A meta-analysis comparing the diagnostic performance of abbreviated MRI (ABB-MRI) and a full diagnostic protocol (FDP-MRI) in breast cancer

Keywords
Breast, Breast Cancer, Magnetic resonance imaging, Meta-analysis, Diagnostic imaging

Introduction
The use of abbreviated magnetic resonance imaging (ABB-MRI) protocols in the detection of breast cancer has gained increasing attention as these have substantially reduced image acquisition and interpretation times. The first prospective reader study of screening patients using an abbreviated breast MRI protocol was reported by Kuhl et al. and showed equivalent diagnostic performance of ABB-MRI to a full diagnostic protocol (FDP)\(^1\). Initial studies created a short protocol from an existing dataset of standard breast MRIs and reported a reading study, generally showing equivalent performance to the standard acquisition\(^2-4\). More recent studies have created enriched cohorts of patients, for whom MRI has been used for problem solving or pre-operative staging, to assess the diagnostic accuracy of ABB-MRI in a robust manner with a sufficient number of cancers\(^5,6\). Varying versions of the shortened protocols have been reported in these studies, with the general definition of an 'abbreviated' protocol using a non-contrast T\(_1\)-weighted (T\(_1\)W) sequence with at least one post contrast T\(_1\)W examination. Before the adoption of abbreviated MRI into mainstream practice it is important to ensure the shortened sequences gives equivalent diagnostic performance.

From a radiologist’s perspective it is important to assess the use of ABB-MRI in a screening context and in a problem solving or pre-operative staging context separately. The advantage of an abbreviated protocol for screening is the ability to reduce healthcare costs, the time patients spend in the MRI scanner, as well as a reduced reading times for the radiologist. For problem solving and pre-operative staging, MRI is used extensively, however the case for abbreviated MRI for this clinical question is less compelling, as a full protocol is more likely to be more diagnostically useful. In order to adopt
abbreviated MRI for screening, prospective trials need to be undertaken with careful comparison
between abbreviated MRI and standard MRI protocols. However, in order to do this safely,
assimilation of the evidence is required to show equivalence or at least non-inferiority using published
data before a randomised trial is undertaken.

While several review articles have examined the protocols and diagnostic performances of published
ABB-MRI studies7–13, to date no meta-analysis has been performed that systematically compares the
diagnostic performance of ABB-MRI with full diagnostic protocol MRI (FDP-MRI). This meta-
analysis examines the evidence from screening only cohorts and separately from enriched cohorts.

**Materials and Methods**

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews
and Meta-Analysis for Diagnostic Test Accuracy (PRISMA-DTA) guidelines14 (PRISMA checklist
available as Electronic Supplementary Material).

**Literature Search**

PubMed and EMBASE databases were searched in August 2019 by one of the authors (X.X.X., with
2 years of experience) for studies assessing the diagnostic performance of abbreviated MRI protocols
in the detection of breast cancer in either a screening or an enriched cohort of women. The patient
population of screening studies consisted of screening mild-moderate or high-risk women, including
women with a personal history of breast cancer. The patient population of enriched cohort studies
included either combinations of screening, suspicious and known cancer cases or cases selected by the
authors. The search strategy used was ((breast)) AND abbreviated) AND (MR OR MRI OR magnetic
resonance imaging)). A full manual search of reference lists from all included studies was also
undertaken.

**Study selection**


Studies were included if they met the following eligibility criteria: (1) published in a peer reviewed journal (abstracts and conference proceedings excluded), (2) in English, (3) the patient population was reported and included either a screening cohort or an enriched cohort of patients, (4) details of the full and abbreviated protocols were reported, (5) the diagnostic performance of both ABB-MRI and FDP-MRI in the detection of breast cancer was reported. Studies focusing on the development of an abbreviated protocol or technique were excluded.

Data extraction

Data extraction was performed independently by two reviewers (X.X.X. and X.X.) and confirmed by two other reviewers (X.X.X. and X.X.X.). The following information was obtained from studies: first author, publication year, prospective or retrospective study design, number of patients, number of cancers, ABB-MRI and FDP-MRI protocol sequences, number of readers and experience in years, examination times and reading times of ABB-MRI and FDP-MRI, and interval of time between reading ABB-MRI and FDP-MRI.

The sensitivity and specificity of ABB-MRI and FDP-MRI protocols for each study was recorded. The number of true-positive (TP), false-negative (FN), false-positive (FP) and true-negative (TN) findings using ABB-MRI and FDP-MRI were either extracted from studies where reported or calculated from the number of included cancers. For studies that reported multiple readers, the number of TP/FN/FP/TN were extracted from only the first reader to ensure integer numbers of lesions for the meta-analysis. For studies that reported multiple ABB-MRI protocols, the diagnostic performance of the protocol that used a contrast-enhanced sequence and the smallest number of additional sequences was extracted.

Data Quality Assessment

The Quality Assessment of Diagnostic Accuracy Studies-2 was used to assess the risk of bias and concerns regarding applicability to the review question. Risk of bias was assessed in four domains:
patient selection (e.g. mild-moderate or high risk patients for screening studies), appropriate index test (interpretation of ABB-MRI and FDP-MRI protocols without knowledge of final diagnosis, appropriate length of time or blinding between reading of ABB-MRI and FDP-MRI protocols), reference standard (use of histological analysis or follow-up), and flow and timing. The degree of heterogeneity between studies was assessed using the Cochran Q test\(^1\)\(^6\) and the Higgins \(I^2\) test\(^1\)\(^7\). A \(p\)-value of < 0.05 for the Cochran Q test or an \(I^2\) value of greater than 50% indicated statistically significant heterogeneity.

### Statistical Analysis

Forest plots of sensitivity and specificity for included studies were constructed. The bivariate model of Reitsma et al.\(^1\)\(^8\) was used to estimate pooled sensitivities, specificities and areas under the curve (AUCs) for ABB-MRI and FDP-MRI on a per-lesion basis, and summary receiver operating characteristic (sROC) curves were constructed. Screening studies and enriched cohort studies were pooled separately to avoid bias. Additionally, the exam times, reading times, sensitivities and specificities of ABB-MRI and FDP-MRI for all studies were compared using a paired t-test, with a \(p\)-value < 0.05 indicating a statistically significant result. Analysis was performed using statistical software (R version 3.1.3; R Foundation for Statistical Computing, Vienna, Austria) using the mada package.

### Results

#### Study Selection and Data Extraction

The literature search of the PubMed and EMBASE databases returned 63 studies after removing duplicates. We excluded 30 studies after a review of the titles and abstracts. We reviewed the full text of the remaining 33 studies and excluded 20 as they did not meet the eligibility criteria. 13 studies (5 screening studies and 8 enriched cohort studies) were included in the meta-analysis\(^{1,2,5,6,19-27}\). One
study was excluded as the patient population contained a subset of patients previously reported by the authors in a study included in the meta-analysis\textsuperscript{28}. Our study selection process is shown in Fig. 1. Details of included screening and enriched cohort studies are given in Tables 1 and 2, respectively. Screening studies included 2588 patients with 62 cancers. Enriched cohort studies included 1432 patients with 540 cancers. Technical details of included studies are given in Table 3. There was a large variation in patient population, study methodology and ABB-MRI protocols reported in included studies. All studies used at least one pre-contrast and one post-contrast sequence in their abbreviated protocol. The mean exam time was 7.4 minutes for ABB-MRI and 19.2 minutes for FDP-MRI (p = 0.002). The mean reading time was 1.4 minutes for ABB-MRI and 3.8 minutes for FDP-MRI (p = 0.01). The time between reading protocols ranged from immediately after to one month after. The majority of readers involved in studies had over 6 years of experience.

**Data Quality Assessment**

Figure 2 shows the results of QUADAS-2 assessment. For patient selection, some enriched cohort studies were found to have applicability concerns due to a combination of screening and patients with known cancers. For index tests, risks of bias found were due to either lack of reporting of the time between the reading of the ABB-MRI and FDP-MRI protocols (unclear risk) or the reading of the FDP-MRI directly after the ABB-MRI protocol (high risk). The use of a reference standard was unclear for one study. Regarding flow and timing, all studies were considered to have a low risk of bias.

**Statistical Analysis**

The results of pooled analysis are given in Table 4. Low heterogeneity was measured between studies using enriched cohorts. $I^2$ values of 0% were measured for screening studies using both ABB-MRI and FDP-MRI, however this was due to an insufficient number of studies included to use this technique as opposed to lack of heterogeneity.
Forest plots for sensitivity and specificity are shown in Fig. 3. For screening studies, the confidence intervals are large, and are much larger for sensitivity than for specificity due to the very small number of cancers in proportion to normal cases (n = 62 for 2588 patients for all screening studies combined). For enriched cohort studies with a more balanced number of cancers and normal cases, the confidence intervals are more similar, though the confidence intervals are still large overall.

Summary receiver operating characteristic curves are shown in Fig. 4. FDP-MRI achieved a higher sensitivity, specificity and AUC than ABB-MRI for both screening and enriched cohort studies. The difference in diagnostic performance between ABB-MRI and FDP-MRI was lower for enriched cohort studies. However, the sensitivities and specificities of ABB-MRI and FDP-MRI were not statistically significantly different for screening studies or enriched cohort studies (p = 0.18 and 0.27, p = 0.18 and 0.93, respectively). The pooled AUC for ABB-MRI was the same for screening and enriched cohorts.

**Discussion**

Our meta-analysis showed that in a screening setting, the diagnostic accuracy of abbreviated MRI was lower but not statistically significantly different to the full diagnostic protocol (pooled AUCs 0.94 and 0.97, respectively). For studies that used enriched cohorts, the performance of abbreviated MRI matched that of the standard protocol (pooled AUCs 0.94 and 0.95, respectively).

Comparison and pooling of ABB-MRI studies through a meta-analysis is complicated by the variation in patient populations reported as sensitivity and specificity performance can be altered by the expected prevalence of cancers in the cohort. It is better not to group abbreviated protocols used for screening and for other clinical indications together. Amongst screening studies, Kuhl et al. and Chen et al. reported results from screening mild or moderate risk patients\(^1,2^5\), whereas Panigrahi et al. and Dialani et al. reported results from screening high risk patients\(^2^2,2^3\). The effective rate of detected cancers will differ between these two groups, and therefore it may not be meaningful to pool their diagnostic performances. Furthermore, though there was a variation in patient populations, an I\(^2\) of
0% was measured between screening studies indicating no heterogeneity. However, it has been shown that conclusions of low heterogeneity for a meta-analysis with a small number of studies are unjustified as confidence intervals for these heterogeneity estimates are large\(^ {17,29}\). Results from screening studies may also be underpowered due to the large number of normal cases, where specificity will be inherently comparable for ABB-MRI and FDP-MRI and the low number of cancer cases results in sensitivity values with large confidence intervals. Amongst enriched cohort studies, Moschetta et al. reported a cohort of combined screening, problem solving and preoperative staging patients\(^ 5\). Bickelhaupt et al. reported a cohort of patients with suspicious mammograms\(^ {21}\). Grimm et al. reported a cohort of selected cases with a balanced number of cancers and benign and normal cases\(^ 2\), though the readers were blinded to the percentage of each case. It is unclear what effect these combinations of patients within a population would have on reading images. While enriched cohorts were able to demonstrate equivalent performance to a full diagnostic protocol, they do not reflect the clinical setting of interest and may not be applicable in a screening setting.

Other than differences in patient population, the assessment of the quality of studies included in the meta-analysis using QUADAS-2 highlighted other variations in study design. Given the claims of equivalent diagnostic performance to standard protocols, it is important to scrutinise the methodology of these reader studies before it is possible to safely adopt abbreviated MRI into clinical practice. While some studies left up to a month between reading images from different protocols, some read the full protocol directly after the abbreviated protocol. This may be appropriate when assessing changes in management with the addition of extra sequences, however both protocols must be tested equally to robustly compare the diagnostic performance of ABB-MRI and FDP-MRI. Given that most studies were performed by readers with many years of experience, it may be that the high diagnostic accuracy and faster reading times achieved using abbreviated protocols would not be possible with less experienced readers. Furthermore, readers in retrospective studies would not be afraid of misdiagnoses and may perform differently when reading images in a real clinical setting. Only three of the studies included were prospective studies, and larger prospective and multi-centre trials with defined inclusion criteria are required to validate the performance of ABB-MRI in a purely screening setting.
The lack of precision in pooled estimates also necessitates large prospective trials, given that the lower end of the ranges of the sensitivity and specificity of ABB-MRI in a screening setting (79% and 86%, respectively) are not good enough to be used in a screening situation and unlikely to be cost-effective. There are multiple ongoing prospective studies, the largest being the multi-centre EA1141 trial (Comparison of AB-MRI and DBT in Breast Cancer Screening in Women with Dense Breasts), finding a higher rate of invasive cancer detection using ABB-MRI compared to digital breast tomosynthesis (DBT) in a screening cohort of 1444 women with dense breasts and only mild to moderate risk of breast cancer. The various reported ABB-MRI protocols have been previously reviewed. In this meta-analysis, only one set of reported sensitivity and specificity values were extracted from each study to avoid overrepresentation of a sample, although many studies have compared the diagnostic performance of multiple combinations of sequences to investigate the added value of extra sequences in increasing specificity and confidence in diagnosis. Overall, studies have dropped the full dynamic time course in order to save time, opting for one pre-contrast and one post-contrast time point. Grimm et al. found that the addition of a second post-contrast time point did not improve diagnostic accuracy. Different studies added either a T2-weighted (T2W) sequence or a diffusion-weighted examination to complement the contrast examination. Dialani et al. found that the addition of a T2W sequence did not result in a significant change in management. A second abbreviated protocol including a diffusion-weighted imaging (DWI) sequence was used by Bickelhaupt et al. which performed better than the protocol using only contrast-enhanced images, matching the accuracy of the full diagnostic protocol. Chen et al. also found that the addition of DWI improved sensitivity and specificity. There is a growing interest in non-contrast-enhanced screening and DWI is increasingly used in the detection of breast cancer, with advanced DWI techniques showing a high sensitivity and specificity in the characterisation of breast lesions.

Our study has several limitations. Firstly, there were a low number of studies contributing to the pooled estimates resulting in relatively wide confidence intervals, particularly for screening studies.
Second, there were many studies that investigated the diagnostic performance of ABB-MRI but did not perform a reader study for the full diagnostic protocol and were therefore not included in the meta-analysis. It has been shown that different results are obtained when pooling non-comparative studies (evaluating only one test) and comparative studies (evaluating both tests equally)\textsuperscript{34}. As such, robustly designed comparative studies where all patients received both tests under the same conditions were preferred. Third, while separate pooled analysis was carried out for screening and enriched cohort studies, there were still variations in patient populations within these groups. Fourth, it was unclear if there was an overlap between patient populations in two studies (both by Chen et al.\textsuperscript{24,25}) which could result in overrepresentation of a sample in pooled estimates, though the full protocols reported were sufficiently different. The authors could not be contacted for clarification. Fifth, as each study population could be used only once, the meta-analysis did not incorporate the potential added value of additional sequences that were investigated in some studies.

In conclusion, our meta-analysis of 13 studies found that abbreviated MRI had an overall high diagnostic performance in the detection of breast cancer. The diagnostic performance was equivalent to that of a full diagnostic protocol amongst enriched cohorts and was lower but not significantly different in a screening setting. While acquisition and interpretation times were significantly reduced compared to a full diagnostic protocol, there was a variation in study methodology and sequences chosen, limiting the conclusions that can be drawn. Further large prospective multicentre trials are required to validate ABB-MRI in a real screening environment.

References


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potential limitations of abbreviated breast MRI: an observer study using an enriched cohort.


Figure Legends

**Fig. 1.** PRISMA flow diagram for study selection and exclusion

**Fig. 2.** Results of quality assessment using QUADAS-2

**Fig. 3.** Forest plots of the sensitivity and specificity of full diagnostic protocol MRI (FDP-MRI) and abbreviated MRI (ABB-MRI) for included A) screening and B) enriched cohort studies with 95% confidence intervals. Vertical lines denote pooled summary estimates of sensitivity and specificity.

**Fig. 4.** Summary receiver operating characteristics (ROC) curves for abbreviated MRI (ABB-MRI) and full diagnostic protocol MRI (FDP-MRI) protocols using the bivariate model with 95% confidence regions. The pooled AUCs of ABB-MRI and FDP-MRI for screening studies were 0.94 and 0.97, respectively. The pooled AUCs of ABB-MRI and FDP-MRI for enriched cohort studies were 0.94 and 0.95, respectively.

Table Legends

**Table 1.** Characteristics of Included Screening Studies

**Table 2.** Characteristics of Included Enriched Cohort Studies

**Table 3.** Technical details of included studies

**Table 4.** Results of pooled analysis