radiologist, and it could be used for the further development of artificial intelligence in radiology. Moreover they can be obtained without the use of contrast material, which would aid to overcome the first two problems mentioned above and could be helpful for the development of new native protocols in the future. In the field of breast imaging the most widely used quantitative parameter is the ADC value, obtained through a DWI-sequence (7–12). Another interesting qMRI method that has been applied in the context of breast imaging is represented by T1 and T2 relaxometry (13–18); however, relaxometry sequences are often characterized by long acquisition times. Faster multiparametric relaxometry techniques, which permit simultaneous production of T1 and T2 maps, are for example Synthetic MRI (SyMRI) (19,20) or Magnetic Resonance Fingerprinting (MRF) (21,22).

MRF consists of three phases: (i) the acquisition of an image series with variable sequence parameters, to which different tissues respond with distinctive signal evolutions, (ii) the simulation of a dictionary of possible signal evolutions, and (iii) the pattern matching which identifies for the acquired signal evolution in a voxel the best matching dictionary entry and hence its T1 and T2 value. The use of fingerprinting to differentiate cancer from healthy tissue in breast has been discussed by Chen et al. (22), who tested a 3D MRF technique with fat suppression, and the repeatability and reproducibility of this method has been proved successfully by Panda et al. (23). Recently Nolte et al. (24) developed an alternative MRF approach in which they examined 2D MRF with Dixon water-fat separation and a spiral blurring correction in the female breast, validating it in both phantom and healthy volunteers. The blurring correction allowed for a reduction in bias in the quantitative T1 and T2 values due to the blurring of fat into water as well as an improvement in clarity of fat-water interfaces. Moreover, the Dixon water-fat separation allows for separate evaluation of water and fat data without the use for fat suppression pulses.

The purpose of this study is to evaluate the feasibility of 2D blurring-corrected MRF for breast cancer diagnosis, to investigate whether quantitative features of breast cancer differ from those of normal fibroglandular tissue (FGT) and to assess whether cancers are detectable on the reconstructed MRF parameter maps.

2. Materials and methods

2.1. Study design

This feasibility study includes phantom and in vivo measurements. It was performed in accordance with institutional review board requirements and was conducted over a period of 2 months in a university hospital.

2.2. MR-Fingerprinting (MRF)

The MRF sequence acquired 500 undersampled images after an initial 180° inversion pulse, employing the flip angle excitation pattern described by Sommer et al. (25) with 500 variable flip angles between 0° and 60°. The sequence is based on a gradient echo (GRE) sequence with gradient spoiling (4-2z over the slice). 3 MRF trains were sequentially acquired, using in- and out-of-phase echo times (TE1/TE2/TE3) = (4.6/6.9/9.2) ms for the (first/second/third) MRF train, respectively, and a constant TR = 21 ms for all MRF trains. In between MRF trains, a delay of 7.5 ms was set to ensure relaxation of the magnetization to equilibrium. A spiral interleaves (7 ms acquisition time) was rotated between consecutive TR intervals by 14.4° to acquire k-space data with an undersampling factor of R = 25. At a slice thickness of 3 mm, acquiring 2 interleaves/image yielded an acceptable homogeneity of the parametric maps and was hence employed throughout the study. A separation of the MRF data into aqueous and fatty tissue fingerprints by a three-point Dixon approach as well as spiral off-resonance deblurring was performed as described by Nolte et al. (24). The MRF dictionary contained simulated signals with T1 values ranging between 5 and 2000 ms (between 5 and 200 ms in steps of 5 ms, between 210 and 500 ms in steps of 10 ms, between 520 and 2000 ms in steps of 20 ms). T2 values ranged from 2 to 500 ms (between 2 and 100 ms in steps of 2 ms, between 105 and 200 ms in steps of 5 ms, between 210 and 500 ms in steps of 10 ms). B1 correction factors, included into the signal model as a constant multiplicative factor to all flip angles, ranged from 0.7 to 1.3 in steps of 0.1. Parametric maps (MRF-maps) were reconstructed offline by inner product (IP) matching after performing water-fat separation and spiral deblurring. The IP is a value between 0 and 1, where 1 indicates a perfect match between measured and simulated signal evolution. For every voxel, B1 correction was carried out by restricting the matching process to the subset of simulated signal evolutions that had the closest B1 correction factor to the measured one, i.e., that was read from the B1 map. The subsequent analysis of T1 and T2 values was performed solely on the ‘water’ dataset to avoid partial volume artifacts of fat, i.e., fatty tissue fingerprints were not analyzed. To discard non-valid voxels that predominantly contain noise, the temporal mean of the water MRF dataset Iw,mean and of the combined dataset Iwf,mean were calculated and voxels for which Iw, mean (x,y) < 0.3 • max (Iwf,mean) were discarded.

2.3. Phantom experiments

2.3.1. MRI acquisition

The MRF acquisition and post-processing were validated in a phantom consisting of 8 vials with mixtures of gelatin and Primovist in different concentrations surrounded by lard (pig fat). A test-retest experiment with the MRF-sequence as well as a comparison against inversion recovery T1 mapping (10 inversion times T1 between 100 and 5000 ms, TR/TE = (10,000/3.6) ms, duration 1 min 40 s per TI) and multi-echo spin echo T2 mapping (30 echoes with a spacing of 35 ms, TR = 10,000 ms, duration 25 min 40 ms) were conducted.

2.3.2. Data analysis

For the phantom experiment, mean values within the phantom vials were calculated for the MRF-maps as well as for the reference maps.

2.3.3. Statistical analysis

Lin’s concordance correlation coefficient (CCC) was calculated using Excel.

2.4. In vivo experiments

2.4.1. Patient cohort

From February 2019 to March 2019, a total of 17 women participated in our study. We included consecutive women with a known, histologically proven breast cancer, who underwent breast MRI for staging purposes, and who consented to participate. Exclusion criteria were presence of a biopsy clip inside the cancer and previous contralateral mastectomy.

2.4.2. MRI acquisition

Each patient received a bilateral breast examination on a 1.5 Tesla MR System (Philips Achieva, Best, The Netherlands) with a 4-channel breast coil (Invivo, Orlando, Florida) in prone position and with immobilization of the breast in the craniocaudal (CC)-direction by the use of two parallel panels (Noras, Würzburg, Germany). All the patients received a standard DCE-MRI protocol, consisting of an axial T2-Turbo spin-echo (TSE) and a coronal T1-TSE sequence, followed by a dynamic DCE-T1-GRE sequence which acquired one image before and four images after the application of 0.1 mmol/kg BW Gadobutrol (Bayer AG, Germany). The MRF sequence was performed before and after the dynamic sequence. The 2D blurring-corrected MRF is a two-dimensional
technique, which so far allows the analysis of one pre-selected slice only. Therefore, the slice where the lesion was best evident was selected on the basis of the pre-contrast, anatomic/structural T2-TSE images. The location of the tumor was identified on pre-contrast images, which was also compared with the patient’s existing ultrasound and mammography images. The MRF sequence was then performed only on this pre-selected slice. In addition to the MRF scan, a B1 map with voxel size and location exactly matching with the MRF scan was acquired using actual flip angle imaging technique [26]. This was done to correct for in-plane transmit (B1) field inhomogeneities (c.f. paragraph 2 of Material and Methods) that are known to be important in breast MRI [27]. Details of the standard breast MRI protocol are provided in Table 1.

2.4.3. Data analysis

For the in vivo experiment, the tumor ROI was delineated on the DCE subtraction images by a radiologist with 1.5 years of experience in breast diagnostic that correspond to the MRF slice using dedicated software (Intellispace, Philips, The Netherlands) and interpolated onto the MRF voxel grid (Matlab, The Mathworks, Massachusetts). The FGT ROI comprised all valid voxels inside the contralateral, healthy breast. Within the tumor and normal FGT ROI, the mean and standard deviation of T1 and T2 values, acquired pre- and post-contrast injection, were calculated using MATLAB. Enhancement rates of the breast cancer and the normal fibroglandular tissue were evaluated by using the same ROI on the DCE images. Enhancement rates in % were calculated, considering the relative intensity increase of the last post-contrast acquisition compared to the pre-contrast image.

2.4.4. Visual assessment

The visual assessment of cancers on T1- and T2-MRF-maps for each patient, acquired before and after contrast injection, was performed independently by 3 radiologists (X1–X3) with 4, 6 and more than 10 years of experience. Readers were blinded to the anamnesis of the patients and to the DCE-MRI sequences and had to evaluate one MRF-map at a time in this sequence: T1-MRF map before contrast injection, T2-MRF map before contrast injection, T1-MRF after contrast injection and at the end T2-MRF map after contrast injection. One patient per time was presented. After the visualization of each single MRF-map, the radiologist was asked to assess on which breast the lesion is and then to point exactly at the lesion with an arrow. To that purpose, T1- and T2-MRF-maps were generated by discarding all voxels for which Iw,mean (x,y) < 0.05 • max(Iw,mean) or IP(x,y) < 0.6. The answers of the radiologists were then compared to the acquired DCE-MRI images, which were used as gold standard. A value of 1 was assigned if the localization of the cancer was detectable on the MRF-maps and of –1 if not. If the radiologist could identify the breast in which the cancer was, but not the lesion, a value of – 1 was equally assigned.

2.4.5. Statistical analysis

The differences between the quantitative mean values of T1 and T2 breast cancer vs. FGT, acquired before and after injection of contrast material, were tested for significance by two tailed student t-tests. A p-value less than 0.05 was considered statistically significant. Pearson’s correlation coefficient (r) between the decrease of T1-relaxation time with the enhancement rate in DCE-MRI was calculated considering the last dynamic DCE-MRI image post contrast. All statistical analyses were performed using Excel.

3. Results

3.1. Patient cohort

14 Patients (mean age 56, age range 42–72 years) with a known, unilateral breast cancer were analyzed. Out of 17 data sets that we acquired, 3 had to be discarded because the cancer was not included in the MRF section. The type of cancer was: No special type (NST) in 79% (11/14), tubular invasive in 7% (1/14); ductal carcinoma in situ (DCIS) in 14% (2/14). Further details on the characteristics of cancers are provided in Table 2.

3.2. Phantom validation

Fig. 1 shows the results of the phantom validation experiment. Between MRF and IR/MESE reference measurements, Lin’s CCC is calculated as 0.999 for T1 and 0.994 for T2, indicating good correspondence between MRF and the reference methods. The MRF test-retest experiment furthermore indicates stability of the MRF measurement at the selected sequence parameters in the phantom experiment.

3.3. Pre-contrast T1 and T2 values of cancerous vs. normal fibroglandular tissue

The T1 mean value of cancerous tissue vs. that of normal fibroglandular tissue is 1146.9 ± 129.1 ms vs. 1051.6 ± 95.4 ms (p = 0.007). The T2 mean value of cancerous tissue vs. that of normal fibroglandular is 83.8 ± 14.4 ms vs. 72.7 ± 12.4 ms (p = 0.03) (Table 2).

| Table 1 |
|---|

| Details of Study Protocol Pulse-Sequence Parameters |
|---|
| **Hardware** | Description |
| Type of magnet | 1.5 T Intera (Philips Medical Systems, Best, the Netherlands) |
| Surface coil | Dedicated multielement four-channel breast coil (inVivo, Gainesville, FL) |
| Breast immobilization | Fixation plates; fixation in cranio-caudal direction (Naras Medical Systems, Hoechberg, Germany) |
| Type of contrast agent | Gadobutrol (Bayer Healthcare, Leverkusen, Germany) |
| Done of contrast agent | 0.1 mmol per kg body weight |
| Injection protocol | 3 ml per second power injection, followed by 20 ml saline |

| Pulse-Sequence Protocol | Fingerprinting | B1 map | T2-Weighted TSE | T1-weighted GE (Dynamic Series) |
|---|---|---|---|---|
| **Parameter** | | | | |
| TR/TE | 20/(4.6/6.9/9.2) ms | 60/1.3 ms | 3954/110 ms | 253/4.5 ms |
| Flip angle | Varying between 0° and 60° | 90° | Axial | Axial |
| Orientation | Axial | Axial | Axial | Axial |
| Acquisition matrix | 256 × 256 | 128 × 128 | 512 × 510 | 512 × 512 |
| Field of view | 430 mm | 430 mm | 380 mm | 380 mm |
| No. of sections | 3 | 11 | 25–31 | |
| Section thickness | 3 mm | 3 mm | 3 mm | 3 mm |
| No. of dynamics | NA | NA | NA | 1 precontrast; 4 postcontrast |
| Acquisition time | 108 s | 4 min 23 s | 230 s | 80 s (per dynamic) |
Table 2
Cancer characteristics in DCE-MRI, their histological findings and MRF T1 and T2 quantitative values pre- and post-contrast injection for both cancers (BC) and for normal fibroglandular tissue (FGT). (NST: No special type; DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; PR: progesterone receptor; HER2neu: human epidermal growth factor receptor 2; BC: breast cancer; FGT: fibroglandular tissue).

| Patient | Age | DCE-MRI | MRI-ACR | Size in mm | Visual kinetics | T2-signal intensity | Cancer | ER/PR/HER2neu | Ki67 % | MRF pre contrast | MRF post contrast |
|---------|-----|---------|---------|------------|----------------|---------------------|--------|---------------|--------|----------------|------------------|
|         |     |         |         |            |                |                     |        |               |        | T1/ms BC        | T1/ms FGT        | T2/ms BC     | T2/ms FGT     | T1/ms BC | T1/ms FGT | T2/ms BC | T2/ms FGT |
| 1       | 42  | 2       | 26 × 15 | Wash out   | Hypointense   | NST                | +/-/- | +/-/-         | +/-/- | 40-50 %        | +/-/-           | 1238 ± 56   | 1161 ± 87   | 87 ± 10 | 66 ± 17 | 335 ± 34 | 733 ± 66 |
| 2       | 54  | 4       | 14 × 10 | Wash out   | Hypointense   | Tubular            | +/-/- | +/-/-         | +/-/- | 14 %           | +/-/-           | 982 ± 98   | 1074 ± 107 | 66 ± 17 | 66 ± 17 | 342 ± 77 | 771 ± 139|
| 3       | 48  | 2       | 18 × 15 | Wash out   | Hyperintense  | NST                | +/-/- | +/-/-         | +/-/- | 95 %           | +/-/-           | 1324 ± 132 | 1164 ± 1314 | 96 ± 12 | 83 ± 15 | 445 ± 45 | 968 ± 133|
| 4       | 63  | 1       | 38 × 16 | Wash out   | Hypointense   | NST                | +/-/- | +/-/-         | +/-/- | 70 %           | +/-/-           | 1213 ± 1213 | 902 ± 107 | 71 ± 10 | 52 ± 19 | 301 ± 301 | 694 ± 117|
| 5       | 64  | 1       | 33 × 20 | Wash out   | Hyperintense  | NST                | +/-/- | +/-/-         | +/-/- | 40-50 %        | +/-/-           | 1099 ± 1099 | 944 ± 240 | 84 ± 16 | 81 ± 34 | 478 ± 478 | 853 ± 236|
| 6       | 68  | 1       | 73 × 11 | Plateau    | Isointense    | NST                | +/-/- | +/-/-         | +/-/- | +/-/-          | +/-/-           | 1139 ± 1139 | 959 ± 61   | 100 ± 9  | 66 ± 12 | 284 ± 284 | 756 ± 86 |
| 7       | 71  | 1       | 19 × 11 | Wash out   | Hypointense   | NST                | +/-/- | +/-/-         | +/-/- | 5-15 %         | +/-/-           | 1051 ± 1051 | 1075 ± 97  | 73 ± 7   | 78 ± 21 | 283 ± 283 | 956 ± 112|
| 8       | 48  | 3       | 22 × 20 | Wash out   | Hyperintense  | NST                | +/-/- | +/-/-         | +/-/- | Up to 20 %     | +/-/-           | 1271 ± 1271 | 1172 ± 92  | 89 ± 9   | 75 ± 15 | 521 ± 521 | 588 ± 86 |
| 9       | 72  | 2       | 20 × 19 | Progressive | Isointense   | DCIS               | +/-/- | +/-/-         | +/-/- | 71 %          | +/-/-           | 1330 ± 1330 | 1020 ± 0   | 113 ± 5  | 96 ± 0   | 677 ± 677 | 289 ± 289|
| 10      | 50  | 2       | 32 × 15 | Plateau    | Hypointense   | NST lobular        | +/-/- | +/-/-         | +/-/- | Up to 2 %      | +/-/-           | 1011 ± 1011 | 1176 ± 93  | 73 ± 18  | 75 ± 28 | 304 ± 304 | 782 ± 160|
| 11      | 64  | 2       | 26 × 20 | Wash out   | Hyperintense  | NST                | +/-/- | +/-/-         | +/-/- | 30 %           | +/-/-           | 1189 ± 1189 | 962 ± 49   | 77 ± 9   | 61 ± 17  | 232 ± 232 | 654 ± 65 |
| 12      | 57  | 2       | 40 × 14 | Wash out   | Hypointense   | NST                | +/-/- | +/-/-         | +/-/- | Up to 15 %     | +/-/-           | 903 ± 903   | 1009 ± 1009 | 68 ± 10  | 77 ± 14 | 273 ± 273 | 331 ± 60 |
| 13      | 44  | 3       | 20 × 8  | Progressive | Isointense   | DCIS LIN           | +/-/- | +/-/-        | +/-/- | 111 ± 111     | +/-/-           | 1207 ± 1207 | 1120 ± 104 | 96 ± 11  | 70 ± 14 | 320 ± 320 | 721 ± 136|
| 14      | 47  | 1       | 19 × 11 | Wash out   | Isointense    | NST                | +/-/- | +/-/-         | +/-/- | 3 %            | +/-/-           | 1099 ± 1099 | 986 ± 90  | 68 ± 15  | 51 ± 11 | 347 ± 347 | 567 ± 124|
3.4. Post-contrast T1 and T2 values of cancerous vs. normal fibroglandular tissue

After contrast injection, the T1 mean value of cancerous tissue vs. that of normal fibroglandular tissue is 367.3 ± 121.5 ms vs. 690.3 ± 200.3 ms (p = 0.0005). The post contrast T2 mean value of cancerous tissue vs. that of normal fibroglandular tissue is 76.9 ± 11.5 ms vs. 69.8 ± 15.2 ms (p = 0.12). All mean values and standard deviations of T1- and T2-MRF-maps before and after contrast injection are provided in Tables 2 and 3.

3.5. Correlation of the decrease of T1 relaxation time and the increase of signal intensity in DCE-MRI

T1 relaxation time of cancer in MRF shows a mean decrease of 68 ± 10 % in cancers and a mean decrease of 34 ± 19 % in normal fibroglandular tissue. In DCE-MRI the mean increase in the enhancement rate in the last image post-contrast is 105 ± 34 % for cancers and 21 ± 14 % for FGT.

The calculated Pearson's correlation coefficient between the decrease of T1 relaxation time and the increase of the enhancement rate was a positive value both for FGT (r = 0.7) and for cancer (r = 0.6).

3.6. Visual evaluation of cancer on T1- and T2-MRF-maps before vs. after contrast injection

Before contrast injection, X1, X2 and X3 detected 50 % (7/14), 50 % (7/14) and 57 % (8/14) of the cancers on the T1-MRF-map; on the T2-MRF-map 36 % (5/14), 64 % (9/14) and 57 % (8/14) were respectively correctly recognized. After the injection of a contrast agent, X1, X2 and X3 detected 79 % (11/14), 86% (12/14) and 86 % (12/14) of cancers on the T1-MRF-map; on the T2-MRF-maps 36 % (5/14), 43 % (6/14) and 79 % (11/14) of cancers were correctly identified, respectively. Fig. 2 and 3 show the MRF maps pre and post contrast injection for two example cases. Information in details in Table 4.

4. Discussion

In this study, MRF maps were acquired both pre and post contrast. Our MRF data on pre-contrast T1- and T2-MRF-maps showed significantly longer T1 and T2 values for breast cancer as compared to FGT. After injection of a clinical Gd-based contrast agent, the expected much stronger reduction of T1 relaxation time of breast cancer was observed, whereas, and again as expected, the contrast injection had no significant effect on the respective measured T2 relaxation times. The calculated correlation coefficient between the increase of signal intensity of cancers and FGT in DCE-MRI (last dynamic) and the decrease of T1-MRF relaxation time showed a linear correlation (r = 0.6 and r = 0.7, respectively). When it comes to post contrast relaxometry, timing
Table 3

| Tissue Type      | MRF Pre-contrast | MRF Post-contrast |
|------------------|------------------|-------------------|
|                  | Mean of T1/ms    | Mean of T1/ms     |
|                  | ± standard deviation | ± standard deviation |
| BC               | 1146.89 ± 129.12 | 72.49 ± 12.29     |
| FG T             | 1051.64 ± 95.35  | 62.31 ± 12.39     |
| P-value          | < 0.05           | < 0.05            |

As the concentration of contrast agent in the tissue changes over time with characteristic enhancement kinetics [28]. We chose to compare the MRF values with the enhancement rates obtained from the last dynamic scan, as it was acquired just before the post contrast T1-MRF-map. It should be emphasized, that our post-contrast MRF acquisition observes the enhancement, as it was acquired after the dynamic series. Even during post contrast MRF acquisition, further wash-out of the contrast medium can take place. It is not surprising to find a higher correlation coefficient for FGT as for cancer, considering that the concentration of contrast agent in cancers might undergo more important changes than the one in FGT, which on the contrary reaches a more stable plateau. Generally speaking, a fast relaxometry technique is hence advantageous. In this regard, our MRF technique needs further technical development. While our post contrast MRF analysis was mainly intended for validation purposes, the assessment of lesion differentiation by absolute T1 changes could be an interesting topic for future research.

As expected, cancers were best visible on the T1-MRF-map acquired after the injection of contrast material, where between 79% (11/14) and 86% (12/14) of cancers were recognized. Surprisingly, for each radiologist at least 50% (7/14) of the cancers were detectable also on the pre-contrast T1-MRF-map. The cancer detectability on the T2-MRF-map varies between 36% (5/14) and 64% (9/14), showing a greater, and probably experience dependent, inter-reader variability.

An aspect that may affect the visibility of T1 and T2 differences in general is the choice of the color map [29]. Indeed, standardization of colormaps for qMRI is an active topic of debate and needs to be addressed by the community.

Since the first description of magnetic resonance fingerprinting in 2013 by Ma et al. [21], several studies focused on its possible clinical applications and possible technical improvements [30,31]. However, MRF poses still technical challenges, especially if used for applications in the breast, where MRF with spiral readout is complicated by the high content of fat tissue that causes off-resonance blurring of the signal. This issue is even more important for spiral readout trajectories with longer acquisition times [23]. A possible solution has been proposed by Chen et al. [22], with the application of a fat-suppression pulses to a multi-slice MRF sequence. Nevertheless, the main drawbacks of the suppression of fat [32] signal are that other essential diagnostic information might be lost and that there is a reduced signal-to-noise ratio. By way of contrast, the technique used in our study separates water and fat signals thus allowing the computation of images with less field inhomogeneity and does, in principle, permit the analysis of both water and fat signals.

The idea behind MRF is tissue identification based on a possibly

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unique spectrum (i.e., fingerprint of MR-physical properties). In this study, we found significantly different changes in the T1 and T2 relaxation times of tumor and healthy FGT. The fact that at least 50 % of breast cancer could be visually detected on the T1 map, which are not normally visible on the native T1 images, point towards a potential of MRF as an additional sequence for the development of a MRI diagnostic protocol without the use of contrast material. However, before its use in clinical practice, future MRF studies should investigate differences in the relaxation times of malignant vs. benign lesions, ideally in large patient collectives. If the resulting relaxation times show potential to non-invasively classify different types of lesions, especially the enhancing ones, this could help in increasing the specificity of breast MRI and help reduce the number of false-positive findings in regular breast DCE.

Nevertheless, this study has its limitations. First of all, due to its feasibility character, the number of patients is small. Especially with respect to differential diagnosis, a much larger patient cohort will need to be analyzed. Secondly, the use of MRF for screening purposes is unrealistic at this stage due to the long time needed to acquire the images of more than 100 s per slice. Indeed, the major drawback of our current approach is the fact that we had to pre-select the area where the MRF pulse sequence was obtained based on the pre-contrast images. In most MR images, the cancer can only be clearly seen after contrast injection. So in cases where the MRF sections were placed at an area that – based on the post-contrast images – included only the periphery of the cancer and the surrounding DCIS, the difference between the absolute values of the cancer vs. fibroglandular tissue was minimal, such as in patient 11, or even reversed, as in the patients 2, 7 and 12.

Thirdly, the pre-selection of a single slice leads to the impossibility of analyzing the whole breast. Since breast cancers are often multifocal or even bilateral, this represents a major disadvantage of this procedure, which therefore has to be further developed before its application in the clinical practice.

Concerning the visual analysis of the MRF-maps, it is worth to underline that the radiologists were aware that each patient had a cancer, which constitutes an important bias for the visual assessment of MRF-maps.

5. Conclusion

In conclusion, MRF is a promising method to distinguish between breast cancer and healthy fibroglandular tissue based on pre-contrast relaxation times. Pre- and post-contrast T1 changes can potentially give additional insight in the character of a lesion. However, the potential of MRF for differential diagnosis, especially to distinguish malignant from benign lesions, needs to be further investigated.

CRediT authorship contribution statement

**Eloisa Zanderigo**: Conceptualization, Methodology, Investigation, Data curation, Visualization, Formal analysis, Funding acquisition, Writing - original draft, Writing - review & editing. **Luisa Huck**: Investigation. **Martina Distelmaier**: Investigation. **Ebba Dethlefsen**: Investigation. **Mirjiam Maywald**: Data curation, Investigation, Methodology. **Daniel Truhn**: Software, Writing - review & editing. **Timm Dirrichs**: Investigation. **Mariya Doneva**: Software, Supervision. **Volkmar Schulz**: Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Christiane K. Kuhl**: Conceptualization, Methodology, Resources, Supervision, Project administration, Funding
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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: I would like to mention the following conflict of interest: my co-author Mariya Doneva is employed by Philips Research Europe and my co-
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