MReadings: Breast MRI

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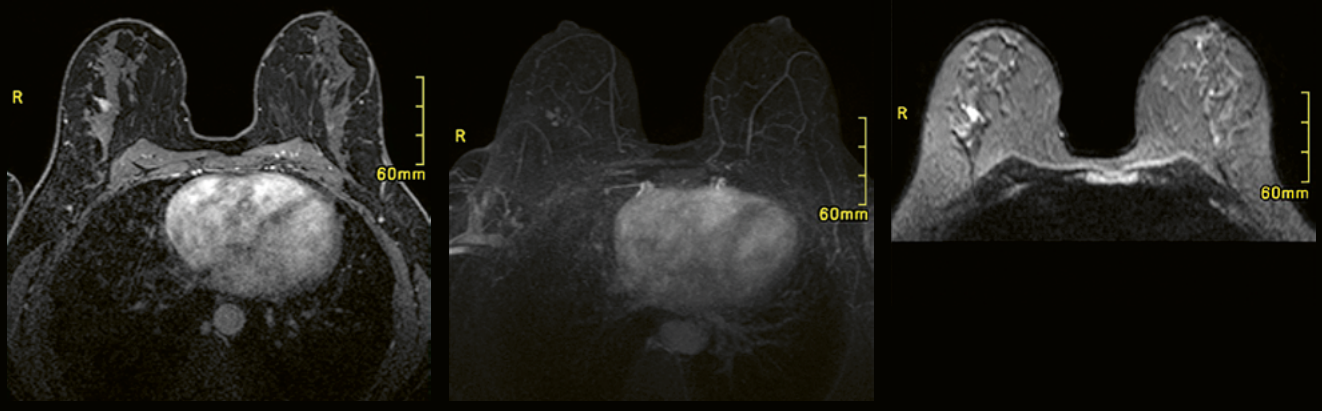

Breast cancer care pathway

Screening & Early Detection
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Improving Patients' Experience of MRI: Why and How Reducing Stress and Anxiety in Patients May Enhance Clinical Operations

Janika Madl[1,2]; Susanne Bay[2]; Rolf Janka[3]

[1]Chair of Health Psychology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[2]Siemens Healthineers, Erlangen, Germany
[3]Department of Radiology, Universitätsklinikum Erlangen, Germany

Introduction

Magnetic resonance imaging (MRI) is non-invasive and painless, with excellent spatial resolution and soft-tissue contrast. These numerous benefits have rendered MRI one of the most important diagnostic tools in modern medicine. In Germany, 150 MRI examinations are performed per 1,000 inhabitants every year [1]. Yet, MRI also has substantial drawbacks: Most MRI protocols are time-consuming and very dependent on the patient's cooperation and ability to lie motionless. One of the main roots for disruptions to MRI workflows is stress and anxiety in patients, who often experience MRI as uncomfortable and frightening [2, 3]. Beyond creating a negative patient experience, feelings of anxiety and stress may relate to unexpected patient-related events such as motion artifacts, the need for sedation, or failed scans; these events result in a substantial amount of revenue lost [4–6]: Andre et al. [4] calculated that US$ 115,000 are lost per scanner every year due to unexpected patient behavior.

The aim of this article is to provide a holistic picture of patients' experience of MRI, related unexpected behaviors and consequences, and approaches to improve the situation for all concerned: patients, healthcare staff, and the medical institutions. The focus is to provide insights into the "Patient Experience (PX) in MRI" collaboration project between Siemens Healthineers, the Chair of Health Psychology (FAU Erlangen-Nürnberg), and Universitätsklinikum Erlangen, Department of Radiology. During this collaboration project, two empirical studies and one systematic review with meta-analysis were conducted and will be presented in the following.

Take-home points

- Although most patients tolerate MRI well, a substantial number of patients experience clinically relevant levels of anxiety; related unexpected patient behaviors disturb clinical workflows and impede efficiency of healthcare providers.
- Patients' response to MRI depends on many different factors; previous negative experiences with MRI and female sex seem to be particularly predictive of a negative patient experience.
- In order to address individual patients' needs, different materials for patient preparation should be offered: Not only informational material, but also measures to support active modulation of anxiety, e.g., relaxation exercises.
- Patients who experience high levels of stress or anxiety tend to lie less still, which may provoke motion artifacts and the need for scan repetitions, thereby prolonging procedural times. Therefore, reducing stress and anxiety in patients might not only improve the patient experience, but also lead to clinical workflows running more smoothly.

Patients' experience of MRI: An introduction

How patients experience MRI has been a topic of interest since the very beginnings of MRI. In the course of MRI paving its way from the 1980s on, it soon became apparent that many patients fear this medical "coffin" [7]; Figures 1A and 1B show that, indeed, early MRIs resembled "mechanical monster[s]" [7]. Since then, many technological advancements have made MRI more patient-friendly: Recent MRI machines produce less noise, are equipped with shorter, wider bores that are open at both ends, and acquire images much quicker, thereby reducing scan duration [8, 9]. Some studies report that these advancements have resulted in reduced levels of stress and anxiety, as well as related operational issues [6, 10, 11]. Yet, others find that – although most patients tolerate MRI well – stress and anxiety are still widespread phenomena reaching levels that are considered clinically relevant in around 30% of patients [12, 13]. Two questions arise from these findings:

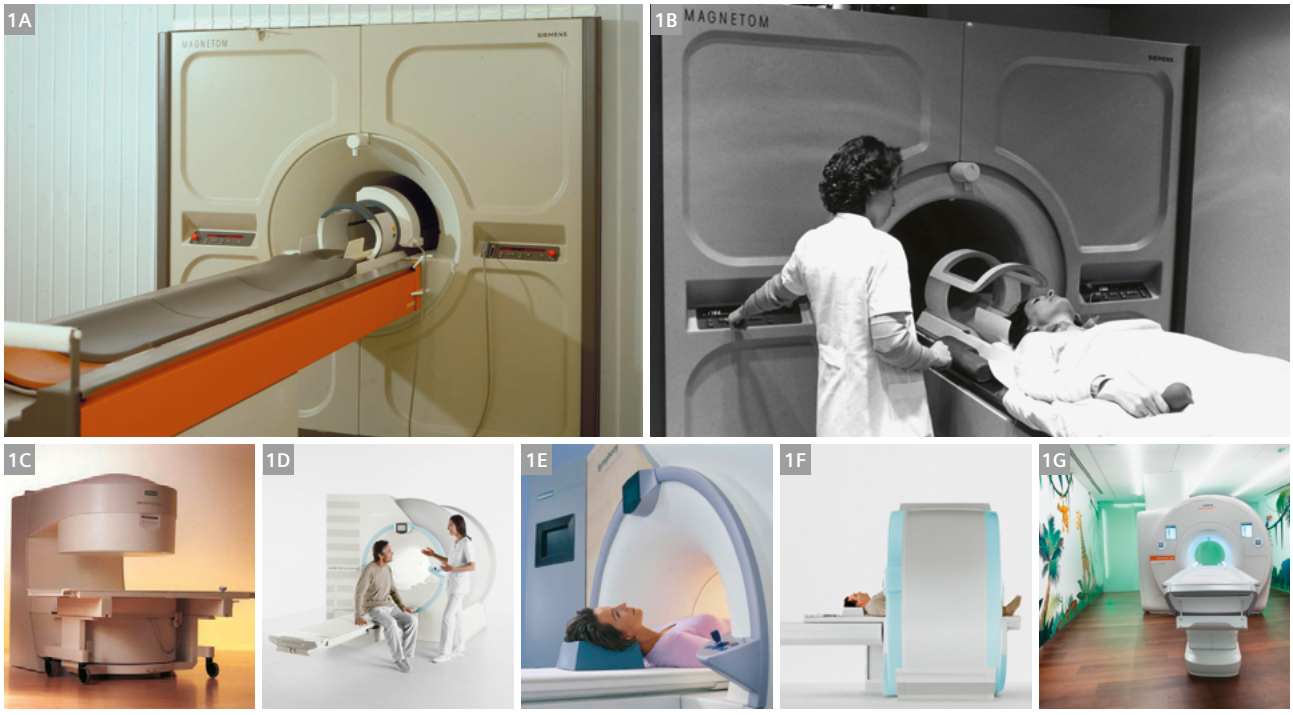
1) What factors differentiate patients who fear MRI from the rest?
2) To what extent have technical advancements brought about improvements regarding the patient experience of MRI examinations and related behaviors?

Adequate patient preparation seems to be most decisive in preventing a negative patient experience and fostering smooth clinical workflows

In our "baseline" study, our aim was to analyze patients' response to MRI in detail including influencing factors and consequences [12]. We thereby considered patients' psychological response (i.e., anxiety), the physiological response (i.e., salivary stress markers), and operational effects on clinical processes (i.e., scan repetitions due to motion artifacts, scan duration).

The study was conducted in the department of radiology of Universitätsklinikum Erlangen. We examined anxiety and physiological stress markers in 96 patients undergoing MRI (M = 49 years, 61.5% female). Anxiety was assessed via questionnaires before and after MRI; at the same timepoints, we took saliva samples to measure salivary stress markers (cortisol, alpha-amylase).

In general, most patients tolerated MRI well. Yet, every third patient experienced moderate to severe levels of anxiety in anticipation of the examination and experienced relief only after having endured the examination. As suggested by Ahlander et al. [14], this implies that efforts to improve the patient experience might be most effective



1 **(1A, B)** While the first MAGNETOM MRI scanner from 1983 [41] might have been a scary sight, only a few years later product development focused also on patient comfort. **(1C)** In 1993, Siemens introduced the 0.2T MAGNETOM Open. **(1D, E)** In 1996 the product line around MAGNETOM Symphony featured a flared bore. **(1F)** In 2004 MAGNETOM Espree was the world's first 1.5-tesla system with a 70-centimeter opening. **(1G)** Today a relaxing atmosphere, noise reduction and fast sequences make MRI easier to tolerate.

when applied in advance. Materials for patient preparation can only reduce anticipatory anxiety when given with sufficient lead time, ideally a few days/weeks before the examination.

We examined a broad range of potentially influencing factors (sex, age, positioning, accompanying persons, pain, previous experiences, examined body part) and found them to interact with patients' response in a complex way. Women receiving breast examinations had a particularly high risk of anxiety. This is in line with previous studies that reported a more negative response to MRI in women vs. men [6, 12, 15]. Further, we found that negative experiences made during previous MRI examinations significantly predicted a negative experience during the current examination. That means that patients who once have a negative MRI experience tend to keep on having bad experiences. When integrating our results on the impact of age and positioning with other studies, the state of research appears to be less clear [6, 12, 16–18]. Most certainly, it can be deduced that patients differ considerably regarding their response to MRI and their needs, which is why they also require different approaches to address these needs.

Furthermore, we found evidence of a link between patients' experience and clinical workflows: Patients' response to MRI predicted the probability of scan repetitions and scan duration [12], thereby supporting previous results that reported a connection between the patient experience and the prevalence of unexpected patient-related events [5, 19–22]. For example, an increase of 1 nmol/L in the stress marker salivary cortisol predicted a prolongation of the scan duration of more than 4 minutes [12].

Apart from individual factors that influence patients' experience of MRI, technological advancements have been proposed that aim to have a positive impact on stress and anxiety as well as related behavioral issues in patients. Yet, until now, no systematic review has summarized the patient experience of MRI, related unexpected patient behaviors, and their evolution along with technological advancements holistically. We sought to overcome this research gap in a systematic review with a meta-analysis that we conducted on patients' response to MRI, its effects (i.e., unexpected patient behaviors related to stress and anxiety), and their evolution over time [20].

Evolution of patients' experience of MRI and related unexpected patient behaviors over time: A systematic review and meta-analysis

We searched four databases and screened more than 12,000 studies. Meta-analysis of 44 studies revealed that, despite the common understanding of patient anxiety, there have been no significant improvements over time in the amount of anxiety experienced: Average values of reported anxiety were close to the cut-off considered as clinically relevant and around 4% of patients reported to be unwilling to undergo further MRI examinations. Similarly, the rates of unexpected patient-related events such as no-shows, failed scans, motion artifacts, and sedation, have not significantly reduced over time. While these findings could be traced back to statistical issues or the fact that we had to use the year of study publication as an indicator of MRI technology as more exact data on scanner technology was unavailable for most studies, it might as well reflect the fact that patients still experience substantial stress and anxiety in the context of MRI. An additional interesting finding was that claustrophobia significantly moderated the overall number of unexpected patient events. The rates of unexpected behaviors such as no-shows, motion artifacts, failed scans, and sedation were higher in patient groups with higher levels of claustrophobia. This supports the notion of a link between the patient experience and clinical workflows as has been postulated previously [5, 19, 21, 22].

Based on the results of the baseline study and meta-analysis, it can be concluded that stress and anxiety in patients have always been and still are a relevant topic in the context of MRI. In short, technological advancements of the MRI scanners alone might not be sufficient to improve the patient experience of MRI or related unexpected events – at least until now. There seems to be a need for interventions that target patients' needs more explicitly. The evidence generally suggests that MRI-related patient anxiety and related effects can be prevented when we enrich standard care and properly address patients' needs.

How patient's experience of MRI can be improved: An overview

A wide variety of interventions to improve patients' experience of MRI has been developed and tested in the past. Approaches range from easy-to-implement measures to very elaborate and complex ones: From the supply of music or having someone accompany the patient, to variations in patient positioning or the environment, mock MRI, aromatherapy, amended patient information, distraction via VR, hypnosis and other relaxation strategies, to communication training for the medical personnel.

Many of these approaches have been proven to be effective (see Munn et al. [17] for an overview), but this article will focus on interventions specifically targeted at patient preparation.

Two major types of interventions for patient preparation can be distinguished:

- The aim of informational interventions is to reduce ambiguity and feelings of uncertainty that may constitute a stressor for patients [2, 23, 24]. Although

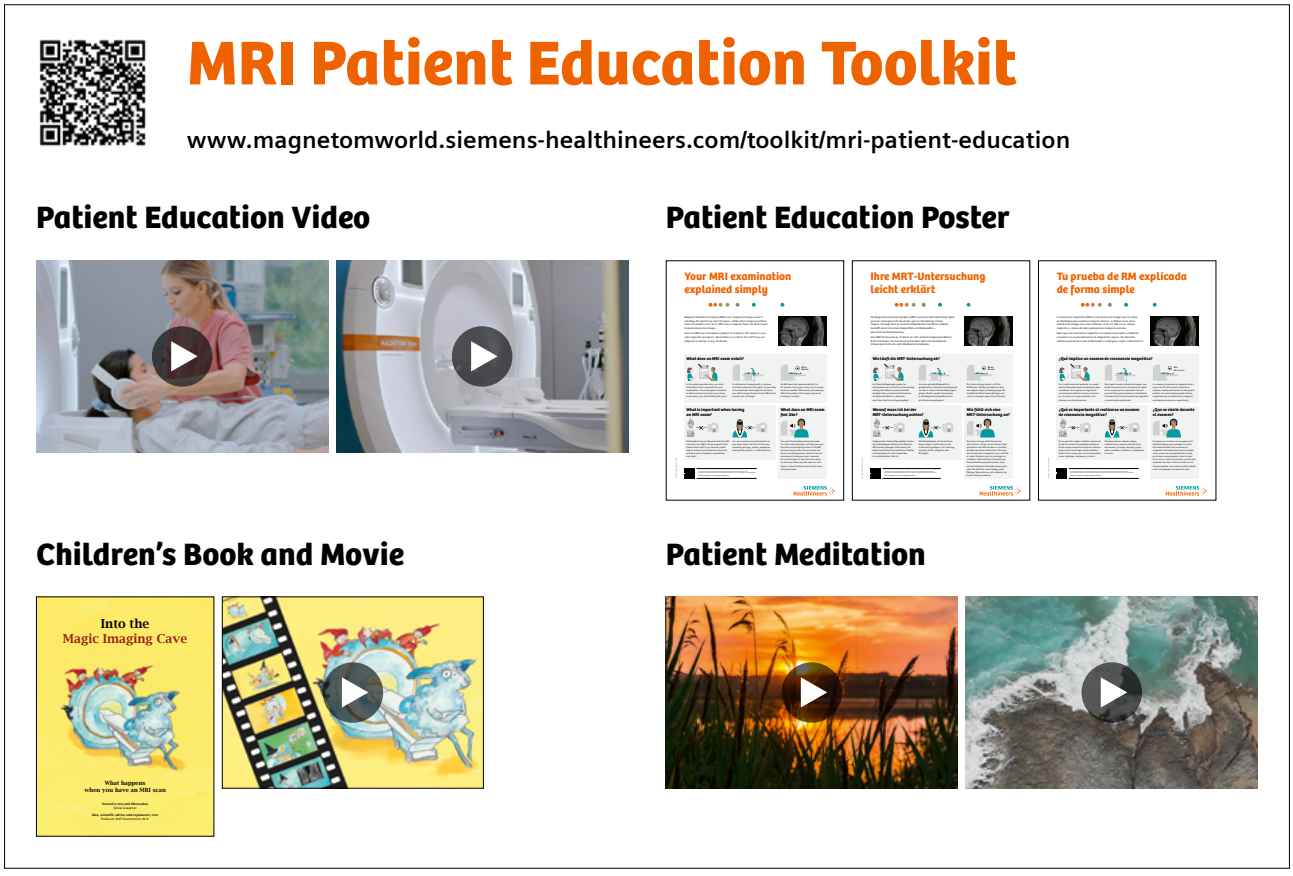
many studies report beneficial effects of additional information, others find even negative effects when information is provided exclusively [17].

- A different approach aims at enhancing a patient's ability to cope with the stressful situation more successfully, e.g., via relaxation techniques [25, 26]. Although consistently positive, the effect sizes of these interventions vary considerably [17].

The majority of the literature points toward substantial benefits of interventions to improve the MRI patient experience; yet, some questions remain unresolved: Why do some studies report positive effects of informational interventions but others don't? Where do the considerable variations in the reported effect sizes of coping interventions trace back to? And is there a link between patient experience and clinical processes?

Patient preparation should cover different needs of patients

In order to address these questions and help to enhance the patient experience of MRI, we developed a patient education toolkit (see Fig. 2) in collaboration with Siemens Healthineers MR marketing and tested it in clinical trial. We based our approach on the assumptions of the "Model of Coping Modes" [27, 28], which may contribute to explaining the inconsistencies described above. The model describes different ways of coping with stress-inducing situations that people tend to employ habitually. The model proposes vigilance and cognitive avoidance as two basic dimensions of how attention shifts when facing stressful situations. While cognitive avoidance means the tendency to divert attention from threatening cues to reduce the bodily arousal induced by these, vigilance refers to the opposite: An increased focus on threatening cues to enhance knowledge about the situation and reduce feelings of uncertainty [25, 27]. Figure 3 depicts the four coping styles that can be differentiated on the basis of these two dimensions. According to this scheme, it can be expected that sensitizers benefit from receiving additional information: It should enable them to reduce feelings of uncertainty successfully. By contrast, repressers should benefit from distraction and relaxation, which supports distracting attention away from the threatening cues that induce arousal.

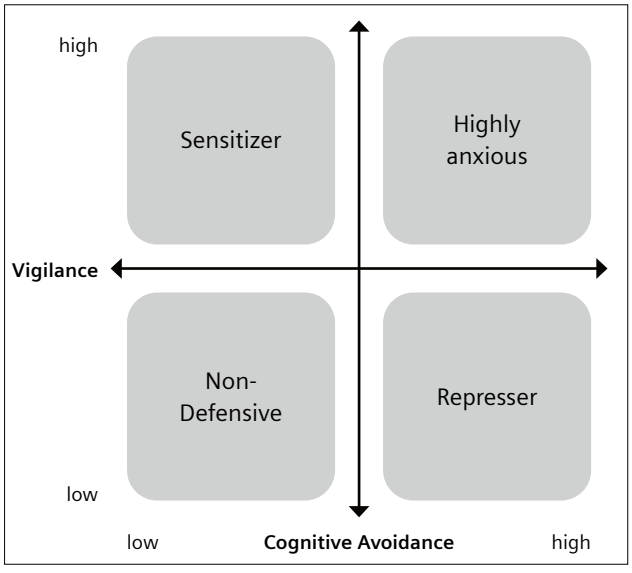


2 QR code for access to the Patient Education Toolkit including the two patient preparation videos and the MRI book for children.

Patient preparation that matches the coping style ("congruent preparation") has been shown to improve patient-related outcomes such as pain, anxiety, and adaptation in other medical fields like surgery [29, 30], cardiac catheterization [31], cancer survivorship care [32], or coloscopy [33]. We therefore hypothesized the same pattern to apply to MRI patients: We expected the psychological and physiological response of patients to improve when they received an intervention congruent with their coping style vs. when they received incongruent preparation or no additional preparation (i.e., standard care control group).

We tested this assumption in a study with a randomized controlled design with 142 patients. While sitting in the waiting room, the patients randomly watched one of two videos developed to address the needs of sensitizers (information video) or repressors (relaxation video) or received standard care (no video). Both videos can be accessed via the QR code presented in Figure 2. We assessed the patients' psychological and physiological responses to the examination, their evaluation of the videos, and recorded procedural outcomes (scan duration, repeated scans, interruptions). Anxiety was assessed via questionnaires on arrival at the hospital, after watching the video (or after a comparable amount of time in the control group), and after MRI. Cortisol as a physiological stress marker was assessed on arrival and after the MRI scan.

We found that cortisol levels were elevated compared with a "normal" day, which meant that undergoing MRI induced physiological stress in patients [34]. As cortisol still followed its normal circadian rhythm, we concluded that this elevation most likely reflected anticipatory effects, which is in line with our findings from the baseline study [12]. The videos were very well received by the patients [35]: Almost all reported that they found them helpful and that they increased their confidence regarding the examination; whereby the information video was evaluated even more positively. When the patients' preparation matched their coping style, anxiety decreased even before MRI, whereas this relief was only observed after the examination in patients whose preparation did not fit their needs. Beyond the positive effects at the patient level, we also found scan duration to be 10–20% shorter in the interventional groups and, descriptively, rates of scan repetitions or interruptions were 30–50% lower. Although our hypotheses were supported on a descriptive level, results failed to reach statistical significance. We believe that this is most likely due to power issues but there has, as yet, been no statistical confirmation of the effects on clinical processes and results must be interpreted with caution.



3 The Model of Coping Modes (based on Krohne [42]).

Improving patients' experience of MRI by addressing individual needs in advance can reduce stress and anxiety in patients and support smooth clinical workflows

Anxiety and stress in patients have always been and still are relevant phenomena in the context of MRI examinations. Based on the results of our studies [12, 34, 35] and the consideration of Ahlander et al. [14], we suggest that patients' response to MRI is most negative in anticipation of the examination. Therefore, changing the way patients are prepared for MRI seems to be a crucial step for improving MRI-related healthcare. Enriching standard care with additional patient preparation can have a positive impact on patients' experience of MRI. Our research suggests that patients vary greatly regarding their needs. Therefore, considering interindividual differences in patients' needs may be a promising approach to reduce stress and anxiety in patients most effectively. We therefore suggest that medical institutions should start providing tailored medicine, also in respect to the patient experience. This may be achieved by providing a variety of different materials for patients to choose from – or amendments of standard care, when thinking more generally. Thereby, it seems to be crucial to reach out to patients in advance: Providing patients with the opportunity to prepare themselves according to their own needs in a calm environment has the potential to maximize the beneficial effects.

Apart from being a relevant end in itself, we found in line with previous research that improving the patient experience could also have beneficial effects on clinical

workflows [5, 12, 17, 19, 21, 35–37]. Research suggests that patients who are calmer are less likely to be no-shows, have a lower need for sedation, premature terminations are less likely to happen, and patients move less, which could result in less need for scan repetitions and therefore shorter scan duration times [17, 19, 21, 36–40]. These effects might be even more pronounced when considering that time for patient education and preparation could also be reduced if patients were to arrive in an enhanced state of preparation. We therefore propose that improving the patient experience could result in positive effects for all stakeholders: Patients will be more relaxed, which also reduces stress for the medical personnel; furthermore, workflows will run more smoothly, thereby also increasing the revenue of an institution.

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Contact

Janika Madl, M.Sc.
Chair, Health Psychology
Friedrich-Alexander-University
Erlangen-Nürnberg
Nägelsbachstrasse 49a
91052 Erlangen
Germany
janika.madl@fau.de

Abbreviated Breast MR Protocol at Radboud University

Ritse M. Mann, M.D., Ph.D.[1,2]; Lejla Kočo, MSc[1]

[1]Department of Imaging, Radboud University Medical Center, Nijmegen, The Netherlands
[2]Department of Radiology, Netherlands Cancer Institute (Antoni van Leeuwenhoek), Amsterdam, The Netherlands

Overview

Motivation for abbreviated breast MRI	At the Radboud University Medical Center, different MRI protocols are used for breast imaging depending on the purpose. • An approximately 20-minute MRI protocol for diagnostic imaging • An approximately 8-minute abbreviated MRI (abMRI) protocol for screening The motivation to implement abbreviated breast MR imaging (abMRI) at the Radboud was to increase cost-effectiveness. The idea was to be able to scan more women within the same timeframe with MRI. This would therefore allow greater access to MRI screening to more women and reduce the time women had to spend inside the MRI scanner (anxiety, claustrophobia, lying still).
Population	According to Dutch[1] and European[2] guidelines, breast cancer screening with MRI is reserved for women with an increased risk of developing breast cancer. This includes women with hereditary germline mutations, especially BRCA1/2 gene mutation carriers, women at increased risk due to family history, women with a personal history of breast cancer, and women with extremely dense breast tissue. All women who are referred for screening by breast MRI are scanned using the abbreviated protocol, unless they have silicone implants (in which case specific silicone sequences are added) or have to be scanned for diagnostic purposes.
Imaging details	MRI systems used for breast cancer screening with the abMRI protocol: • MAGNETOM Prisma fit 3T, Breast 18 coil • MAGNETOM Vida Fit 3T, Breast 18 coil Breast MRI scans are generally scheduled weekly with a few dedicated timeslots of a couple of hours (for example, Thursday morning and Friday morning, whereby this can differ week to week). At the start of the timeslot, the scanner tables are adapted to facilitate breast imaging by positioning the breast imaging coil and placing the corresponding pillows and head rests. The table does not have to be adapted between scans, only cleaned for the next scan. For all imaging appointments, preparation time of 10 minutes per person is taken into account in the scheduling.
Consequence of implementation	• The major advantage of the abbreviated MRI protocol is that three patients can be scanned per hour. If DWI is omitted, it is also possible to scan four patients in one hour. • Another important benefit is that the MRI scanner is almost continuously in use. • However, the workload for technicians does increase. Due to the preparation time of 10 minutes per patient, the time overlap between scans decreases. Technicians have several tasks during and after the scan (e.g., processing and transferring images), for which there is now less time. If one scan is delayed, the whole schedule is delayed. It is therefore important to ask women to come to the appointment slightly in advance to ensure that patient flow is uninterrupted.

[1]*Dutch guidelines source: https://richtlijnendatabase.nl/richtlijn/borstkanker/screening/screeningsmiddelen/mri.html*
[2]*European guidelines source: https://link.springer.com/article/10.1007/s00330-022-08617-6*

Imaging study

Patient preparation

- Patients register at the front desk and are directed to the MRI waiting room. A technician walks to the waiting room to personally call the patient and bring them to the changing room. Patients should remove upper body clothing and all other items containing metal. They are provided with a blue gown for coverage until getting to the MRI scanner. The intravenous cannula (IV) for the injection of contrast is inserted after the patient has changed into the gown.
- Injection of contrast agent
- Patients can sometimes go directly to the MRI scanner, but sometimes they have to wait a little until the MRI scanner is ready.
- Patients are then positioned on the table. When positioning is done, the technician leaves the room and the scan is started.
- Afterwards, the IV is removed immediately on the table in the MR room, and the patients can go to the changing room, change, and leave as soon as they are ready.

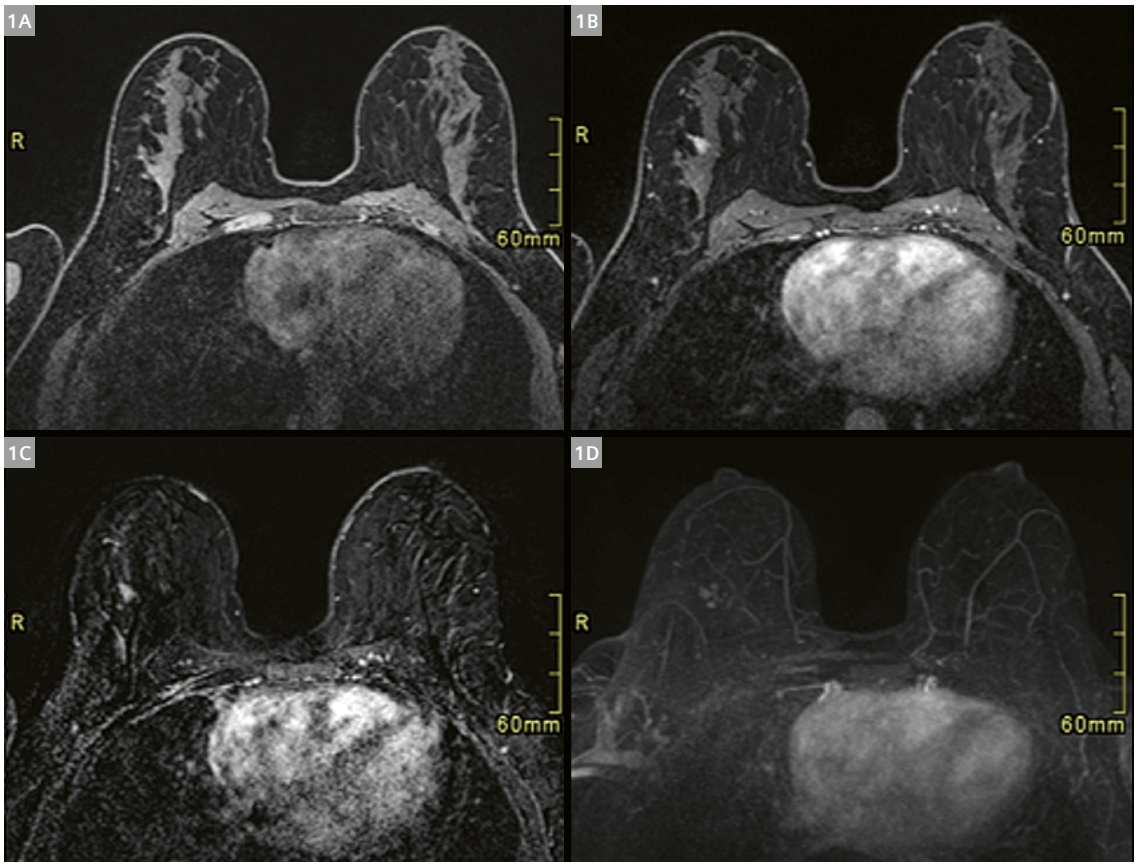
Patient setup

Patients lie prone on the scanner table, either head-first or feet-first, depending on the individual situation. Breasts are positioned in the Breast MR coil.

Imaging protocol

Download the .exar1 file for 3T MAGNETOM Prisma fit and MAGNETOM Vida Fit at
https://www.magnetomworld.siemens-healthineers.com/clinical-corner/protocols/breast-mri/abbreviated-breast-mr-protocol

Sequence	Scan time (min)	Sequence details
Localizer	0:08	
T1 VIBE Dixon pre-contrast (axial)	1:31	FOV: 360 x 360 mm^2 In-plane resolution: 0.9 x 0.9 mm Slice thickness: 1 mm Number of slices: 144
T1 dynamic TWIST (axial)	2:03	FOV: 360 x 360 mm^2 In-plane resolution: 0.9 x 0.9 mm Slice thickness: 2.5 mm Number of slices: 60 Temporal resolution: 4.57 s
T1 VIBE Dixon post-contrast (axial)	1:31	FOV: 360 x 360 mm^2 In-plane resolution: 0.9 x 0.9 mm Slice thickness: 1 mm Number of slices: 144
RESOLVE SPAIR (axial)	2:53	FOV: 340 x 170 mm^2 In-plane resolution: 1.5 x 1.5 mm Slice thickness: 4 mm Number of slices: 28 *b*-values: 0, 800 s/mm^2
Total acquisition time:	8:06 min	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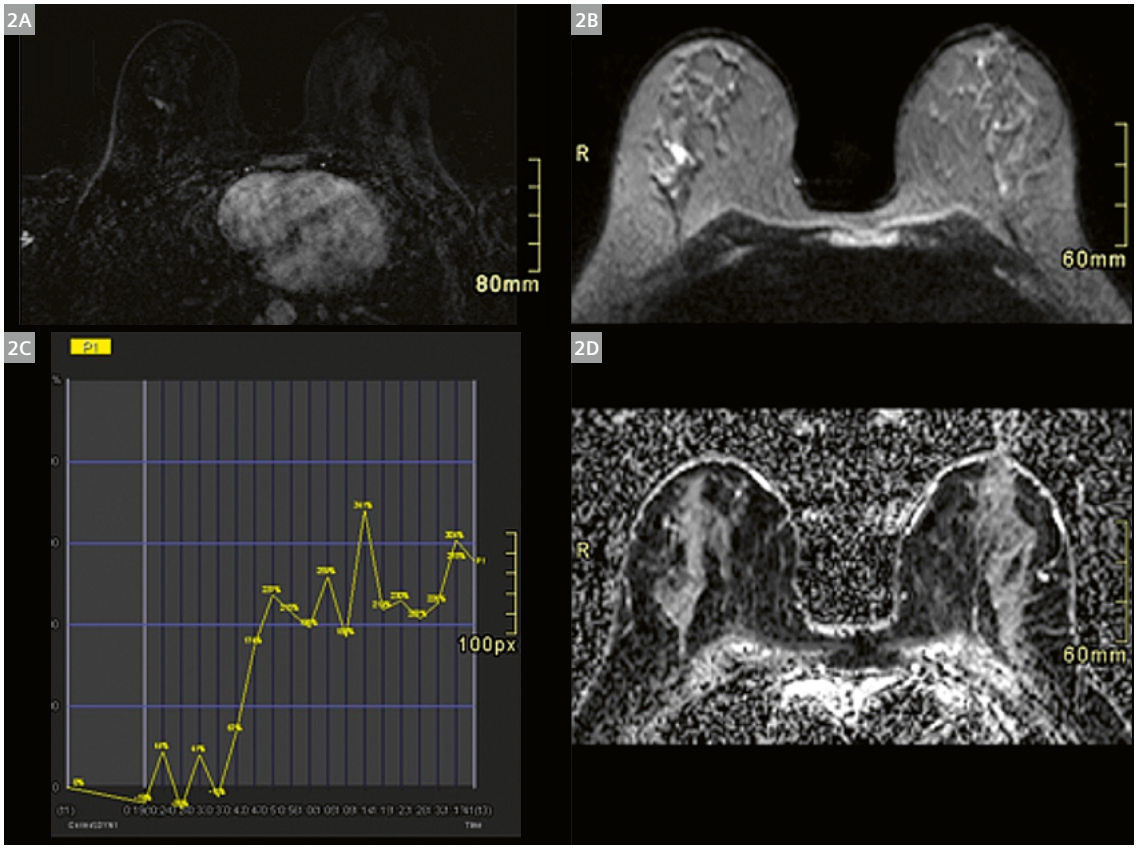
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Example case

Screen-detected mamma carcinoma in a 43-year-old BRCA1 gene mutation carrier. Primary assessment is performed using (1A) pre-contrast T1 VIBE, (1B) post-contrast T1 VIBE, (1C) subtraction image, and (1D) dynamic MIP obtained from the ultrafast T1 VIBE acquisition. Given the presence of abnormalities, additional information used for the complete evaluation of the lesions are: (2A) perfusion with T1 dynamic TWIST, (2C) inflow curve, and (2B, 2D) DWI with RESOLVE (*b*-value = 800 s/mm^2 and ADC map).

Reading practice

- For baseline evaluation, we use a 4-view hanging protocol, with the pre-contrast T1 water image top left (1A), the post-contrast T1 water image top right (1B), the subtraction bottom left (1C), and the dynamic MIP bottom right (1D) obtained from the ultrafast dynamic acquisitions.
- Evaluation starts with the MIP, followed by a quick scroll through the subtractions. If they are negative, reading the study is finalized within seconds.
- Reporting always contains statements about the amount of fibroglandular tissue in the breast and background parenchymal enhancement.
- In the presence of abnormalities, we judge morphology of a lesion on the subtraction and the T1 post-contrast images, time to enhancement on the dynamic MIP, and create inflow curves when required for the assessment of maximum slope. In addition, lesions are judged on the *b*800 DWI acquisition and the corresponding ADC map.

Tips & tricks

- Tip 1: Assess screening examinations in the context of the baseline risk of the patient (i.e., you need to know!). Small focal areas of non-mass enhancement that enhance relatively late can, for example, easily be dismissed in women at relatively low risk, whereas they might warrant a biopsy in women with specific genetic mutations (e.g., BRCA2 or CDH1).
- Tip 2: Look at the dynamic MIP to appreciate the lightbulb effect: The first lesion you see, is the lesion that most warrants your attention.

Contact

Ritse Mann, M.D., Ph.D.
Radboud University Medical Centre
Department of Radiology
huispost 766
P.O. Box 9101
6500 HB
Nijmegen
The Netherlands
ritse.mann@radboudumc.nl

Full-scale vs. Abbreviated Sequences in MR Mammography – the Best of Both Worlds

Clemens Kaiser, M.D.

Department of Radiology and Nuclear Medicine, University Medical Center Mannheim, Germany

Background

According to the current state of the literature, MR Mammography detects breast cancer with the highest accuracy of all imaging techniques. Since 1984, when the first scientific results were published, more than 15,000 publications have followed, proving the diagnostic benefit of this method [1].

MRI offers unique soft-tissue contrast that can be enhanced using contrast agents to reliably detect tumor-angiogenic processes and carcinomas from a size of 2–3 mm [2, 3]. A significant portion of carcinomas are verifiable by MR Mammography only [4–6]. In addition, this method enables the dependable detection of carcinomas in an early stage [6–8]. This can be prognostically very important for patients.

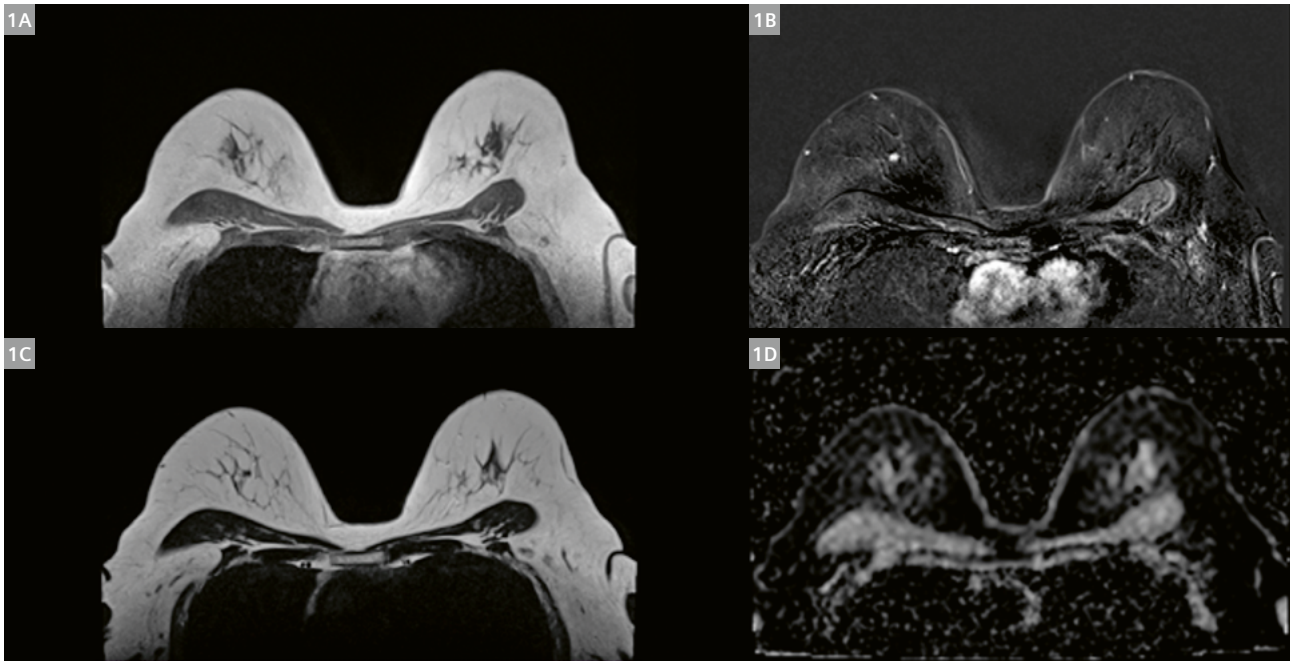
Literature has shown that preoperative staging with MR Mammography reduces the local rate of recurrence and influences therapy decisions significantly [9–12]. In 3% of all cases, this led to detection of contra-lateral carcinomas, too.

With a negative predictive value of 100% [13], MR Mammography can, moreover, exclude invasive carcinomas with certainty, impacting on biopsy rates and leading to reduced patient stress due to a more reliable diagnosis.

Screening women with dense breast tissue

Despite these well-known diagnostic benefits, only a few patients get to profit from MR Mammography in Germany (and many other countries) because the examination is currently only indicated and reimbursed in a few exceptional indications, e.g., high-risk screening collectives [14].

At the same time, conventional breast cancer screening programs have not managed to decrease mortality



1 **(1A)** First minute post application of 1 mmol/kg Gd; **(1B)** First min subtraction, **(1C)** T2-weighted scan; **(1D)** ADC map. The scan reveals a 3 mm carcinoma in the upper inner quadrant. The lesion shows a type 3 curve, pos. Root Sign and hypointensity in T2. Due to its size and the resolution it is not visible in the ADC map.

rates from breast cancer significantly – neither nationally nor internationally [15]. This could indicate a possible new diagnostic role for MR Mammography, especially as a screening tool for women of average risk of developing breast cancer but with dense breast tissue, following the experience of, for example, Dutch screening algorithms.

There has, however, been critical discussion in the past of the financial aspects in particular, as these present the main barriers to the acceptance of MR Mammography as a screening tool.

In 2019, extensive new data on the screening of women with dense breast tissue using MR Mammography was published, indicating a significant reduction in interval carcinomas [7, 8] and giving a first hint of evidence of a reduction in mortality through the use of MR Mammography as a screening tool with interval carcinomas as an accepted surrogate marker for mortality.

Cost-effective MR Mammography

In addition to delivering gratifying clinical results, these data also enabled a cost-effectiveness analysis that showed that MR Mammography is cost-effective [16].

Early detection of small carcinomas in the breast saves on subsequent additional therapy costs. Especially for women with breast tissue of high density, MR Mammography offers a cost-efficient and accurate screening tool. That is why its role in prevention should be reconsidered.

An additional approach to reduce the costs of examination with MRI, is "abbreviated protocol magnetic resonance imaging" (AB-MRI). The aim of AB-MRI is to reduce scan time and thereby the costs of examinations by omitting some sequences for better use in high-throughput screening settings.

As early as 2012, Fischer et al. proposed [17] that acquiring just pre- and post-gadolinium (Gd) injection T1-weighted sequences could reduce scan times and costs significantly while at the same time benefiting from the high negative predictive value of MR Mammography as breast cancer could be excluded without evidence of Gd enhancement. In cases when gadolinium enhancement is visible, a full-scale examination, including T2-weighted images and a complete dynamic series is required. This results in additional costs and nevertheless a second charge of contrast medium.

Further publications, for example by Kuhl et al. [18], showed that such an approach represents a full-featured alternative to conventional diagnostic mammography and is at least equivalently cost-effective in comparison.

Over the last 10 years, more and more publications have investigated various approaches to reducing costs by applying different sets of selected sequences, sometimes relying on diffusion-weighted images only, and have reported varying results.

Abbreviated vs. full-scale protocols

As of today, there is still a lack of definition of abbreviated protocols. The major studies commonly agree on a pre-contrast and a post-contrast image as well as T2-weighted images if the total length of the protocol does not exceed 10 minutes in total length [19].

While the study has impressively demonstrated that AB-MRI allows to detect significantly more invasive carcinomas at an earlier point in time than digital breast tomosynthesis (DBT) in women with dense breast [19] it remains unknown how the overall performance characteristics would have been improved with a full scale MR Mammography protocol.

MR scanners from Siemens Healthineers with NumarisX software now offer new acquisition techniques that enable radiologists to perform a full-scale MR examination in under 10 minutes, the time frame of abbreviated protocols and far below regular acquisition times of full-scale protocols.

The best of both worlds

At University Hospital Mannheim, a 1.5T MAGNETOM Sola is being used for standard MR Mammography examinations. This scanner is equipped with the Turbo Suite Excelerate package that includes the Simultaneous Multi-Slice (SMS) acquisition technique.

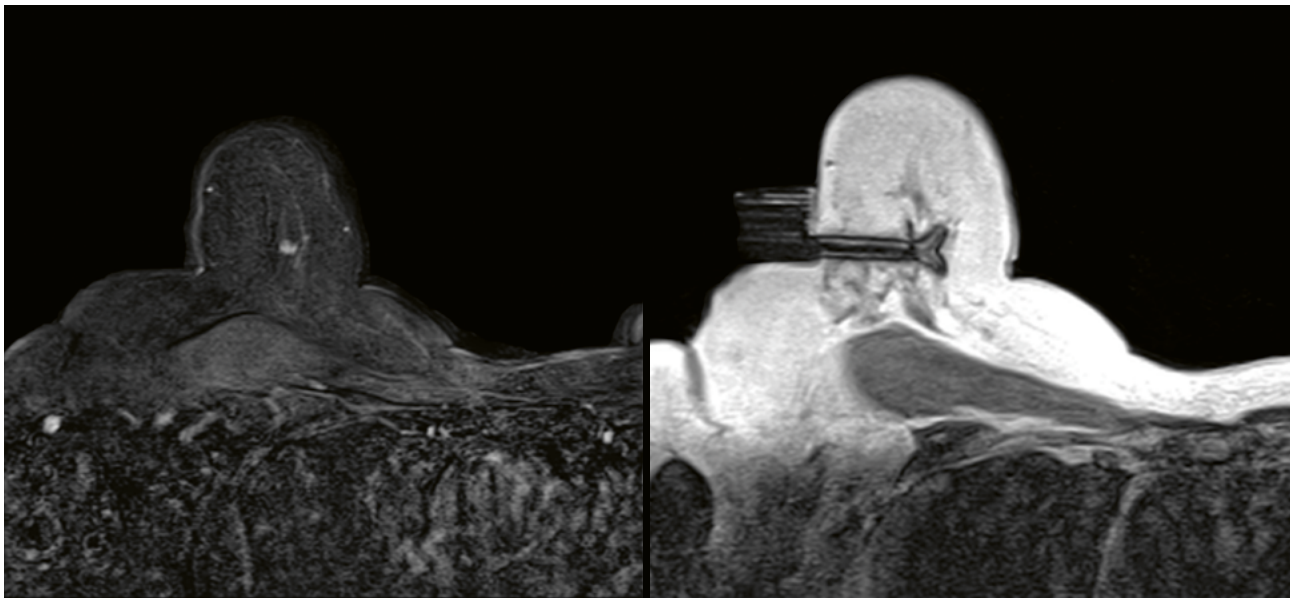
With SMS, it is possible to excite and readout multiple slices simultaneously, effecting a remarkable acceleration. SMS can be used for TSE sequences as well as for diffusion-weighted imaging (DWI) and can also be combined with iPAT.

MR Mammography for clinical diagnostic routine was set up with the following protocols:

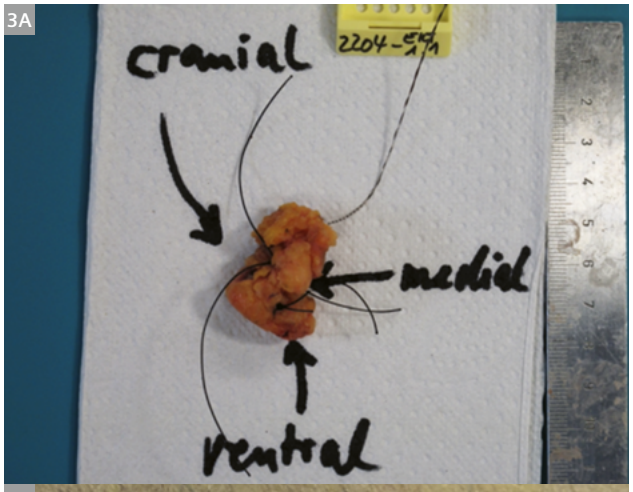
- 3 mm axial T2 TSE with iPAT 2 and SMS 2.
  Inplane resolution: 0.8 × 0.8 mm², 56 slices,
  TA: 1:36 min.
- 3 mm axial EPI Diffusion (b-values 50 s/mm² and 800 s/mm²) 3-scan trace with iPAT 2 and SMS 2.
  Inplane resolution: 1.5 × 1.5 mm² (interpolated), 56 sl.,
  TA: 1:46 min.
- 1.5 mm axial T1 fl3d as dynamic series
  (1+5, 20s delay), with iPAT 3.
  Inplane resolution: 0.9 × 0.9 mm², 112 sl., TA: 6:21 min.

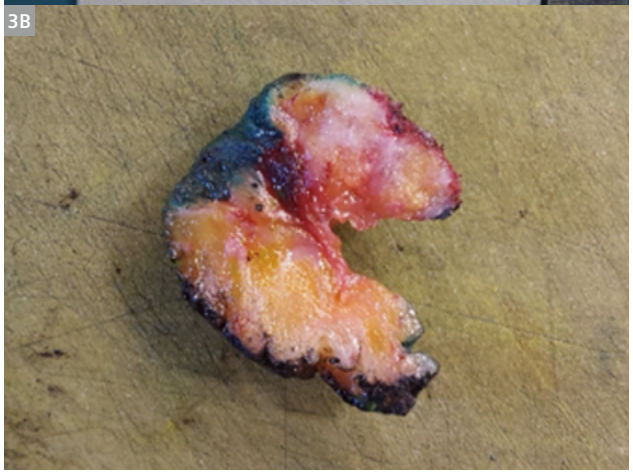
The .exar1 protocol is available for download at:
www.siemens-healthineers.com/magnetom-world
> Clinical Corner > Protocols > Breast MRI

At our institution we are using an 18-channel BI Mammography coil; the program, however, may also be used with other (high-channel) MR Mammography coils with very similar or the same parameters.

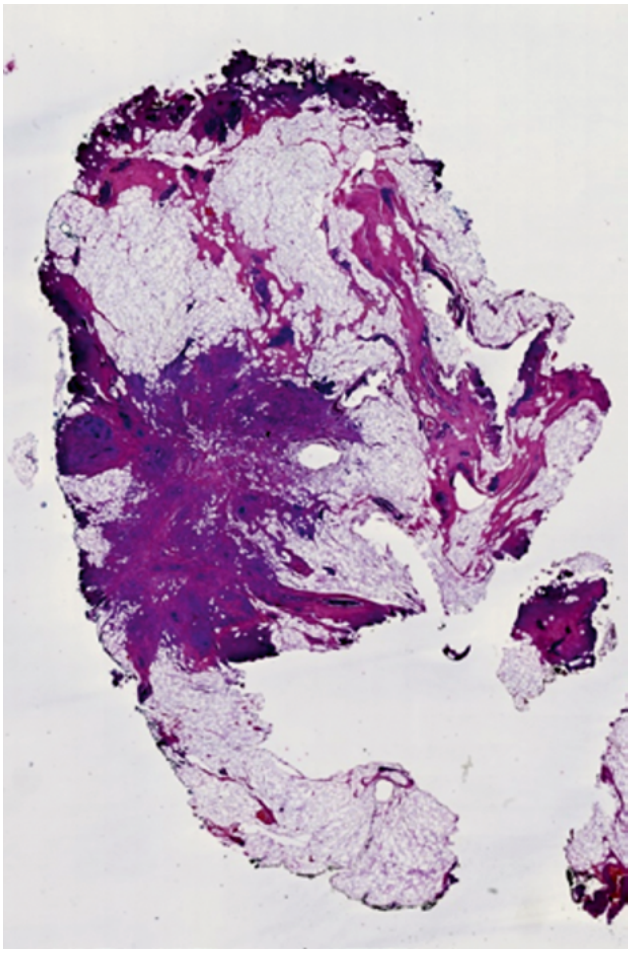


2 MR-guided wire localization before open surgical excision.





3 **(3A)** Excised specimen, **(3B)** excised specimen after coloring.



4 Histopathological slice revealing an invasive ductal carcinoma, 3 mm.

The full set of dynamic T1-weighted sequences (pre-injection and 5 minutes post injection of 1 mmol/kg Gd) with a time resolution of exactly 1 minute each is hereby adopted from standing protocols as suggested in the BIRADS Lexicon. The full dynamic set covering 6 minutes enables the reader to evaluate kinetic details in depth, a key requirement in optimizing the specificity of MR Mammography. Depicting all 6 minutes has been considered most time-consuming in the formation of abbreviated sequences and was therefore the main subject of protocol abbreviation.

T2-weighted sequences – as they are indicated in abbreviated as well as in full-scale protocols – are essential in assessing morphological aspects of lesions as they usually cover the field of view with a significantly higher resolution. T2-weighted sequences also deliver highly important diagnostic information, such as micro bleeding, perifocal, or prepectoral edema [20, 21].

Diffusion-weighted imaging enables the assessment of diffusibility and offers additional room to increase specificity [22–25], although a certain resolution bias makes assessing small and non-focal lesions difficult.

Both T2- and diffusion-weighted sequences can be acquired without significant loss of image quality in half the acquisition time using SMS [26], paving the way to a full-scale protocol in under 10 minutes and making screening women outside current indications feasible.

Conclusion

With SMS the need for abbreviated protocols may be overrated. You no longer need to decide between full-scale or abbreviated protocols, because the measurement time is now so short that you can confidently run a full-scale protocol just as efficiently as an abbreviated one.

This should be a giant step towards a feasible solution for screening women outside current indications.

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Contact

PD Dr. med. Clemens Kaiser, M.D.
Section Chief Breast
Department of Radiology
and Nuclear Medicine
University Medical Center Mannheim
Theodor-Kutzer-Ufer 1–3
68167 Mannheim
Phone: +49 (0)621 383-0
clemens.kaiser@umm.de

Breast MRI in India: Practice and Challenges

Pratiksha Yadav, MBBS, M.D., Ph.D.

Dr. D. Y. Patil Medical College, Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth, Pune, India

Background

Breast cancer is one of the most common malignancies in women worldwide, and the leading cause of cancer mortality. Although the incidence of breast cancer is thought to be higher in developed countries, it is also increasing in developing countries, where the majority of cases are detected at already advanced stages. According to data from Surveillance Epidemiology and End Results Program (SEER), there were 231,840 new cases of breast cancer in 2015, and 14% of those were newly detected cases. In the same year, breast cancer resulted in an estimated 40,290 deaths, which constituted 6.8% of all cancer deaths [1].

In India, the age-adjusted incidence of breast cancer is 25.8 per 100,000, which is lower than in the United Kingdom, where it is 95 per 100,000. However, the mortality rate is about 12.7 versus 17.1 per 100,000 respectively [2]. The global burden of breast cancer cases is expected to be about 2 million by 2030, with an increasing proportion of cases from developing countries [3, 4]. Breast cancer incidence in India varies across the country. Breast carcinomas in younger women are more aggressive than in older women, and studies suggest that breast cancer diagnoses peak at about 40–50 years of age in Indian women [7]. Indian women with breast cancer are estimated to be one decade younger than respective women in western countries [5–7]. Diagnosis of breast cancer at advanced stages contributes to the high mortality rate in Indian women.

Early detection is key for better prognosis. As lumps are not typically associated with pain, this leads to a delay in seeking diagnosis and treatment, and most of the symptomatic patients are already at stage II or III. The late diagnosis can be attributed to less awareness and limited access to diagnostic and treatment facilities in rural and suburban areas. India has no national screening program, and many women cannot afford the expensive examinations that would be required. Middle- and low-income countries face infrastructure and resource constraints, which are obstacles to improving breast cancer outcomes with early detection and treatment.

There are vast differences in the availability of breast imaging infrastructure and expert radiologists between big cities, rural regions, and suburban areas [8]. On one side, bigger cities have state-of-the-art infrastructure and expert radiologists who excel at early detection of breast cancer. On the other side, in rural and suburban areas, many breast cancer cases are missed or wrongly diagnosed as benign due to a lack of adequate diagnostic availability.

It is a real challenge that, in India, women present at late stages of breast cancer with large lumps, secondary changes of malignancy, multiple lesions, and sometimes bilateral cancer or metastatic lesions in the contralateral breast.

Magnetic resonance imaging (MRI) has exceptional sensitivity to detect breast lesions that sometimes might remain undetected on X-ray mammography, i.e. in women with dense breast tissue, which is more common in the aforementioned age range of 40–50. Dynamic contrast-enhanced MRI (DCE-MRI) is the most sensitive method for the detection of breast carcinomas, with reported sensitivities greater than 90% [9]. Even though both fat-suppressed T1- and T2-weighted MRI and DCE-MRI are excellent techniques for the characterization of breast lesions, sometimes it is not possible to distinguish between benign and malignant lesions using only these methods. Diffusion-weighted imaging (DWI) is a technique where the image contrast is derived from differences in the diffusion rate of water molecules in normal and pathological tissues. Malignant lesions, which typically have a higher degree of cellularity, demonstrate restricted diffusion. Studies have demonstrated that multi-parametric MRI of

the breast using DCE-MRI and DWI together significantly improve the diagnostic accuracy [10, 11].

To overcome the limitation in specificity of DCE-MRI [12], other functional MRI parameters can be used in multi-parametric MRI to primarily improve the specificity of breast MRI.

My practice in breast MRI

At our institution we use a dedicated 16-channel breast imaging coil on a 1.5T MAGNETOM Avanto and an 18-channel breast imaging coil on a 3T MAGNETOM Vida scanner (Siemens Healthcare, Erlangen, Germany). Patients lie prone with both breasts in the apertures of the coil. Compression is not applied but both breasts are softly fixed using foam.

Protocol and scanning parameters

The MRI sequences acquired are T2W, non-enhanced T1W, dynamic post-contrast T1W, and DWI. The sequence parameters are listed in Table 1.

The dynamic T1W sequences are acquired in transverse plane for better assessment of both breasts. A T1W with SPAIR fat suppression is acquired before the intravenous injection of contrast agent. The contrast, MultiHance (gadobenate dimeglumine; Bracco Imaging, Milan, Italy), is administered at 0.1 mmol per kilogram of body weight, followed by a 20 mL flush of saline using a power injector set at a flow rate of 2 mL/s. After the intravenous contrast injection, five T1W post-contrast series are acquired to evaluate the enhancement characteristic of the lesion.

Postprocessing and reading

The reading and interpretation of a breast MRI examination is performed following the American College of Radiology BI-RADS guidelines to differentiate benign and malignant lesions. It starts by analyzing first the pre-contrast T1W images, then the post-contrast images, and the post-processing information.

Subtraction images are obtained by subtracting the T1W pre-contrast images from the post-contrast series. Then, the maximum intensity projection (MIP) of the post-contrast images is also obtained.

Kinetic analysis is performed by calculating the mean curve in the region of interest (ROI) from the dynamic scans. The type of post-contrast enhancement is analyzed in each lesion (foci enhancement, mass or non-mass enhancement). The evaluation of the enhancement kinetics involves assessing the contrast uptake in the early post-contrast phase (wash-in), the peak of lesion enhancement, and the wash-out. In a type I curve, there is persistent enhancement with continued increased signal intensity throughout the dynamic phase. A type II curve has a plateau pattern, in which the signal intensity of the lesion remains approximately constant in the delayed phase. A type III curve shows early uptake and early wash-out.

Apparent Diffusion Coefficient (ADC) maps are obtained on the workstation.

In vivo high-resolution MR spectroscopy (MRS) is performed using a single-voxel proton spectroscopy method with spectral lipid suppression and weak water suppression. Postprocessing is performed using a spectroscopy evaluation tool available at the MR console, and metabolite information is obtained for the ROI.

After reading and interpretation of the data, the diagnosis is correlated with the histopathological analysis following core biopsy or surgical excision.

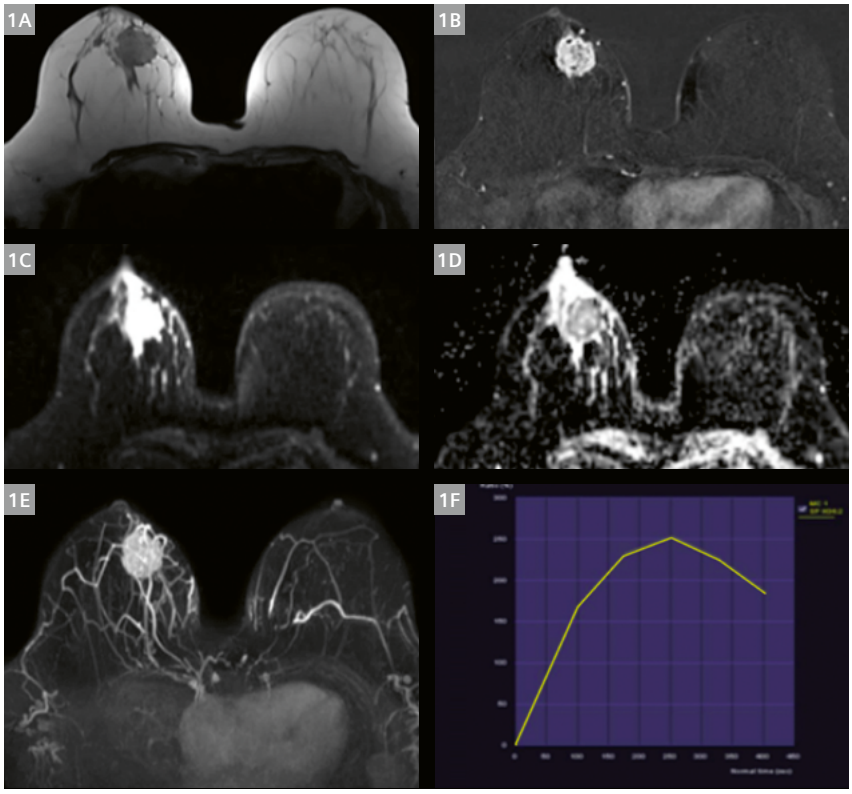
My clinical and research experience with breast MRI

Indian women often have a dense fibroglandular pattern, so there are more chances that lesions are missed on

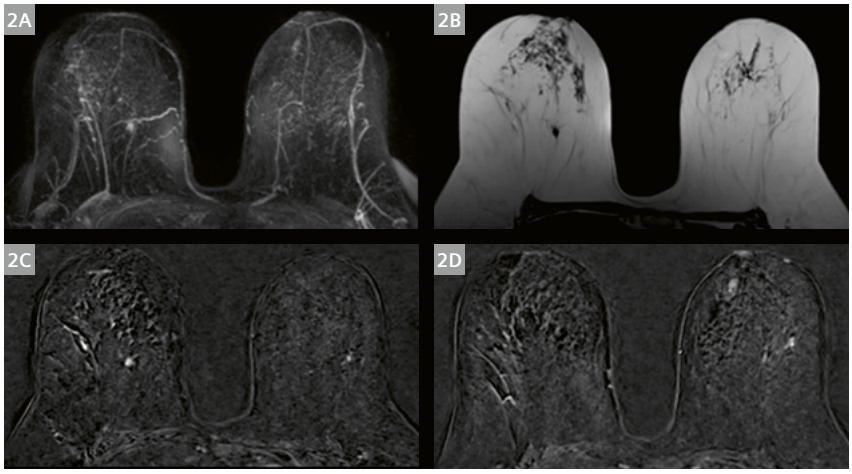
Sequence	Orientation	TR/TE (ms)	FOV read (mm)	Slice thickness (mm)	Base resolution	Phase Resolution (%)	b-value (s/mm²)
T2W STIR	Transverse	3800/70	300	3	448	70	–
T2W STIR	Coronal	3800/79	300	3	448	70	–
T2W	Transverse	3000/71	320	3	448	70	–
DWI	Transverse	6800/70	360	3	360	50	0, 800, 1500
T1W SPAIR pre/ post-contrast	Transverse	6.13/3.30	320	0.8	448	80	–
T1W SPAIR	Transverse	4.54/1.73	320	1.5	448	90	–
T1W SPAIR	Sagittal	4.58/1.96	230	1	230	70	–

Table 1: Sequence parameters

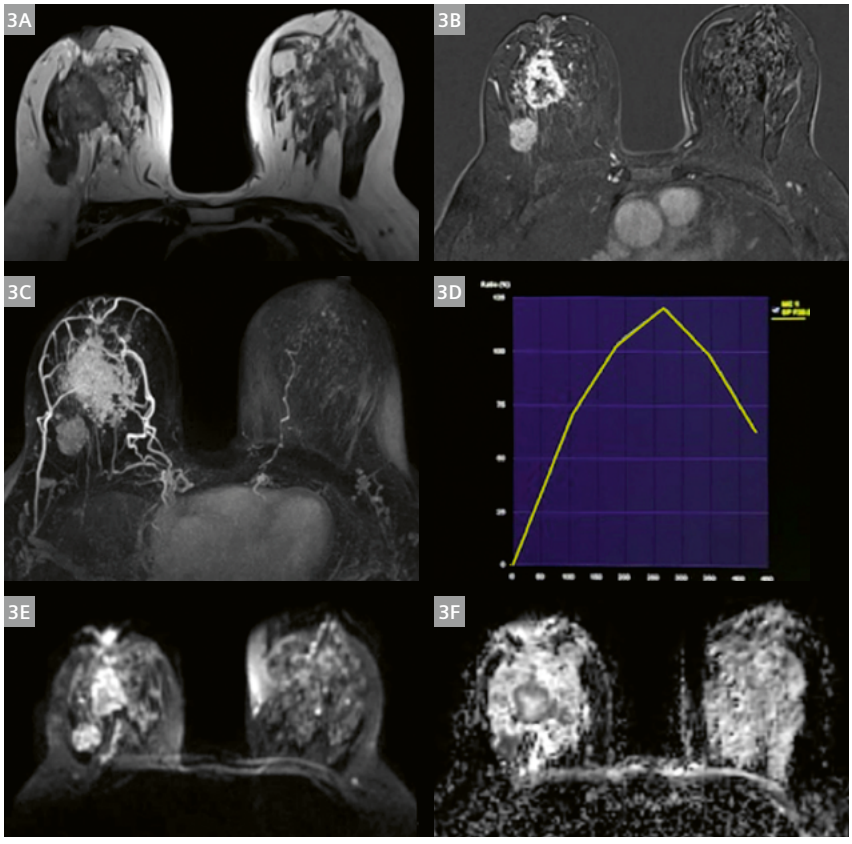
mammography (Fig. 6). However, MRI is very good at detecting even small lesions in the dense breast parenchyma and is highly sensitive for the detection of breast carcinoma (Fig. 2). MRI has multiple indications such as preoperative evaluation for staging (Fig. 1), treatment monitoring, detection of disease recurrence, screening for high-risk women (Fig. 2), assessment of breast implants, and as a problem-solving tool for indeterminate findings on mammography and ultrasonography. MRI is also useful in the evaluation of multicentric breast cancer (Fig. 3) and bilateral breast cancer (Fig. 4). Advanced MRI techniques and various functional MRI parameters can help improve the characterization of breast cancer lesions. MR spectroscopy is helpful in cases of granulomatous mastitis, which is very common in India and typically gives indeterminate imaging findings on conventional imaging techniques



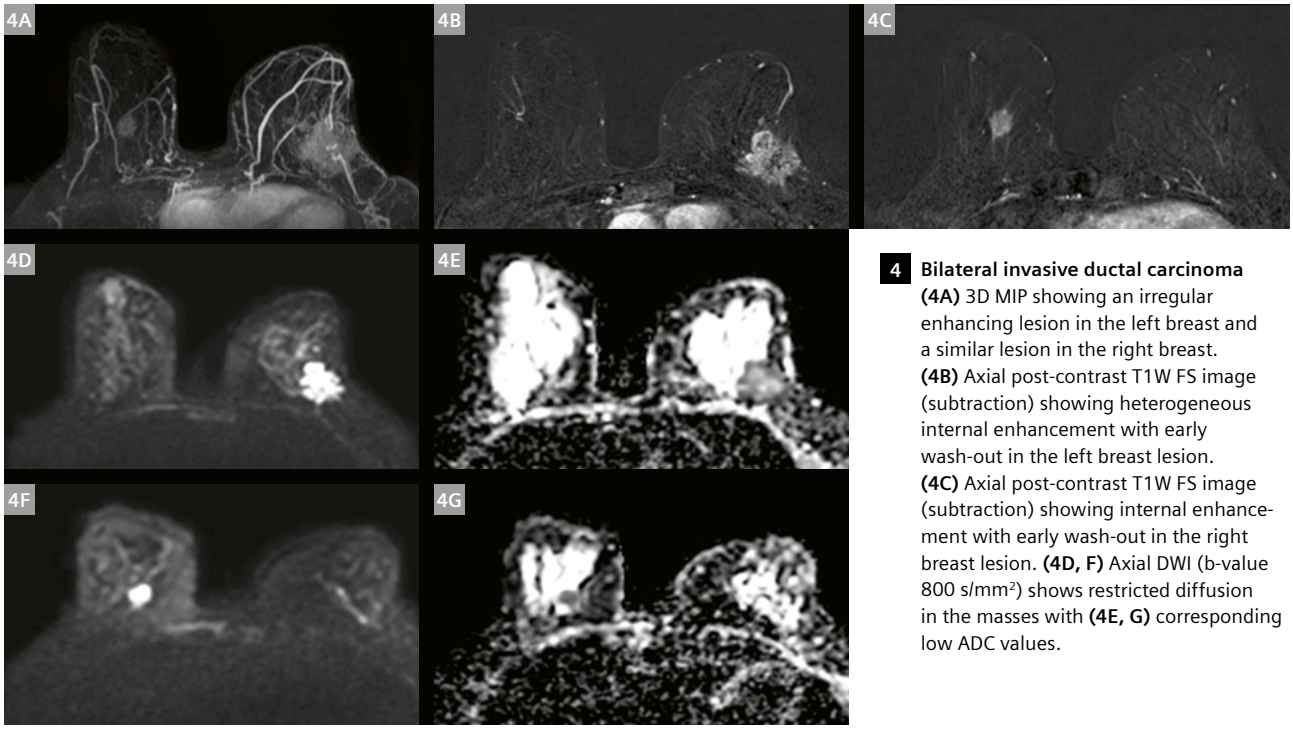
1 **Invasive ductal carcinoma**
(1A) Axial T2W image showing an irregular-shaped mass with irregular margins in the upper inner quadrant of the right breast. **(1B)** Axial T1W FS dynamic post-contrast subtracted image showing heterogeneous internal enhancement of the mass. **(1C)** Axial DWI (b-value 800 s/mm^2) showing the mass with restricted diffusion. **(1D)** Corresponding ADC map of the mass characterized by low ADC. **(1E)** MIP of the dynamic contrast-enhanced T1W images. **(1F)** The mass showed a type III kinetic curve of contrast enhancement, with early uptake and early wash-out.



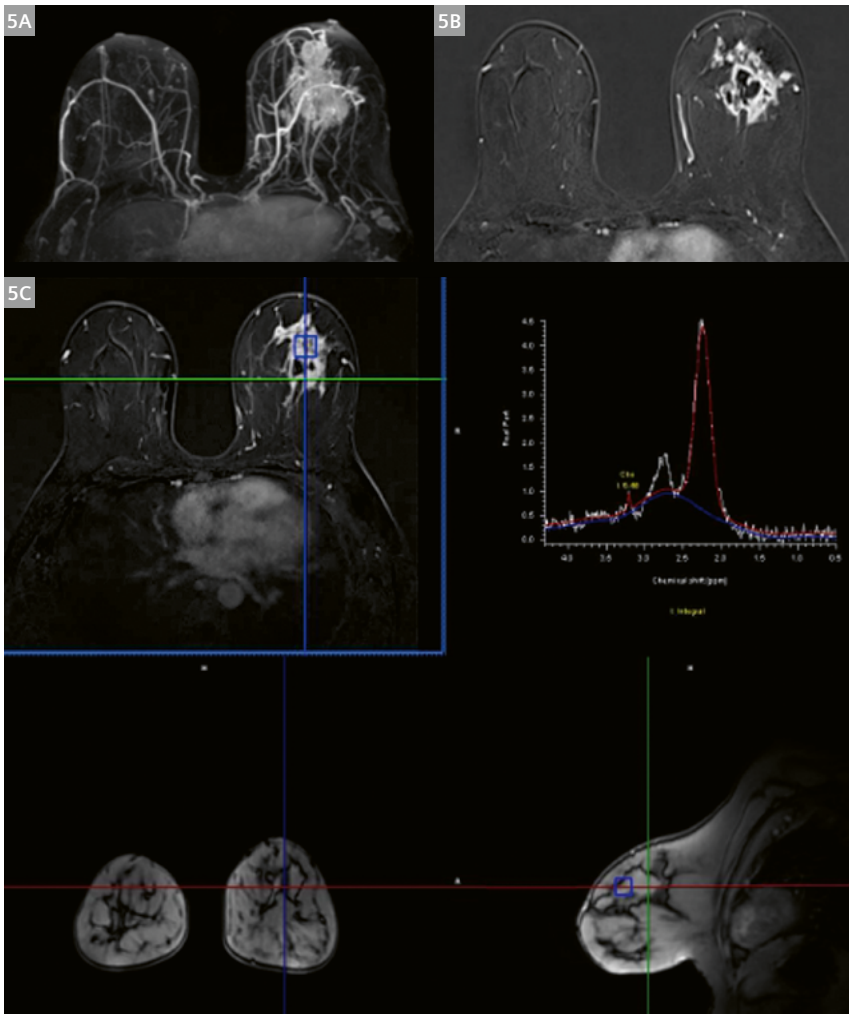
2 61-year-old woman with suspected invasive ductal carcinoma detected on screening mammography. MRI was performed to confirm and evaluate the left breast lesion, which turned out to be benign. **(2A)** MIP of the dynamic contrast-enhanced T1W images. **(2B)** Axial T2W image showing hypointense spiculated mass in the right breast. **(2C)** Axial T1W FS dynamic post-contrast subtracted image showing enhancing mass in the central region of the right breast. **(2D)** Mild type I enhancement of the lesion in the left breast, which turned out to be benign on regular follow-ups.



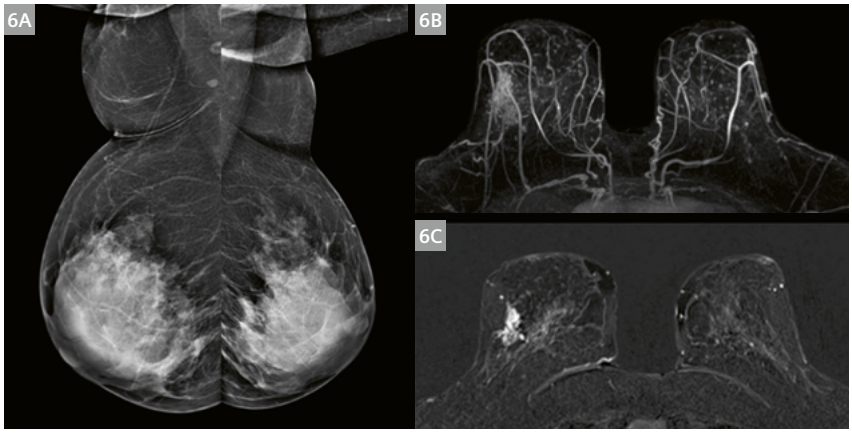
3 Multicentric breast cancer in a 41-year-old patient. **(3A)** Axial T2W image showing two ill-defined, irregular masses in the right breast with irregular margins and architectural distortion. Nipple areolar complex was involved with retraction of the nipple. **(3B)** Axial post-contrast T1W FS image showing heterogeneous rim enhancement of the largest mass and heterogeneous internal enhancement of the other mass. Multiple small enhancing foci can be seen in the adjacent parenchyma. **(3C)** 3D MIP showing the multicentric carcinoma with intense heterogeneous enhancement with **(3D)** type III kinetic curve. **(3E)** Axial DWI showed restricted diffusion in the masses with **(3F)** corresponding low ADC values.



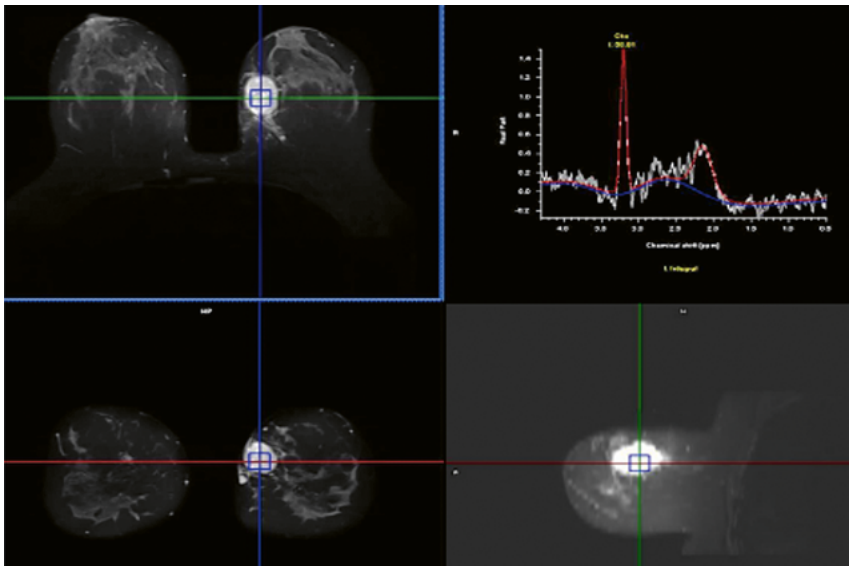
4 Bilateral invasive ductal carcinoma **(4A)** 3D MIP showing an irregular enhancing lesion in the left breast and a similar lesion in the right breast. **(4B)** Axial post-contrast T1W FS image (subtraction) showing heterogeneous internal enhancement with early wash-out in the left breast lesion. **(4C)** Axial post-contrast T1W FS image (subtraction) showing internal enhancement with early wash-out in the right breast lesion. **(4D, F)** Axial DWI (b-value 800 s/mm^2) shows restricted diffusion in the masses with **(4E, G)** corresponding low ADC values.



5 Granulomatous mastitis with abscess
(5A) 3D MIP showed heterogeneous diffuse enhancement. **(5B)** Axial TW FS dynamic contrast image showed diffuse enhancement and an abscess with rim enhancement. **(5C)** MR spectroscopy showed low Choline level in the lesion.



6 Ductal carcinoma in situ
A 43-year-old woman presented with bloody nipple discharge from the right nipple. **(6A)** Digital breast mammogram (MLO) views. **(6B)** 3D MIP showed non-mass enhancement in the right breast. **(6C)** Axial post-contrast T1W FS image (subtraction) showing non-mass enhancement. Histopathology: invasive ductal carcinoma with DCIS.



7 MR spectroscopy
A 28-year-old patient with MRS showing a Choline peak in malignant phyllodes.

such as ultrasound or X-ray mammography (Figs. 5, 6). On MR spectroscopy, high Choline was found in most of the malignant lesions (Fig. 7), so MRS can be useful in the differentiation of benign and malignant breast lesions, but also in predicting the aggressiveness of tumors, and for monitoring response to neoadjuvant chemotherapy. MR Ductography is another non-invasive imaging technique that can be useful in the evaluation of intraductal lesions.

In India, when patients present with large masses it is very common to perform a radical mastectomy. However, in bigger cities there is now increasing awareness about breast cancer among women who prefer the option of conservative breast surgery. MRI is extremely helpful for adequate planning, management, and follow-up. As breast carcinomas are being detected in more and more young women in India, breast MRI is gaining a crucial role as it is safe, radiation-free, and very useful even in dense breast parenchyma.

Conclusion

Breast MRI is a highly sensitive examination to detect breast carcinoma. It has excellent tissue contrast with high sensitivity, however the specificity is still relatively low. To overcome the limitations in the specificity of contrast-enhanced MRI, additional functional MRI parameters such as diffusion-weighted imaging and MR spectroscopy can be used for a multiparametric evaluation of the breast. As shown in various research studies [10, 11], such a multiparametric breast MRI approach has significantly improved the diagnostic accuracy of breast MRI at our institution and has the potential to reduce unnecessary biopsies.

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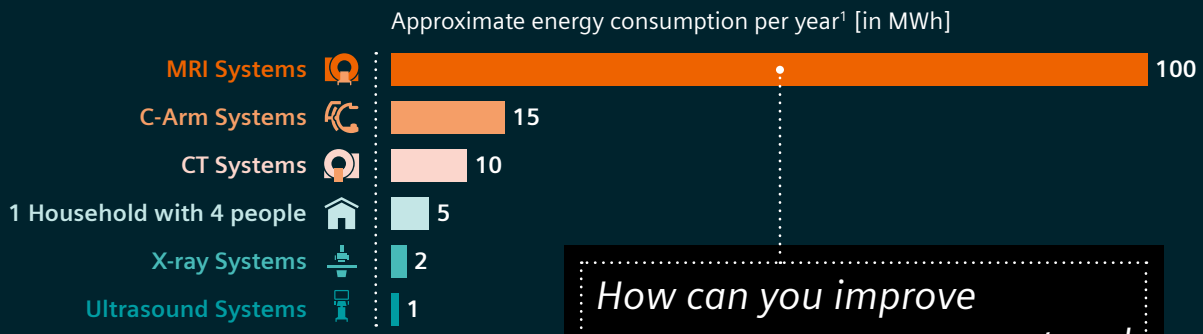
Contact

Professor Pratiksha Yadav, M.D., Ph.D.
Head, Interventional Radiology
Director, Breast Imaging Fellowship, Women Imaging Fellowship
Dr. D. Y. Patil Medical College, Hospital and Research Centre
Pimpri
Pune, 411018
India
Tel.: +9120 27805900
yadavpratiksha@hotmail.com

Environmental Sustainability in Magnetic Resonance

MRI is the major contributor in radiology to energy consumption



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It was first introduced in 2004 and prevents helium boil-off throughout your scanner's lifetime. It is available for all our MAGNETOM systems.

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A significant reduction in helium inventory is possible with our latest scanner generation.

- Improved magnet & gradient architecture
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Our new class of MRI systems offers you the most compact whole-body MRI with virtually helium-free infrastructure and radically simplified infrastructure requirements:

- Only 0.7 liters liquid helium
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- No quench pipe
- New benchmark in ramp-up times

Values are computed for a 1.5T MAGNETOM Sola system for illustration purposes.

1 Data Siemens Healthineers own measurements and assumptions; Actual consumption can vary depending on use pattern, system type, and configuration.

2 Assuming the system is turned on during the weekends and overnight.

3 Results are quantified assuming scanning operations as per COCIR standards.

How to save energy with your MRI system:

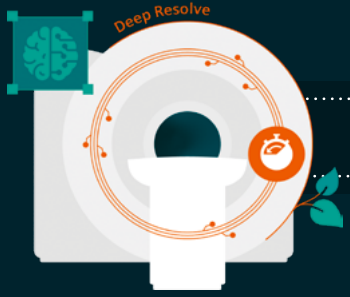
Energy consumption for an MRI system in one year, if the scanner is always on[2]: **100 MWh**

Save ~20% energy by turning off your scanner when not in use[3] **~80 MWh**

Did you know?

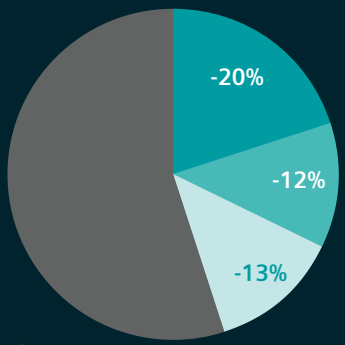
The start-up time for our scanners is only approx. 5.5 minutes and with our System Start-Up Timer you can enable automatic start-up of your scanner. So your system is ready when the workday starts!

Save ~12% energy by using Eco Power mode[3] **~70 MWh**



Save ~13% energy by using Deep Resolve **~60 MWh**

Make the most of our innovations and save **~40%** energy!



Breast Biopsy Workflow with *syngo* MR XA20 – How I Do It

Sarah-Jane Lewis

Siemens Healthineers UK and Ireland

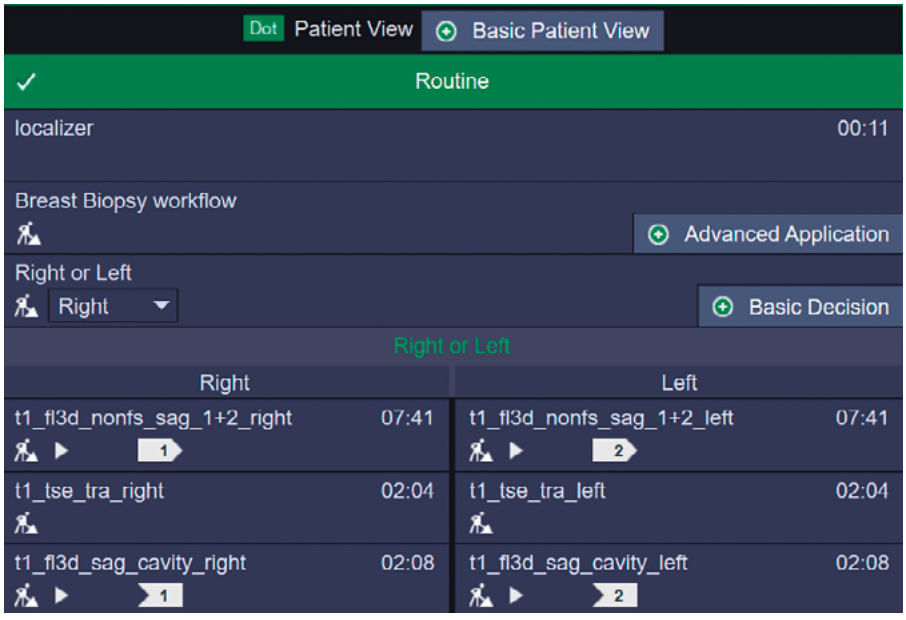
Background

During the investigation of a breast lump or suspicious lesion, the patient may undergo several modality examinations. The dynamic contrast-enhanced MRI scan is highly sensitive [1] at demonstrating lesions and may lead to the discovery of a lesion only visible on the MRI scan, a so-called MRI-only lesion. If the lesion is only visible with MR imaging, the biopsy must be performed under MRI guidance. Clinical sites that perform breast MRI in the UK are expected to either perform or have access to a referral site that performs MRI-guided biopsy.

This article provides an overview of MR-guided breast biopsy performed using the Breast Biopsy software, *syngo* MR XA20 version (Siemens Healthcare, Erlangen, Germany).

Introduction

A breast biopsy itself may involve several stages: A standard procedure involves a vacuum-assisted biopsy (VAB) using an MRI-compatible biopsy system. The biopsy console unit is not MRI-compatible and must remain outside the scan room. There are several manufacturers of such devices and the biopsy arm should be checked for MRI compatibility along with the foot pedal used to control the tissue removal. Targeting is performed using an MR Safe introducer kit that includes a needle guide for accurate positioning and an obturator that helps both to stem the flow of blood and to confirm the location. Once the main biopsy has been performed, the radiologist may leave a hookwire or marker *in situ* for further surgery or biopsy site evaluation. Sterile disposable grids are also required. Consequently, good preparation is essential before each examination due to the large amount of specialist consumable items needed. It is recommended that procedures are reviewed and workflows are practiced regularly at the clinical site to maintain the competency to perform breast biopsy. Clinical sites are expected to perform at least 10 biopsies a year to maintain their competency [1].



1 Right and left breast may be separated to activate specific coil elements

Equipment

The procedure was performed on a 1.5T MAGNETOM Sola system with *syngo* MR XA20 software and the Breast Biopsy software license. A grid system was used, which is available for the 2-/10-/16-channel and 2-/4-/8-channel Sentinelle Breast Coils, and the Breast BI 7 coil. The grid is the biopsy system used most in Great Britain and Ireland (GB&I) and is the method described in this article. The Breast Biopsy software, however, also supports the post and pillar approach in combination with the Breast BI7 coil.

Preparation

The patient is required to lie prone, and the procedure may take as long as 45 minutes. It would be advisable to encourage the patient to empty their bladder and to avoid heavy meals for a couple of hours prior to the procedure. A cannula is required for IV contrast. The patient may need to place their hands above their head in a "Superman-style" position, so it may be advisable to place the cannula in the wrist if the elbows are to be bent for the procedure. A useful procedure seen at several sites within GB&I is to have a meeting prior to the procedure and delegate the tasks required. For example, a metallic scalpel may be used, and a designated person will be responsible for making sure it is safely brought into, and removed from, the scanning room. Additionally, the radiologist performing the procedure should confirm the anatomical site or sites to be biopsied. This can be performed at a PACS workstation or the MR system itself. The location of the potential biopsy site is important as this can influence how the breast is positioned within the grid. With a biopsy site toward the axilla, the patient may need to lie slightly obliquely on the table to ensure the axillary tissue is pulled into the grid area. Equally, if the biopsy site is toward the chest wall, the breast tissue needs to be pulled quite firmly away from the chest into the grid. If a medial approach is considered, then the contra-lateral breast will need to be lifted out of the way using the breast plate and the grid and fiducial placed on the medial side. If the exact approach is not known beforehand, the breast will need to be compressed medially using a second grid with a second fiducial. Most radiologists will generally attempt a lateral approach if possible as the access is more open, therefore making the procedure easier. Once the patient is lying on the patient table with the cannula attached to the contrast pump, the breast should be immobilized within the biopsy grid device by providing moderate compression. The positioning of the grids should be supervised by the radiologist to ensure optimum compression. Compression is needed to immobilize the breast but also to prevent stretching or tenting of the subcutaneous tissue when the introducer needle is pushed in and out of the breast. Compressing the breasts also has the advantage of creating a smaller volume of tissue to scan, which is useful in volume scanning to reduce the number of slices required. The level of compression also needs to be balanced against the risk of reducing visibility of the lesion by applying too firm a compression [2].

The fiducial should be placed in a grid opening. With the Sentinelle Breast Coil, the fiducial is placed at C4 as standard. The use of the same grid opening every time a biopsy is performed allows continuity and reduces any potential user error due to a wrong fiducial position. As the grid position is not fixed, a marker is crucial as it is used to establish a reference position for needle insertion.

Scanner protocols

The design of the biopsy scanning protocols varies slightly from that of the diagnostic protocol. The number of different sequences should be truncated to reduce the scanning time. The sequences will always start with a localizer. These should be looked at to assess the quality of the compression and to ensure that a good proportion of the breast tissue is included in the coil. If there is a roll of tissue above the grid, it may be possible to reposition the patient by releasing the grid and allowing more tissue to fall into the grid area. The localizer can also be used to assess the filling of the fiducial marker with diluted contrast medium when using the Siemens Healthineers Breast BI 7 coil and NORAS Breast Biopsy Set (NORAS MRI products, Höchberg, Germany). It may not be necessary to include any sequences prior to the dynamic run, the exception to this is if the suspected tumor area is shown particularly well on a non-enhanced sequence, such as T2 axial. Dynamic sequences will consist of a 3D gradient echo T1 in the sagittal plane without fat saturation. Sagittal acquisition is performed so that the slices are parallel to the grid plane. No angulation can be used. Inline subtraction is included for easier visualization of the tumor. The number of phases required should be discussed at the site level as there may be some delayed enhancement due to the compression of the breast and feeding blood vessels [2]. The initial phases are automatically loaded into the workflow as soon as they are reconstructed so these can be used to start the configuration whilst the later phases are obtained. Therefore, there is no time-saving advantage to keeping the number of dynamic phases too low. The automatic opening of the Breast Biopsy workflow is triggered by the **Advanced Application** add-in and, once completed, subsequent sequences will be loaded into the appropriate segments of the workflow. A decision within the strategy can be used to separate right and left breasts to have specific coil elements activated, as shown in Figure 1. Additionally, predetermined offsets in the sagittal dynamic blocks can be used to save a small amount of time when setting up the sequence.

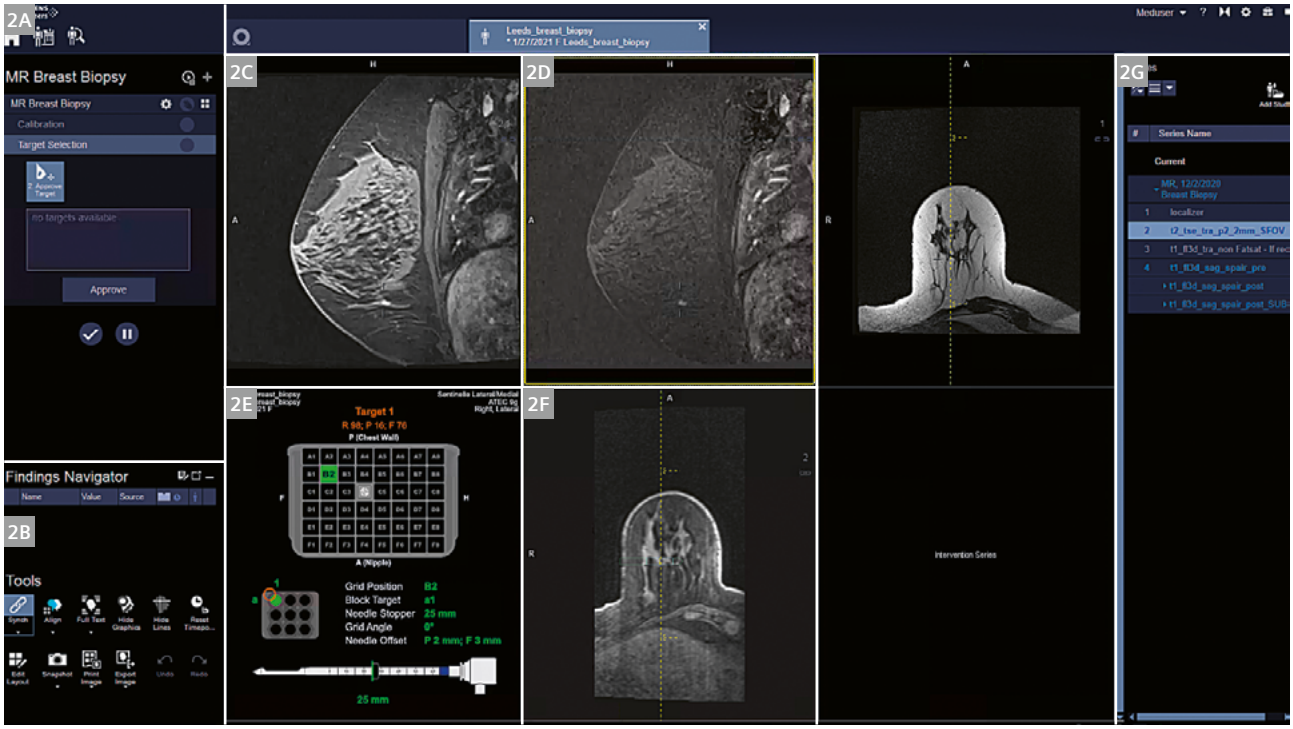
Biopsy workflow

The patient is registered. During registration, the previous diagnostic images can be recalled from the PACS and will be available in the Breast Biopsy workflow. If this step is missed, then the images can be added to the Breast Biopsy workflow using the **Add Study** button in the Series Navigator. An overview of the whole layout is shown in Figure 2. Once the dynamic run is started, an IV injection is performed between the first and second phases, with the first phase acting as the subtraction mask or subtrahend. When the injection has been completed, your attention can turn to the Breast Biopsy workflow. The automated loading of sequences should have started, and the first dynamic phase can be used to begin the calibration step. The calibration workflow step contains all the information relating to the equipment used and the position of the fiducial. This step can be completed by the technologist in conjunction with the radiologist. The device menu enables the user to select from a list of pre-configured settings, depending on what equipment is in use.

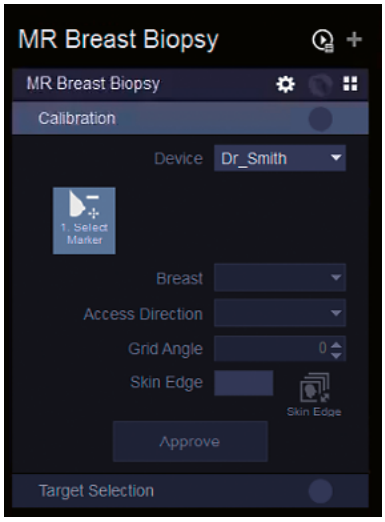
In the normal scenario, only a small number of presets should be needed as similar methods will be used each time. Usually, a site only possesses one biopsy coil and the same type of needle device kit is normally used. If the fiducial is placed into the same grid square each time, this naturally limits the number of presets needed. When configuring presets for the Sentinelle Breast Coils, only a C4 marker position is possible. These presets can be configured prior to scanning and quickly amended during the exam, if needed. Configuration of the device setting presets is accessed via the cogwheel icon as shown in Figure 3. The presets can be named as required after the radiologist using them or the individual needle types as shown in Figure 4.

Once the device preset has been selected, then the fiducial needs to be located. As soon as the images start arriving in the workflow, they will load with the native sagittal images in the top-left segment and the inline subtractions in the top middle segment. The middle mouse button or the keyboard arrows allow you to scroll through the images to locate the fiducial, which will be seen in cross-section on the sagittal as a dot. In the bottom middle segment, an MPR image allows you to see the length of the fiducial in the transverse plane. Click the **Marker Position** icon to activate the crosshairs. To mark the fiducial, place the crosshairs on the end of the fiducial closest to the breast as shown in Figure 5. Click the **Approve Marker** icon to confirm the marker position and set the **Access Direction**, which can be seen in the drop-down field. As the breast is compressed and the fiducial is pushed against it in the grid, the fiducial is marking the skin surface.

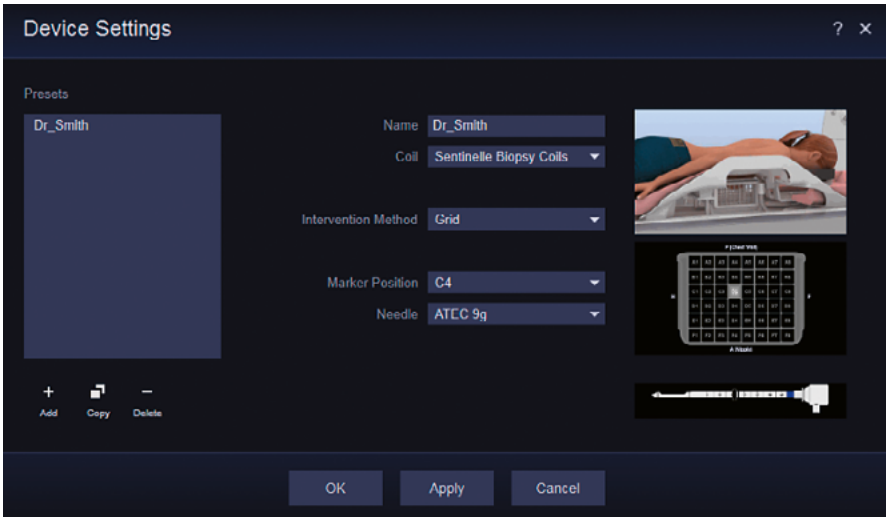
The slice position of the skin surface is visible in the **Skin Edge** field, which gives a slice position in the right or left direction. This skin surface location is needed for the depth measurement calculation. If the radiologist wants to



2 **2A** Workflow steps, **2B** Tools and Findings Navigator, **2C** targeting segment with native sagittal images, **2D** subtracted sagittal images, **2E** graphics for the targeting information, **2F** MPR of native images, **2G** Series Navigator

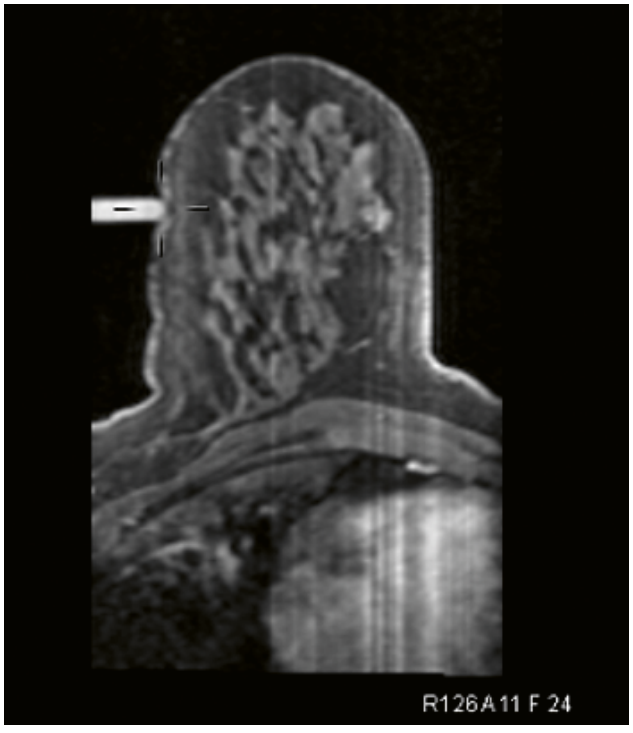


3 Calibration step



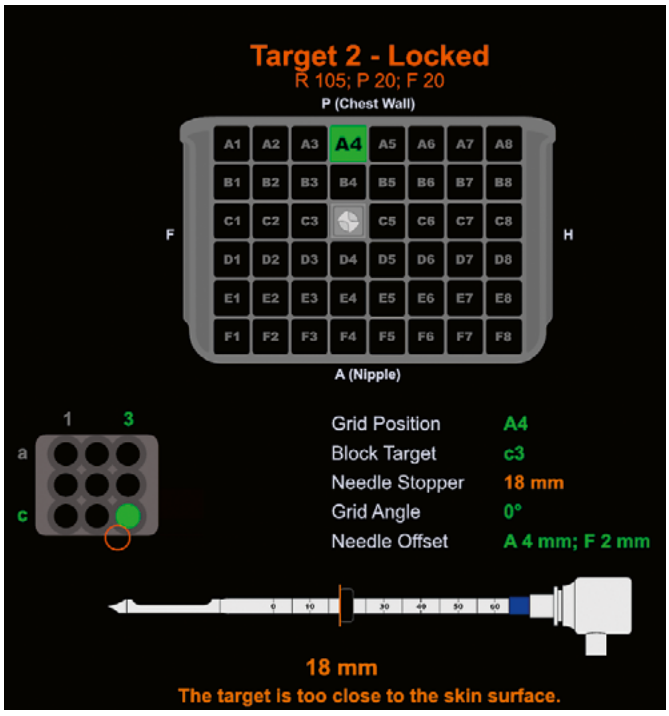
4 Device settings

change this skin surface, this can be done by clicking the **Skin Edge** button. By scrolling through the native sagittal images, you can visualize the grid and the skin protruding through the grid squares. By clicking **Approve** (skin edge), you reset the skin edge and a purple grid overlay allows you to visualize where the skin edge and grid are. Selecting the device preset and determining the marker position are necessary calibration steps that must be completed prior to locating the target lesion. Click **Approve** to complete the **Calibration** workflow step and lock these values in. If a double fiducial method has been used and then subsequently the alternate fiducial needs to be used, the preset can be changed mid-workflow. This might be needed if a lateral approach was planned but then the tumor position dictated that a medial approach was needed.

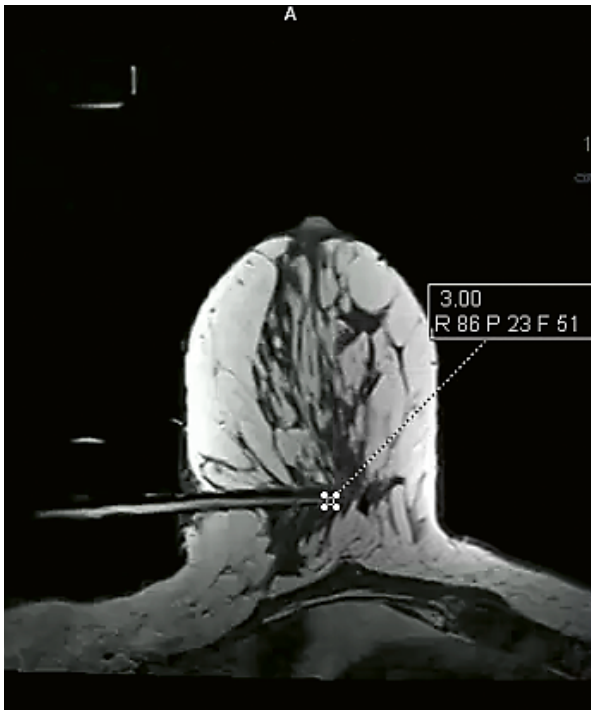


5 Marking the fiducial

After approving the **Calibration** step, the **Target Selection** step is opened. The **Approve Target** tool is active, and the mouse pointer is displayed as crosshairs. If this is not required at this time, then the escape key can deactivate the tool. The radiologist can now view all images to see where the biopsy needs to be performed. Once a site has been chosen, the **Add Target** tool can be activated again and a mouse click on the lesion creates a target. At this point, the target has not yet been confirmed and pressing **Escape** removes the target. Alternatively, simply clicking in another place moves the target. Once the radiologist is satisfied with the target, the **Approve Target** button can be clicked. After this action, a finding will be created with images of the target, which can then be sent to the PACS. The target also appears in a list of targets that can be displayed on the Select&GO panels in the scan room. This is useful if multiple targets are obtained. The software has now calculated the depth and position of the target and this is displayed in the bottom-left segment. The graphic (Fig. 6) shows the exact position in the coordinate system, so this can be cross-referenced later with the pixel lens, if needed. Additionally, the needle system is displayed along with the depth measurement. If the target is within 20 mm of the skin surface on the fiducial side, then a warning will be displayed. The decision to proceed or not then lies with the radiologist. The side of the breast on the non-fiducial side has not been marked or delineated from the system, so the only limitation here is the depth of the lesion and the limitations of the needle system. On a small



6 Graphic showing the exact target position in the coordinate system



7 Transversal scan at the level of the obturator

breast, the targeting can be quite close to the far edge of the breast and no warning is issued, so the staff must carefully check that they are not going to biopsy partially outside of the breast. The biopsy needle samples from a trough or notch along the length of the needle. The calculated depth positions the target in the middle of the notch, meaning that some of the needle and notch extends beyond the target point. The target coordinate display also gives information about the target selected by the radiologist and the nearest possible needle block position. The available target positions are limited by the grid walls themselves, and the needle block only has pre-determined positions. The red circle shows the target position marked and the green circle shows the nearest possible grid block opening. The **Needle Offset** shows the distance in mm that differs between these two positions. If the position is not precise due to the internal wall of the needle block, then the radiologist can make the decision to remove the needle block and perform the biopsy freehand. This requires experience and a steady hand as the needle block helps keep the biopsy arm perpendicular to the grid. If the position of the biopsy is not perfect due to the grid wall, not much can be done to move the needle itself to this position. However, when performing the vacuum biopsy, the radiologist can decide to concentrate the biopsy in this direction. So in Figure 6, the red circle/lesion is in a 7 o'clock position relative to the green circle/needle, so the radiologist could decide to perform more biopsy samples here rather than more posteriorly toward the chest wall. Select the desired target and click **Send** to display the target coordinates on the Select&GO display in the scan room. In the example in Figure 6, the target is within 20 mm of the skin surface, so a warning is issued.

The first part of the intervention involves inserting the coaxial introducer sheath to create a pathway to the target. The patient table should be moved out of the scanner bore and the table lock applied from the Select&GO display. The radiologist will then inject some local anesthetic into the desired area through the biopsy grid. As soon as the area is numb, a small cut is made with a scalpel. Then the needle block can be inserted into the appropriate grid segment. If the required segment happens to be C4, where the fiducial is, then this will need to be carefully removed to make way for the needle block. Once the needle block is *in situ*, the radiologist can view the Select&GO display and select the depth measurement. Depth markers on the introducer sheath are used to insert the needle to the calculated depth, within the correct position in the needle block. Once the coaxial introducer has created the pathway, then the inner stylet can be withdrawn and replaced with the obturator. The table is unlocked, and the patient table is moved back into the scanner bore. A transverse scan is performed at the level of the obturator as shown in Figure 7. This scan can be performed at a slightly higher resolution than the dynamic run and is used to confirm the position of the obturator and can be positioned using the

known coordinates of the target as given in the target graphic. The transverse scan is looked at to confirm that the obturator is in a good position relative to the target. This workflow needs to be performed quickly as ideally the lesion would still retain some contrast on this scan, to be able to visualize it. If the obturator is not in the ideal position, the radiologist can either decide to reinsert the stylet and adjust the depth or can adjust on the fly. For example, frequently the intervention pushes the lesion slightly further away, toward the far side of the breast side. In this case, radiologists may make the adjustment to this as they go, simply by pushing the biopsy device further in.

Once the vacuum biopsy is completed, a post-biopsy image is acquired. A large void will be seen at the site of the biopsy and it can be confirmed that the lesion has been removed or sampled. It is likely that a post-biopsy clip will then be implanted to act as a marker for further imaging or interventions. Many sites do not perform imaging after the implantation, as it can be difficult to see a small clip in a large area of bleeding.
The findings created contain images that can be sent to the PACS using the **Save and Send** function when closing the MR Breast Biopsy workflow.

Troubleshooting tips

There may be occasions when the configuration needs to be changed during the exam. For example, the needle type may need to be changed if the biopsy is located quite close to the skin edge. This can be done by configuration of a device preset on the fly. This can be performed in the device settings by copying the current preset and then changing the needle type. This will be loaded automatically without any changes to the original images, fiducial position and targeting. However, you can only access the **Device Settings** menu if you selected **Modify** in the **Calibration** step. Also, you may want to change the direction from lateral to medial approach. Again, this can be done by clicking the **Modify** button in the **Calibration** step and redefining the marker position on the medial sid.
Sometimes you will need to view the sagittal images in an alternate orthogonal plane. This can be done by using the blue orientation cube on the right side of the display segments. By left mouse clicking on the cube you rotate through sagittal, transverse and coronal in turn. By right-clicking on the cube, you can select the orientation of choice. Additionally, you may want to view the subtraction images as a maximum intensity projection (MIP), which is done by selecting **MIP** in the bottom-left corner menu. With **MIP** selected, you can scroll through the phases using the movie tool, which you can start by pressing the spacebar or by opening the top-left corner menu. If you have left the orientation of the images in a slightly odd position and wish to reset them, double-clicking the blue orientation cube will reset the orientation back to sagittal.

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Contact

Sarah-Jane Lewis
MRI Applications Specialist
Siemens Healthcare Limited
United Kingdom
Phone: +44 7808 822444
sarah-jane.lewis@siemens-healthineers.com

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Assessing Breast Cancer Phenotypes with MRI Biomarkers in Clinical Practice

Elizabeth Morris, M.D.

Chief, Breast Imaging Service, Larry Norton Chair & Professor of Radiology,
Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY, USA

Introduction

Advances in our understanding of the human genome have transformed the way we understand and treat breast cancer. Today, oncologists and gynecologists are no longer saying "this is invasive ductal carcinoma," but they can classify each breast cancer as one of four molecular subtypes based on its genetic expression. In this context, breast MRI provides a highly valuable and non-invasive tool to differentiate between subtypes due to the differences in imaging phenotypes between subtypes. In addition, as the cancer subtype has a significant impact on the individual patient's response to the currently available treatment options, MRI biomarkers may be used to predict complete response to therapy including non-surgical options and improve patient outcomes.

Breast cancer subtypes

While every breast cancer is unique, breast cancer can be classified into one of four distinct subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) positive, and basal-like. Luminal cancers are the most prevalent breast cancer subtype, representing 70% (55% luminal A, and 15% luminal B) of all breast cancers. Non-luminal cancers are less common but still substantial, representing 30% (15% basal-like and 15% HER2) of all breast cancers (Fig. 1).

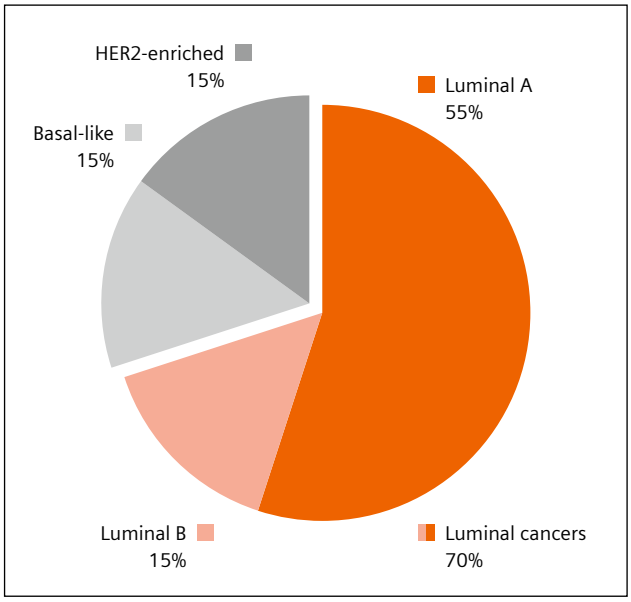
The breast cancer subtype that is present in an individual patient has a significant impact on the cancer's aggressiveness. HER2-positive cancers and triple negative cancers are more highly aggressive whereas luminal A cancers (which are the most frequently diagnosed breast cancer) have a relatively good prognosis. In addition to the subtype, it must also be noted that intracellular receptors that respond to estrogen (ER) and progesterone (PR) hormones as well as HER2 receptors have been shown to also impact cancer aggressiveness. All cells have HER2 receptors on them, but if they overexpress these receptors to a certain degree, then they are associated with a much more aggressive form of breast cancer with uncontrolled growth.

Luminal A

Luminal A cancers are low-grade cancers that are strongly ER positive and/or PR positive as well as HER2 negative. They show no amplification of HER2, the proto-oncogene for increased growth, or Ki-67, a biomarker for cellular proliferation.

Luminal A cancers have a five-year survival rate of over 80%, which is highest among the subtypes. Luminal A cancers respond favorably to hormone therapy with tamoxifen or aromatase inhibitors (AI). Nonetheless, they are associated with the risk of late mortality more than ten years after the original diagnosis. It is hypothesized that the cancer cells remain inactive for a long time, probably suppressed by the immune system, before late relapse takes place. Late relapse is not uncommon with this subtype and luminal A cancers are highly likely to metastasize to the bone.

On MRI, luminal A presents as a typical spiculated mass with significant desmoplastic response (Fig. 2).



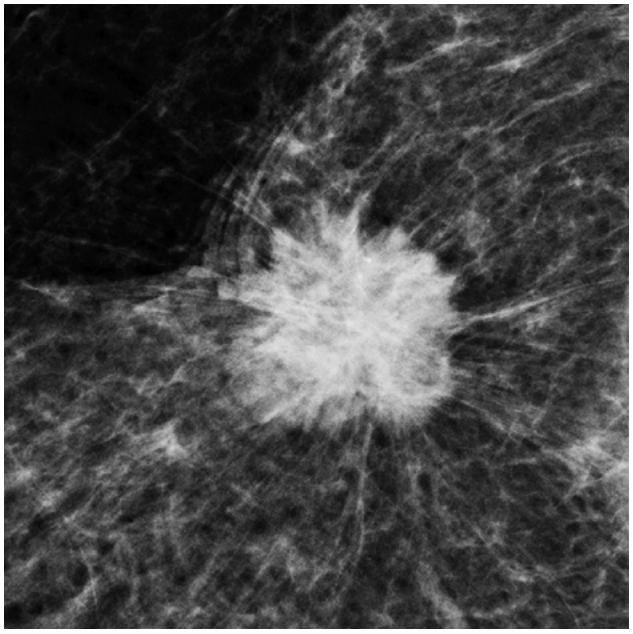
1 Breast cancer subtypes and their respective prevalence.

Luminal B

Luminal B cancers have a lower level of expression of ER and PR than luminal A cancers, and 20–30% of these cancers have a concomitant amplification of HER2. Compared with luminal A cancers, luminal B cancers are higher grade (always medium- to high-grade), showing a higher Ki-67 index and likely having lymph node involvement. Hence, luminal B cancers have a definite decrease in long-term survival, with a five-year survival of approximately 40%. Like luminal A cancers, luminal B cancers metastasize to the bone.

Mammoprint, Oncotype DX, and PAM-50 multigene assays identify breast cancers with an increased risk of recurrence based on gene expression arrays using formalin-fixed paraffin-embedded (FFPE) specimens. They help to identify which patient can forego chemotherapy. For luminal B cancers, a low Oncotype DX recurrence score permits the recommendation of hormonal therapy alone, whereas a high recurrence score indicates that chemotherapy is required as an adjunct treatment.

On imaging, luminal A and luminal B cancers look very similar. Tumor grading is the preferred mechanism for differentiating luminal A and luminal B cancers. Ki-67 can also provide great assistance but is not routinely recommended. Ki-67 as a prognostic marker is associated with larger tumor size, lymph node involvement, and shorter disease-free survival (DFS) and overall survival (OS). Ki-67 has shown to be positively associated with response to neoadjuvant chemotherapy (NAC).



2 Zoomed T1-weighted post-contrast images (subtracted from T1-weighted pre-contrast) showing the typical representation of a luminal A breast cancer: a hyperdense, spiculated mass with irregular margins and significant desmoplastic response.

HER2 positive

15% of all breast cancers are HER2 positive. These tumors usually have an intermediate to high nuclear grade. Prior to the introduction of traztuzumab (brand name Herceptin) and pertuzamab (brand name Perjeta), the untreated clinical five-year survival rate was 31%; with these treatments, treating physicians have achieved a 33% reduction in mortality and a 52% reduction in recurrence.

Patients with HER2 positive cancers are more likely to have metastases that go to the viscera and the brain.

Basal-like

The fourth subtype of breast cancer is basal-like. Basal-like cancers have cells that are similar to epithelial cells (i.e., basal cells) that line the surface of the basement membranes along the ducts.

While there are many different types of basal cell cancer, the clinical focus is on triple-negative invasive ductal cancers. The discussion of triple-negative cancers generally centers on the very aggressive nature of this cancer and that it is more common in African-American women. In this population, this cancer represents 27% of the overall cancer burden and 41% of the cancer mortality.

Adenoid cystic carcinoma is a rare type of invasive ductal cancer; however, while it is triple negative, it has very positive prognosis and outcome.

Basal-like breast cancer is usually high grade with an aggressive clinical course. Recurrence normally occurs in the first five years after diagnosis. Once a patient is beyond the five-year mark, the prognosis is normally positive; this is in stark contrast to luminal A type breast cancer. Basal-like breast cancer also has a high occurrence of metastases to brain, lung, and viscera. This subtype of cancer has the highest mortality rate.

The role of MRI and radiomics

Over the past few decades, breast MRI capabilities have improved dramatically. With radiomics and radiogenomics, MR images can now be analyzed so that the image is related to the genome, rendering a host of data that might positively affect patient outcome. Radiologists can identify volumes to be segmented on MR images. Computers can then extract hundreds of descriptive and quantitative features that, when combined with medical and genomic data, create a comprehensive database. Clinicians can compare pixels with adjacent pixels and analyze them in this context to render many different datasets.

As opposed to traditional human interpretation where radiologists interpret the shape, margin, internal enhancement patterns, and kinetic curve of the lesion, computers can automatically segment abnormal lesions and parenchyma in the MR image, produce data on kinetic features, and analyze morphological texture features rendering a

more quantitative phenotype analysis. Radiomics has provided deeper analytic features in datasets, e.g., inter- and intra-tumor heterogeneity, site entropy, kurtosis, and site cluster dissimilarity, by extracting information from images that is imperceptible visually. This information is combined with clinical data and genomic profiles to facilitate the establishment of a clinically applicable prognosis prediction model. For example, MR images of a patient pre- and post-NAC as shown in in Figure 3 could render feature data that provide the clinician with a greater ability to predict pathologic complete response (pCR) by showing whether viable tumor persists.

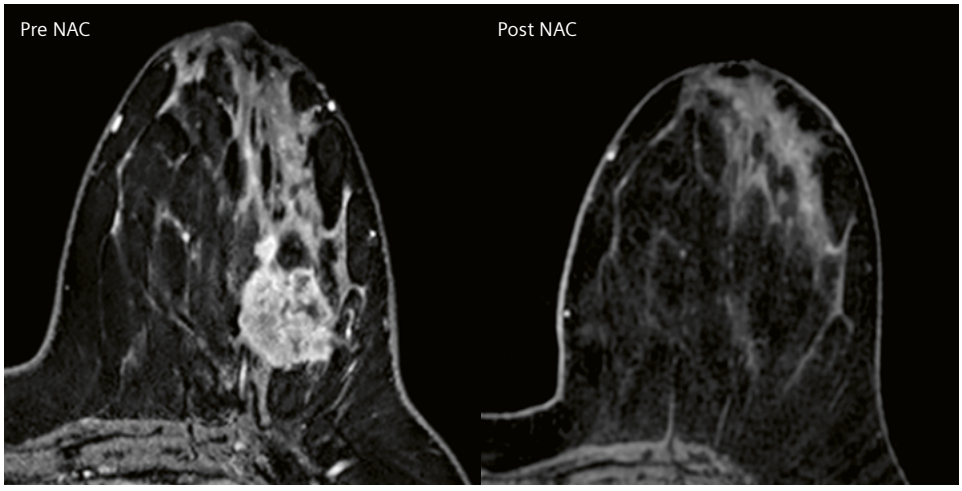
While radiomics encompasses numerous potential features, these features tend to be standardizable and quantifiable. Many research organizations have been investigating the utility of radiomics to determine breast cancer phenotype groups. At Memorial Sloan Kettering Cancer Center (MSK), we have found that clinicians are able to predict breast cancer phenotypes with radiomics nearly as accurately as Oncotype DX and PAM50. Therefore, it is possible that in the future radiomics could establish oncologic signatures in the same way that tissue sampling currently does but without the need for invasive procedures.

Neoadjuvant Chemotherapy

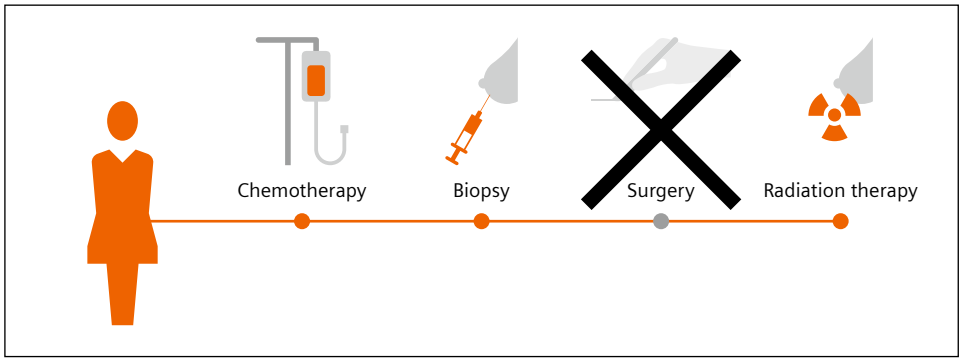
Neoadjuvant Chemotherapy (NAC) is increasingly used to treat breast cancer because it enables breast-conserving surgery in women who traditionally require a mastectomy. The goal of NAC is pCR, defined as the absence of any residual in-situ or invasive cancer. pCR has served as a surrogate of DFS and OS for a long time.

Currently, the most accurately predictive test for pCR is MRI. MRI is more accurate in determining residual disease than physical examination, mammography, and ultrasound [3, 6]. However, MRI is not universally utilized as it still renders many false positives and false negatives. The absence of enhancement on MRI is called a radiologic complete response (rCR) even when there is a residual mass, and the pattern of the residual tumor is defined as contiguous or scattered to allow for better surgical selection.

With radiomics, it is possible that clinicians will achieve better response prediction with MRI, and MRI could potentially be used to replace surgery in the identification of patients with a complete response. Preliminary studies at MSK have shown that radiomics may be able to differentiate responders from non-responders.



3 Subtracted, post-contrast T1-weighted images pre and post neoadjuvant chemotherapy. Patient showing complete imaging response which was confirmed as complete pathological response by biopsy. Highest response rates are seen in patients with TNBC and HER2+.



4 Proposed Care Pathway for patients with predicted pCR based on radiomic MRI profiling and biopsy-derived genetic profiling. In a planned trial patients shall proceed directly to radiation therapy without surgery.

New study conducted by Memorial Sloan Kettering Cancer Center

Currently, the NAC course of treatment involves MRI monitoring at critical points. We have been conducting a trial to perform a percutaneous MRI-guided biopsy in patients who have had an rCR as determined on MRI with radiomic analysis prior to surgery. We hypothesized that MRI-guided biopsy will accurately diagnose a pCR in women with complete response on MRI comparable to surgery, thus allowing us to avoid unnecessary surgery in these patients. For the pilot phase, so far ten patients have undergone the MRI-guided biopsy (with a marker to allow targeting of the biopsy) post NAC but prior to surgery. Results from the pilot phase indicate that MRI-guided biopsy can yield a high level of accuracy in diagnosing a pCR.

Therefore, we are currently proposing a full trial where the management of breast cancer in women with a pCR (as diagnosed by MRI-guided biopsy post-NAC) will proceed without surgery to the indicated duration of radiation therapy (Fig. 4). The salient open question is what quantity of residual disease precludes bypassing the surgical option for the less invasive method. Also, given that this would represent a new treatment protocol, the type of follow-up that would be required has yet to be determined.

Topics for further research

Another topic that is also worthy of further investigation is the association between parenchymal enhancement using contrast-enhanced MRI and the outcome of patients with breast cancer, as studied earlier by van der Velden et al. [4]. This study found that parenchymal enhancement is associated with long-term outcomes and higher parenchymal enhancement is associated with better outcomes. Women who have higher background enhancement who are treated experience better outcomes than women with lower background enhancement even though high background enhancement is associated with higher risk of developing breast cancer [4]. These results have been reproduced [5].

Contact

Elizabeth Morris, M.D.
Chief, Breast Imaging Service,
Larry Norton Chair & Professor of Radiology
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY, 10065
USA
Tel. +1 646 888 4510
morrise@mskcc.org

MRI features can also be investigated to predict cancer aggressiveness. For example, Lee et al. [1] found that spiculated margins were an indicator low grade ($p < 0.001$) and a low Ki-67 ($p = 0.007$); these are typical of luminal A breast cancers which have a high chance of pCR. Lee et al. also found that tumors with a high grade ($p < 0.001$) and that were ER negative were associated with poor patient outcome ($p = 0.001$).

Lastly, peritumoral edema, which indicates increased vascular permeability with local cytokines, is associated with early metastatic disease and can also be investigated for its clinical utility [2].

Conclusion

MR imaging is moving into an era of technology where the status quo is being disrupted. Artificial intelligence (AI) and machine learning will produce marked advancements in risk prediction and cancer detection.

As advances continue to be made in the tools available to clinicians, clinicians must ask themselves to find uses for these advancements that will improve treatment options, patient outcomes, and quality of life. Clinicians must be intellectually agile to use these tools to create new possibilities for the treatment of patients as individuals, guiding clinical practice toward personalized medicine.

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Observing Endocrine Therapy Resistance in Metastatic Breast Cancer with Whole-body MRI

Anwar R. Padhani

Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, Middlesex, UK

Introduction

Approximately 70% of breast cancers are estrogen receptor (ER) positive, and are, therefore, treated with endocrine therapies. However, about 25% of patients with primary disease and almost all patients with metastases will present with or eventually develop endocrine resistance [1]. The mechanisms underlying the development of resistance remain largely unknown but in the last 2 years, several studies have shown ER independent gain-of-function mutations in ESR1, the gene that encodes the ER, in approximately 20–30% of patients with metastatic ER-positive disease who received endocrine therapies, such as tamoxifen and aromatase inhibitors. These mutations lead to ligand-independent ER activity that promotes tumor growth, promoting resistance to endocrine therapy, and potentially enhancing metastatic ability. The emergence of endocrine therapy resistance via this mechanism suggests that, under selective treatment pressure, clonal expansion of rare mutant clones occurs, thus contributing to resistance. Rationale-based novel therapeutic strategies that target these ESR1 mutants have the potential to improve treatment outcomes for patients. Fulvestrant is a hormonal therapy that specifically targets the ESR1 mutation, that seems to work well in metastatic breast cancer patients with endocrine resistance. Multiple studies suggest greater therapy efficacy in those with bone disease.

In this case study, we demonstrate the potential of quantitative whole-body MR imaging (WB-MRI) to monitor response of breast cancer to hormonal therapy, showing that (1) morphological response does not work as well as diffusion MRI for monitoring response to therapy, (2) that ADC histogram analyses can depict the emergence of treatment resistance, and (3) that spatially discordant response to targeted therapy can emerge when bone disease is effectively treated.

Patient history

50-year-old woman with metastatic invasive breast cancer, ER positive and HER-2 neu negative disease was initially treated with first line hormonal therapy (Exemestane, Goserelin) and bisphosphonates (Zoledronic acid) for bone only metastatic disease. She was switched to 2nd line hormonal therapy with Fulvestrant and Zoledronic on bone disease progression, with good response in her bone disease

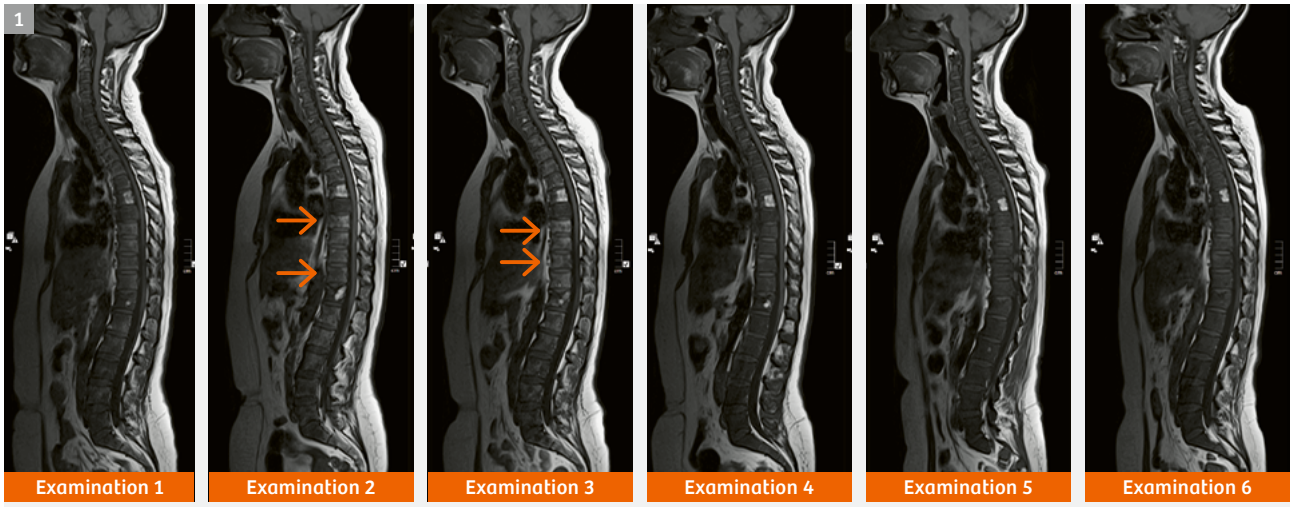

Figure 1: Whole-spine T1-weighted images show diffuse bone marrow infiltration with some return of bone marrow fat on examinations 2 and 3 (arrows) with first-line hormonal therapy. The bone marrow fat disappears at therapy relapse on examination 4 and no further T1w changes are detected after therapy change to second-line on examinations 5 and 6. There is a hemangioma in T6.

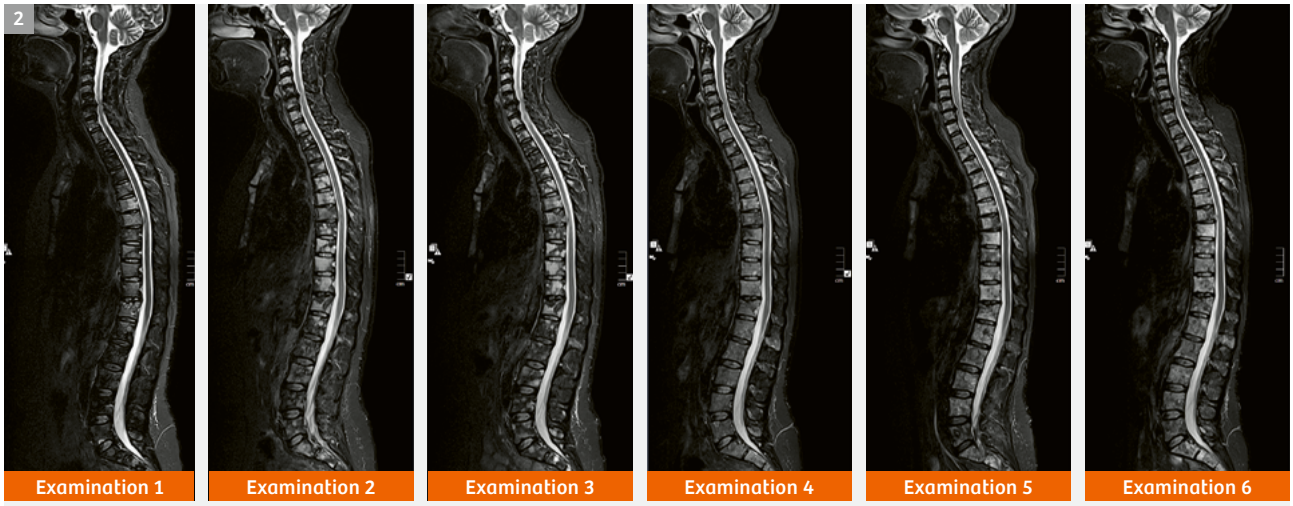

Figure 2: Whole-spine STIR show diffuse bone marrow infiltration with subtle increases in signal intensity with first-line therapy on examinations 2 and 4, but signal intensity lowers by examination 4 at the time of disease relapse (relapse). The bone marrow signal increases again after change to second-line hormonal therapy on examinations 5 and 6. These increases in bone marrow signal intensity are consistent with alternations in tissue water associated with the cell kill mechanism of hormonal treatment (apoptosis).

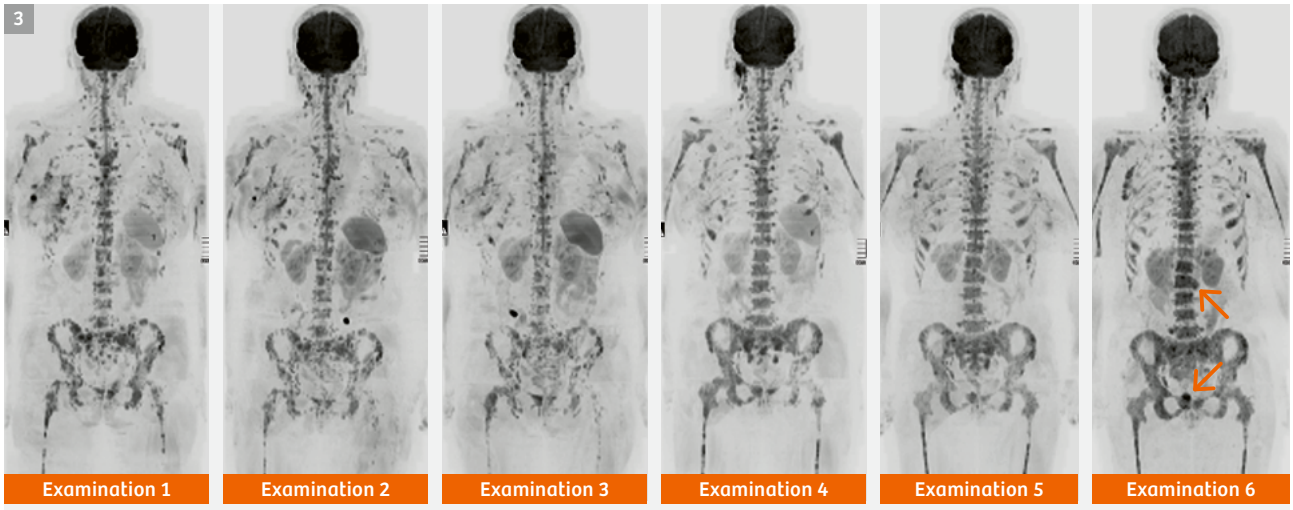

Figure 3: Whole-body b900 3D MIP (inverted scale). The bone marrow is diffusely involved with multiple small focal and confluent regions of high-signal intensity in the axial skeleton and in the proximal limb bones. The primary right-sided breast cancer is *in-situ* with axillary nodal disease visible also. Decreases in the signal intensity of bone marrow with first-line therapy can be seen to occur slowly, but there are focal areas of persistent hyperintensities indicating the likely presence of active disease (examination 3). On examination 4, full-blown relapse can be seen, indicated by increases in signal intensity extent in the bones (see article by Padhani & Tunariu on page 64 in this MAGNETOM Flash for progression criteria for bone disease). On changing to second-line hormonal therapy, no response can be confidently identified but there is increasing disease in the anterior ribs, on the left side of L2 and pubic symphysis (arrows).

only shown on quantitative diffusion imaging. Unfortunately, she also developed liver and pancreas metastases needing further therapy change to chemotherapy. No regional radiotherapy has been administered.

Serial examinations with whole-body diffusion MRI were undertaken using published protocols [2]. Whole-body diffusion sequences using b-values of b50, b600 and 900 s/mm^2 were undertaken together with spinal T1-weighted and STIR sequences, to monitor response to treatment. Six examinations were performed in total. Following the baseline examination, three further examinations were done while on first-line hormonal therapy and two examinations while on second-line hormonal therapy.

Figure 4: WB-tumor load segmentations were undertaken on *syngo*.via Frontier MR Total Tumor Load software (Siemens Healthcare, Erlangen, Germany; released research prototype). The whole-body b900 images are segmented using computed high b-value images of 1000–1200 s/mm², setting a signal intensity threshold of approximately 100 AU. Extraneous signals (such as the brain, kidneys and bowel) are removed, to leave only recognizable bone disease sites including the right breast and axilla. The color the b900 MIP images are overlaid with ADC value classes using the following thresholds. The green voxels are values ≥1500 µm²/s (representing voxels that are 'highly likely' to be responding). The yellow voxels are set to lie between the 95th centile ADC value of the pre-treatment (examination 1 or examination 4) histograms (1256 and 1127 µm²/s respectively) and 1500 µm²/s. Thus, yellow voxels represent regions 'likely' to be responding. Red voxels represent mostly areas that are untreated disease or have no detected response.

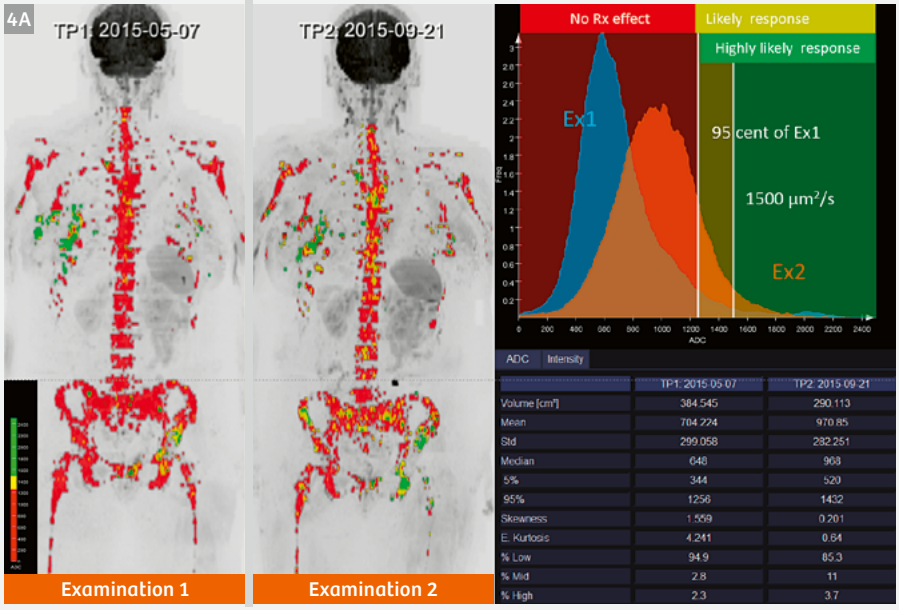

Figure 4A: Histogram analysis of examination 1 and 2.
384 ml of tumor was segmented before therapy and 290 ml on therapy. Note that there is a significant global increase in ADC values (704 µm²/s and 971 µm²/s) and a decrease in kurtosis (4.2 and 0.6) on the corresponding relative frequency histograms indicating some response on a whole-body basis. Note increasing numbers of yellow and green voxels occurring in patches (for example the left hip – note no radiotherapy has been given). These appearances taken with morphologic assessments indicate a favourable response overall with no evidence of progression.

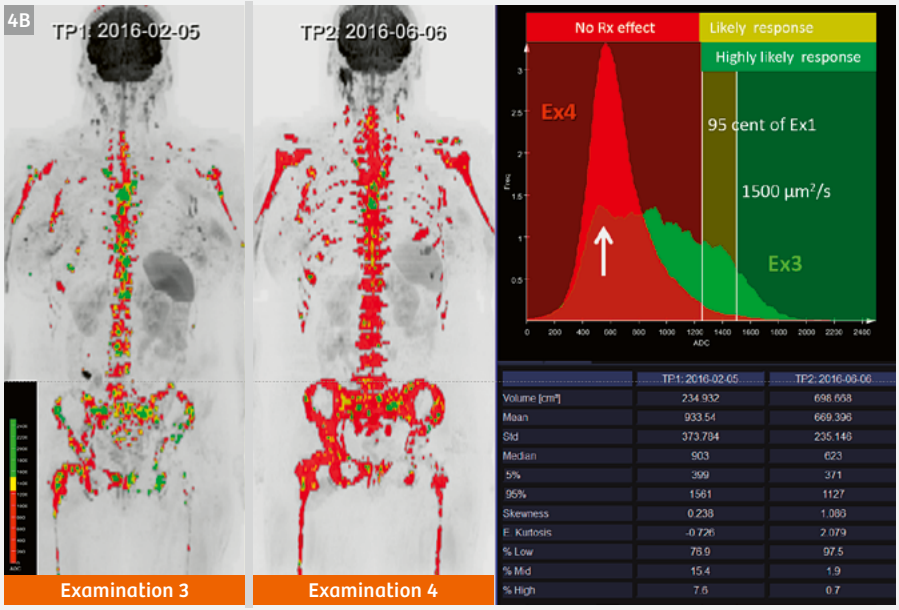

Figure 4B: Histogram analysis of examination 3 and 4.
235 ml of tumor was segmented on examination 3 and 698 ml on examination 4 at disease relapse. Note that on examination 3 there is a flattened histogram (green histogram) with a significant global increase in ADC values (933 µm²/s) compared to baseline and a marked decreased kurtosis (-0.7) on the relative frequency histograms, indicating a good response to first-line hormonal therapy. Note increasing numbers of yellow and green voxels. These appearances taken with morphologic assessments indicate a good response overall. However, note persistent red voxels on examination 3 and a corresponding peak on the examination 3 histogram, indicating areas of therapy resistance (vertical white arrow). On examination 4, the patient has relapsed with a histogram that is identical to the baseline pretherapy study (examination 1).

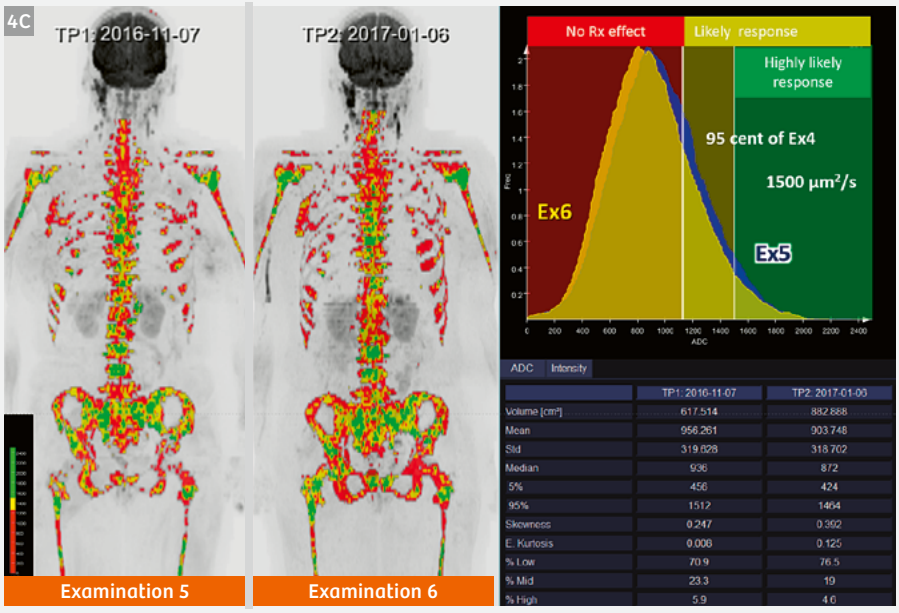

Figure 4C: Histogram analysis of examination 5 and 6.
617 ml of tumor was segmented on examination 5 and 883 ml on examination 6. Note that on both examinations, the histograms show significant global increases in ADC values (956 and 904 µm²/s) compared to examination 4 (pre-second-line treatment baseline) indicting a good response to second-line hormonal therapy. The diffusion imaging appearances indicate a good response overall not observable on the T1w spine images. However, note that there are persistent red voxels on both examinations 5 and 6, indicating persistent areas of therapy resistance in the bones. Note also increased volume of right axillary nodal disease. Therapy was changed because of new liver and pancreatic metastases.

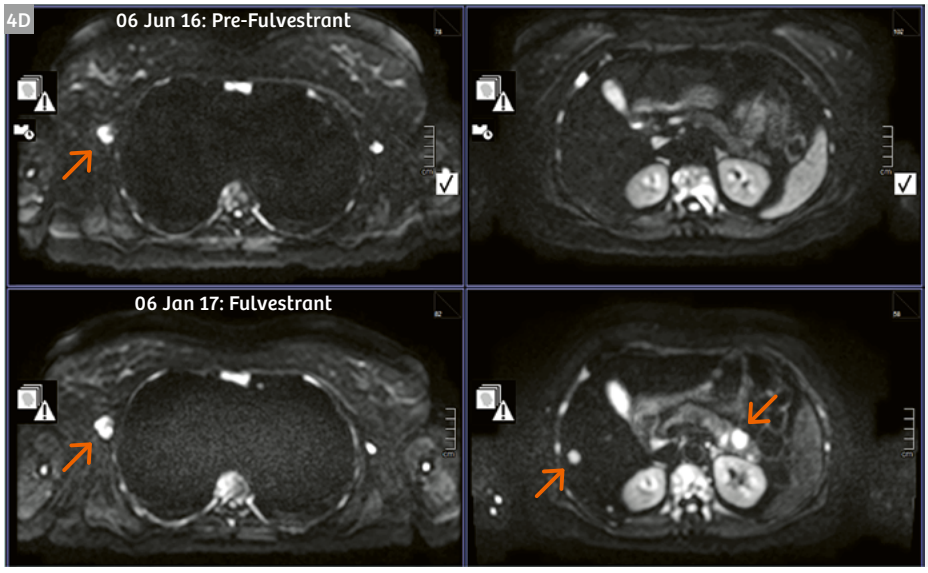

Figure 4D: Axial b900 images of the upper abdomen for examinations 4 (pre-second-line hormonal therapy) and 6 show the emergence of new disease in liver and pancreas (arrows), resulting in a change to chemo-therapy therapy. Right axillary nodes are also enlarging.

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Contact

Professor Anwar R. Padhani
MB, BS, FRCP, FRCR
Paul Strickland Scanner Centre
Mount Vernon Hospital

Rickmansworth Road
Northwood, Middlesex HA6 2RN
United Kingdom
anwar.padhani@stricklandscanner.org.uk

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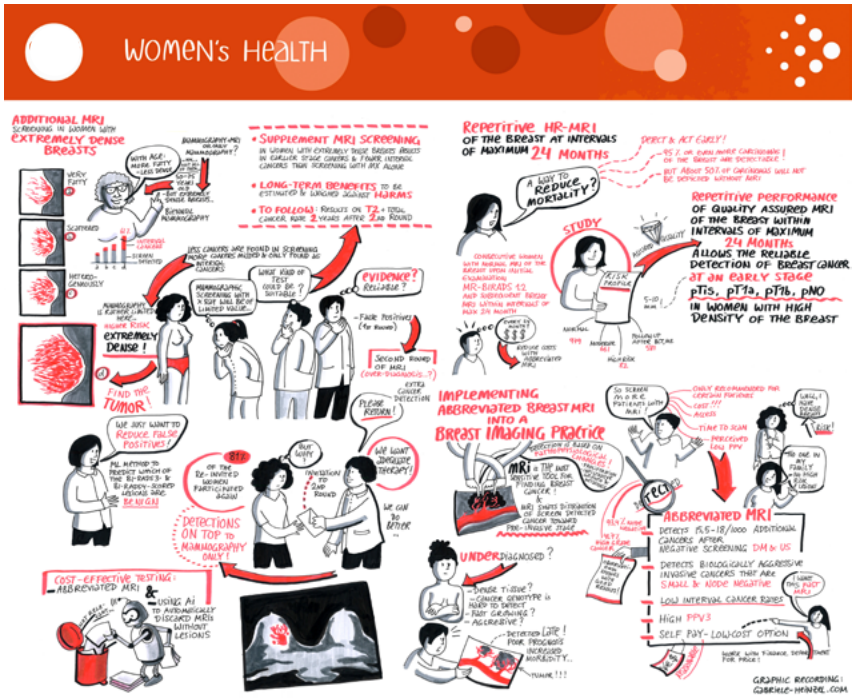

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Siemens Healthineers Headquarters
Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
siemens-healthineers.com

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