Review

Eur J Breast Health 2019; 15(1): 1-6
DOI: 10.5152/ejbh.2018.4402

Changing Paradigms in Breast Cancer Screening: Abbreviated Breast MRI

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ABSTRACT

Breast magnetic resonance imaging (MRI) is the most sensitive imaging method for breast cancer detection. In this review we discuss the vastly superior performance of MRI compared to traditional breast cancer screening modalities of mammography, tomosynthesis and ultrasound. We discuss an abbreviated breast MRI (AB-MRI) protocol utilizing Dixon sequences which is compliant with American College of Radiology (ACR) guidelines for accreditation of breast MRI but with significantly reduced scan times. Adaptation of such an AB-MRI protocol significantly increases patient throughput and may allow MRI to serve as a stand- alone breast cancer screening tool.

Keywords: Breast MRI, abbreviated breast MRI, Dixon, fast spin echo triple echo Dixon

Cite this article as: Mootz A, Madhuranthakam A, Doğan BE. Changing Paradigms in Breast Cancer Screening: Abbreviated Breast MRI. Eur J Breast Health 2019; 15(1): 1-6.

Introduction

The Current State of Breast Cancer Screening

Mammography is a widely available breast cancer screening tool with established performance metrics, and is the only imaging modality proven in multiple prospective randomized clinical trials to decrease the breast cancer mortality rate by 25% to 40% (1-4). While mammography remains the mainstay of breast cancer screening, some studies show that biologically aggressive tumors (i.e., high grade, hormone-receptor negative cancers) are less likely to be detected by mammography screening alone (5-7). Furthermore, the rate of advanced breast cancers did not decrease in countries that implemented nationalized mammography screening programs (8, 9). These facts have led to the controversial claim that mammography may result in over diagnosis of small in situ or estrogen receptor positive remove, indolent invasive cancers (10) while it fails to detect the more aggressive and fast growing ones, including triple negative breast cancers that are negative for estrogen, progesterone and human epidermal growth factor 2 (HER- 2) receptors or those which overexpress HER- 2 (HER-2 amplified). These tumors may be masked by the presence of dense breast tissue or have imaging findings that make their detection more difficult or suggestive of benign disease (11, 12). The decrease in mammographic sensitivity is exacerbated in younger women with dense breast tissue and in women at high risk for the development of breast cancer, particularly BRCA 1 and BRCA2 mutation carriers (12). Failure to detect these biologically aggressive tumors results in the development of interval cancers: i.e., cancers that become clinically apparent between two rounds of routine screening with mammography. Screening-detected and interval cancers appear to be distinct, both in underlying genetics and tumor biology (13, 14).

The addition of supplemental screening modalities to mammography, including breast ultrasound and digital breast tomosynthesis (DBT), has been shown to increase the cancer detection rate (CDR) in women with dense breast tissue. The addition of breast ultrasound to mammography in women with dense breast tissue detects an additional 3.7 cancers per 1000 patients screened (15, 16). While ultrasound is more likely to identify small, node negative, invasive cancers, it is time consuming to perform, even with automated breast ultrasound methods (ABUS), with scanning times that range upwards of 20 minutes for hand held devices (17, 18). More importantly, ultrasound has a much lower positive predictive value of biopsy (PPV3=0.11) compared to mammography (PPV3=0.29), resulting in many more biopsies being performed for benign disease (15, 18).

Digital breast tomosynthesis (DBT) detects 1.2 additional cancers per 1000 patients screened (19) but produces many more images for the radiologist to inspect and increases the time required for interpretation. Furthermore, DBT fundamentally remains a type of mammography, in which the lack of soft tissue contrast in women with dense breast tissue results in the very modest gain in cancer detection.

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Submitted: 17.10.2018
Accepted: 02.12.2018

High Risk Breast MRI Screening

Currently, dynamic contrast enhanced breast magnetic resonance imaging (DCE-MRI) is the most sensitive imaging method for breast cancer detection. DCE-MRI relies on the contrast enhancement characteristics of breast cancer relative to the background breast parenchyma. Numerous studies have shown DCE-MRI to be superior to mammography and ultrasound in identifying breast cancer at a significantly earlier stage in high-risk screening populations (12, 20, 21). Not only does screening with breast MRI result in a higher sensitivity (71-100%) than mammography (13%-59%) and ultrasound (13%-65%), a significant number of MRI detected cancers (43%) are less than 1 cm in size when compared with those detected by mammography and ultrasound ($p<0.001$) (12, 20-22). Furthermore, the sensitivity of MRI in detecting these additional cancers is unaffected by the age of the patient, their breast density, or their genetic mutation status (23).

Magnetic resonance imaging-detected breast cancers have the advantage of being less frequently associated with axillary nodal metastases (21.4%) when compared with mammography detected cancers (54.6% $p<0.001$) (12). The improved performance of MRI over traditional screening modalities translates into improved overall survival in patients with BRCA1 and 2 mutations. Evans et al. (24) used the prospective magnetic resonance imaging breast screening study (MARIBS) patient survival data on 649 women aged 35–55 years who received annual MRI screening based on the presence of a proven or likely BRCA1, BRCA2, or TP53 mutation in addition to 338 patients who underwent screening MRI after the implementation of the National Institute for Health and Care Guidance (NICE) criteria endorsing MRI screening. Ten-year overall survival (OS) rate for patients screened with MRI in addition to mammography was 95.3% compared to 87.7% in patients screened with mammography alone. In light of compelling evidence that supports MRI's superior sensitivity, the American College of Radiology (ACR) and the American Cancer Society (ACS) currently recommend intensive imaging screening with DCE-MRI for women with BRCA 1 and BRCA 2 mutations or women at a greater than 20% lifetime risk for the development of breast cancer using computer-based risk assessment models (25, 26).

Magnetic resonance imaging is a highly technical and expensive imaging modality, traditionally requiring multiple pulse sequences for diagnostic evaluation. The acquisition and table times required for standard DCE- MRI protocols range between 20-60 minutes (27) and are a limiting factor in the population-based use of DCE-MRI for breast cancer screening. Women who refused breast MRI screening as part of the American College of Radiology Imaging Network (ACRIN) 6666 trial reported that the long scan times required and the claustrophobia of the magnet bore itself were reasons for their refusal to undergo a breast MRI as a supplemental breast cancer screening tool (15, 28).

The Concept of Abbreviated Breast MRI

Similar to the paradigm of screening and diagnostic mammography, some have proposed that a stripped-down, shortened contrast-enhanced MRI protocol containing the minimum number of sequences required for the detection of suspicious enhancing lesions (abbreviated MRI, or AB-MRI) might be sufficient for breast cancer screening, with a full diagnostic MRI protocol reserved for the characterization and differentiation of benign from malignant disease (29). In 2014, Kuhl et al. (30) reported a retrospective reader study in which a full diagnostic DCE-MRI consisting of 8 different pulse sequences was obtained on a cohort of 443 women with a mildly elevated risk of breast cancer or dense breast tissue. Separate interpretations of the complete DCE-MRI and a subset of images containing only the unenhanced images and the first post contrast dynamic sequence had equivalent diagnostic accuracy and negative predictive value for detecting breast cancer. AB-MRI had a very high cancer yield: using the AB- MRI images only, 11 cancers were detected, resulting in a cancer detection rate of 18.1 per 1000. Four of the cancers were ductal carcinoma in situ (DCIS), and seven were invasive cancers. All of the invasive cancers were less than 1.0 cm in size, and there were no axillary metastases identified clinically or at sentinel lymph node biopsy. The specificity and positive predictive value of AB-MRI was equivalent to the full DCE- MRI (94.3% versus 93.9% and 24.8% versus 23.4%) (30). The negative predictive value of the AB-MRI was 99.8%. The mean acquisition time was three minutes for the AB-MRI versus 17 minutes for the full DCE-MRI, with a reading time of less than 30 seconds for the abbreviated protocol. Other retrospective reader studies have reported similar results (31-33).

The AB-MRI protocol reported by Kuhl did not include a T2 weighted series as required by the ACR for accreditation of breast MRI, nor did it include the full dynamic series of post contrast images. While the European Society of Breast Imaging recommends either a pre-contrast T1 weighted or T2 weighted series be obtained (34), both societies require that a full dynamic series before and after the administration of contrast be obtained. The full dynamic sequence allows the use of computer aided detection and time-intensity-curves that help differentiate benign from malignant enhancing lesions (35, 36) (Figure 1). The T2 weighted sequence allows for the differentiation of benign,

Table 1. Diagnostic performance of abbreviated MRI in the screening setting

	Study Type	Sequences	Patient Risk factor	*CDR	Sensitivity	Specificity	**PPV	¥NPV
Kuhl et al. (30)	Retrospective	1. Pre- and postcontrast T1, non-fatsat 2. MIP	Dense breast tissue or Family history of breast cancer	18.2	100%	NA	NA	99.8%
Kuhl et al. (45)	Prospective	1. T2-weighted axial 2. Pre- and postcontrast T1, non-fatsat	Average risk	15.5	100%	97.1%	97.1%	100%
Choi et al. (46)	Prospective	1. T2-weighted axial 2. Pre- and postcontrast T1	Personal history of breast cancer	15.0	100%	89.2%	61.5%	100%

*CDR: Cancer detection rate, per 1000 screened women; **PPV: Positive predictive value; ¥NPV: Negative Predictive Value

enhancing, fat containing masses such as fibroadenomas, intramammary lymph nodes, and fat necrosis from malignant enhancing masses (Figure 2). Thus, while obtaining a full dynamic sequence and a T2-weighted series may increase the overall scan time by 4-6 minutes, the advantage is being able to have all the signals (fat, water, and contrast) available should a cancer be detected, and pre-operative lesion extent derived from MR images be required, without having to perform a second dedicated diagnostic scan.

In 2018 Dogan et al. (27) reported the development of an AB-MRI protocol consisting of a single T2-weighted series combined with a dynamic contrast-enhanced T1-weighted series before and after the administration of intravenous contrast. This protocol used Dixon based imaging for fat suppression with both series, where T2-weighted images were acquired using a fast spin echo (FSE) triple echo Dixon sequence (37) and T1-weighted images were acquired using a dual-echo fast spoiled gradient echo (FSPGR) sequence (38). The Dixon method acquires two or more echoes after a single radiofrequency (RF) excitation, followed by advanced reconstruction algorithms to achieve uniform fat/water separation. This method generates both a water-only (i.e. fat-suppressed) image and a fat-only image, which can be subsequently combined to reconstruct the in-phase (i.e. non-fat-suppressed) image in a single acquisition (39), and is well-suited for the AB-MRI protocol. In contrast to the traditional methods of fat suppression using chemically-selective

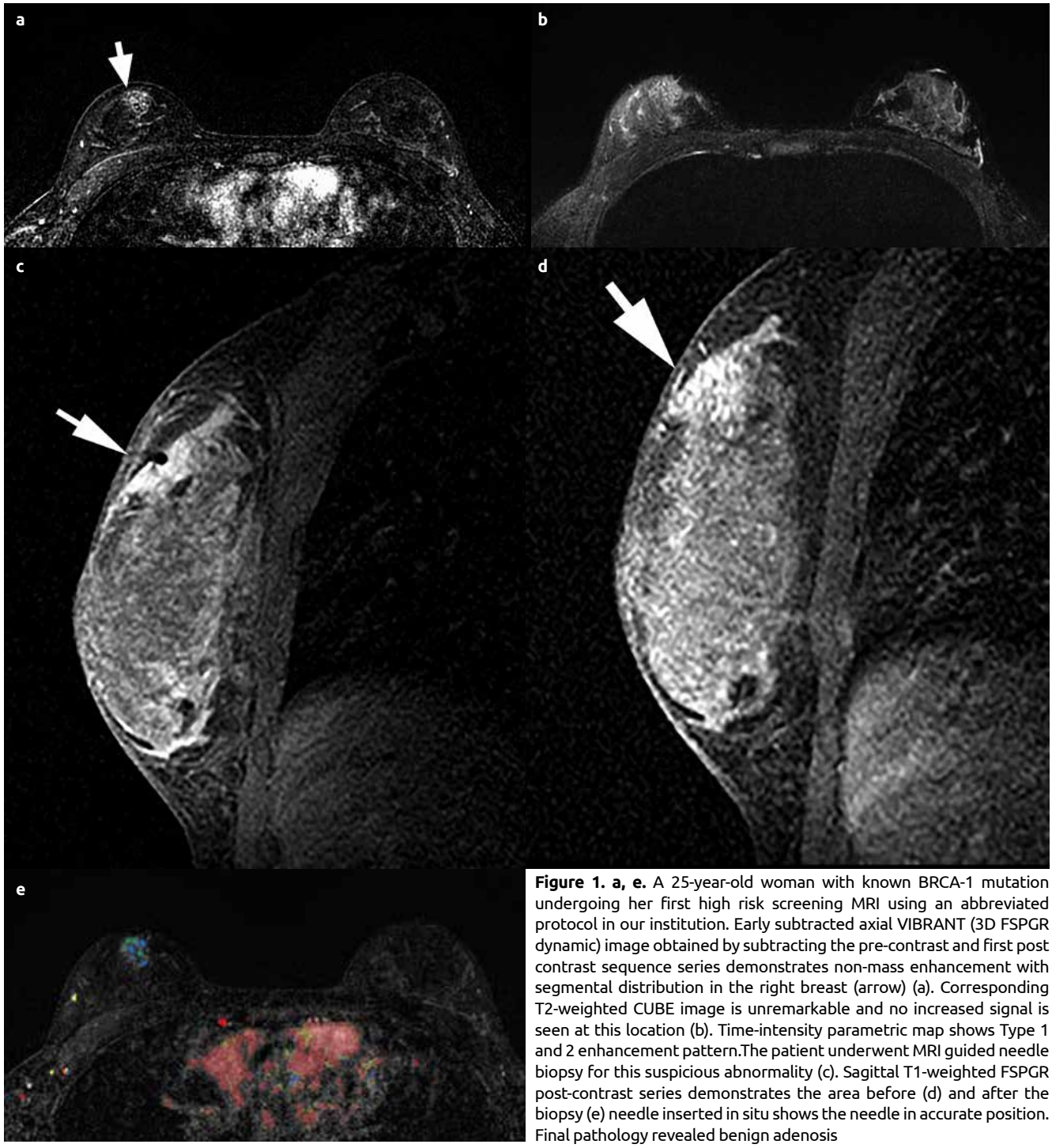

Figure 1. a, e. A 25-year-old woman with known BRCA-1 mutation undergoing her first high risk screening MRI using an abbreviated protocol in our institution. Early subtracted axial VIBRANT (3D FSPGR dynamic) image obtained by subtracting the pre-contrast and first post contrast sequence series demonstrates non-mass enhancement with segmental distribution in the right breast (arrow) (a). Corresponding T2-weighted CUBE image is unremarkable and no increased signal is seen at this location (b). Time-intensity parametric map shows Type 1 and 2 enhancement pattern.The patient underwent MRI guided needle biopsy for this suspicious abnormality (c). Sagittal T1-weighted FSPGR post-contrast series demonstrates the area before (d) and after the biopsy (e) needle inserted in situ shows the needle in accurate position. Final pathology revealed benign adenosis

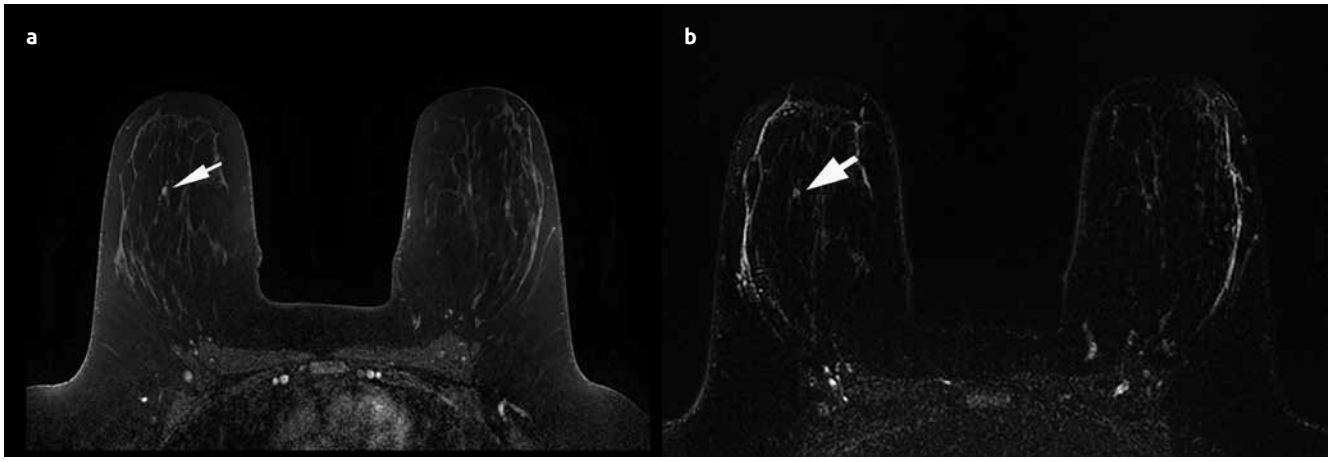

Figure 2. a, b. A 36-Year-old woman with known BRCA-2 mutation undergoing abbreviated high risk MRI screening. A 6mm enhancing focus in the right breast 6 o'clock position (arrow) is noted, with corresponding CUBE image at the same slice location (a) demonstrating T2-hyperintensity suggesting a benign process and internal hypointense septa favoring a benign myxoid fibroadenoma (large arrow) (b). The T2- weighted CUBE images helped establish the benign diagnosis for this case. The mass has been stable on prior MRI studies dating back 3 years

fat saturation, Dixon-based methods achieve uniform fat suppression even in the presence of B0 inhomogeneities (40), which are commonly encountered in breast MRI (41). Large abbreviated MRI series using differing protocols are compared in Table 1.

The flexibility of Dixon acquisitions make this approach compatible with both T1-weighted gradient echo (GRE) based acquisitions (38) and T2-weighted FSE based acquisitions (37). By combining the advantages of fast scanning of FSE with the efficient fat/water separation of the Dixon method into a single scan, significantly shorter scan times (1-1.5 minutes) were realized for T2-weighted imaging (37, 38, 42). Since this approach also generates T2-weighted images with and without fat suppression in a single acquisition, this eliminates the necessity of additional T2-weighted acquisitions, significantly decreasing the total scan times. Similarly, the use of dual-echo FSPGR for DCE-MRI generates T1-weighted images with and without fat suppression in a single acquisition. In addition to providing uniform fat suppression, this approach also eliminates the necessity of subtracting post-contrast images from the pre-contrast image, thus minimizing motion artifacts. In Dogan's study, the AB-MRI incorporating T2-weighted FSE-Dixon and T1-weighted FSPGR-Dixon, required a mean acquisition time of 9.4 minutes with a total table time of 13.92 minutes which was statistically significantly different ($p<0.0001$) than the 22 minute mean acquisition time and the 35.87 minute total table time required by the traditional DCE-MRI (27).

The use of Dixon sequences with AB-MRI allows for both T2- and T1-weighted images with and without fat suppression, which are then used for reading. Since these provide all the signal and anatomical information of a conventional DCE- MRI protocol, these image sets can be accessed by the reader on an as needed basis for the further evaluation of enhancing lesions, thereby obviating the need for the patient to return for an additional "diagnostic" MRI for further evaluation.

In addition to decreasing MRI scan time to almost the same as mammography acquisition time, there is evidence that AB-MRI can provide image quality benefits (43). Standard DCE-MRI and AB-MRI were compared in a reader study for adequacy of fat saturation, degree of fat saturation, presence and severity of artifact, and the image quality of normal anatomic structures (nipple, fibro-glandular tissue, lymph nodes, and chest wall) (27). Compared to the DCE-MRI protocol, the AB-MRI protocol had statistically significant less motion artifact ($p<0.0001$) and better fat saturation ($p=0.004$). The reduced motion artifact was attributable to the much shorter scan time in which patient motion is reduced. The fat saturation was most improved in the posterior aspect of the breast allowing for better evaluation of the chest wall and axillary lymph nodes. There was no significant difference regarding lesion type, lesion margin, or enhancement pattern between the standard DCE-MRI and the AB-MRI, and the final BIRADS assessment of each was identical (27).

AB-MRI in Average Risk Women

If AB-MRI protocols are adopted successfully, AB-MRI for screening may become more widely available to women at average or mildly elevated risk for the development of breast cancer, such as women with dense breast tissue or those with a personal history of breast cancer (44). In a study of AB-MRI in a cohort of women at average risk for the development of breast cancer, with no evidence of cancer with traditional screening methods, Kuhl et al. (45) found an unexpectedly high cancer detection rate of 15.1 per 1000 women screened. Like the cancers detected in high risk women, the majority were small, T1 invasive cancers and over 90% were node negative. The cancers detected were of intermediate (39%) or high histologic grade (43%) with one third of cancers being of the triple negative subtype. The positive predictive value (PPV) of the AB-MRI was 35.7% well within the range of PPV accepted for mammographic screening (25-40%). Additionally, the interval cancer rate in women undergoing several rounds of screening with AB-MRI was zero. After conclusion of the study, when the women returned to traditional breast cancer screening methods, no cancers were detected by mammography or ultrasound within the first three years.

In the United States, contrast-enhanced breast MRI current procedural terminology (CPT) code is currently the same independent of the time required for the examination. However, decreasing scan time can potentially have a downstream effect of driving down the AB-MRI cost to the patient. Furthermore, finding aggressive breast cancers at an earlier stage would decrease the severity and cost of treatment, resulting in further cost savings. Furthermore, the fact that patients had

no mammography or ultrasound-detected cancer for three years after screening MRI in the study by Kuhl et al. (45) suggests that AB-MRI screening may have a "protective" effect on subsequent breast cancer detection so that the frequency of screening might be reduced in average risk women, another significant cost saving.

AB-MRI for Screening Women with Dense Breast Tissue--The EA1141 Trial

The effect of breast density legislation in the United States has prompted the evaluation of supplemental screening methods for breast cancer detection in women with dense breast tissue who are without other breast cancer related risk factors. "Comparison of AB-MRI and DBT in Breast Cancer Screening in Women with Dense Breasts", the EA-1141 Trial, is a prospective multicenter trial of the ECOG/ACRIN. Women ages 40-75 with dense breast tissue (BIRADS C or D) but not at increased risk of breast cancer will undergo DBT and AB-MRI in randomized order for two consecutive years. Metrics assessed will be the cancer detection rate (CDR) of the two modalities as well as the histopathological profiles of cancers detected by the two imaging methods. The study will also assess patient reported quality of life as well as their willingness to undergo repeated breast MRI for breast cancer screening. The trial leaves the specific sequences of the abbreviated protocol up to the individual centers and only requires that the scans be obtained in less than ten minutes. Patient accrual has been completed and results are expected within the next year.

AB-MRI in Women with a Personal History of Breast Cancer

Abbreviated breast MRI has more recently been shown to be of benefit for women with a personal history of breast cancer but no other breast cancer risk factors. Choi et al. (46) reported the outcomes of AB-MRI in a cohort of 725 women with a personal history of breast cancer. AB-MRI detected 12 cancers in 12 women (CDR 15 per 1000 women screened). At the time of AB-MRI screening there was no evidence of malignancy with previously performed mammography or ultrasound. The sensitivity of the AB-MRI was 100% and the specificity was 89.2%. All AB-MRI detected cancers except one were node negative, T1 invasive cancers, or DCIS. These outcomes are comparable to outcomes reported in other series of women with a personal history of breast cancer, but who underwent a full DCE-MRI (47, 48).

Conclusion

Abbreviated breast MRI consisting of a single T2 weighted fast spin echo (FSE) triple echo Dixon sequence and a dual echo fast spoiled gradient echo sequence (FSPGR) before and after the administration of contrast, compliant with ACR standards for the accreditation of breast MRI, with sensitivity for breast cancer detection equivalent to full protocol DCE-MRI, but with greatly reduced scan and table times, is feasible. While cancers detected with AB-MRI are usually small T1, node negative invasive cancers, they often have aggressive histopathological tumor profiles. Given its superior performance and the greatly reduced scan times resulting from the use of abbreviated protocols, AB-MRI has the potential to replace mammography as a stand-alone imaging tool for the detection of breast cancer, not only in high risk women, but in women of average or mildly elevated risk, such as women with dense breast tissue or a personal history of breast cancer.

Informed Consent: Externally peer-reviewed.

Author Contributions: Concept - B.E.D., A.R.M.; Supervision - B.E.D.; Literature Search - A.R.M.; Writing Manuscript - A.R.M. , A.J.M., B.E.D.; Critical Review - B.E.D.

Acknowledgements: The authors wish to acknowledge Susannie Washington for her assistance with manuscript preparation and submission.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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