GE HealthCare

Diagnostic accuracy of SenoBright™ HD compared to breast MRI and abbreviated breast MRI (AB-MRI)

Whitepaper

1. Abstract

This whitepaper evaluates the evidence on the diagnostic performance of GE HealthCare's contrast enhanced mammography (CEM) solution, SenoBright HD, in comparison to breast MRI and abbreviated breast MRI (AB-MRI). The analysis is based on a sub-analysis of the CONTRRAST trial[1], and a targeted literature review (TLR).

The CONTRRAST trial, conducted in the United States, assessed the non-inferiority of CEM to breast MRI and AB-MRI in detecting breast cancer. The sub-analysis focused on the diagnostic population, excluding screening cases, and demonstrated that the diagnostic performance of GE HealthCare's CEM, as measured by the area under the receiver operating curve (ROC AUC), is comparable to AB-MRI and MRI. Additionally, the TLR confirmed that GE HealthCare's CEM offers comparable diagnostic accuracy to MRI across various clinical settings and patient populations. Most studies indicate that breast MRI has higher sensitivity, while CEM demonstrates higher specificity.

These findings support the use of SenoBright HD as a viable, comparable alternative to MRI and AB-MRI for breast cancer diagnosis.

2. Introduction

2.1 Background

The limitations of conventional digital mammography, particularly its low sensitivity in dense breast tissue, is well documented[2].

Several clinical studies have demonstrated that contrast enhanced imaging techniques are beneficial in detecting lesions that are not clearly visible on standard mammography or ultrasound. This is especially true for masses and architectural distortions that are difficult to interpret due to overlapping breast glandular tissue.

The FDA now mandates that mammography facilities inform patients about their breast density, which often leads to recommendations for supplemental imaging using additional modalities for those with dense breast tissue.

Dynamic contrast-enhanced MRI (DCE MRI or CE MRI) of the breast, which utilizes gadolinium-based contrast agents, is effective in detecting cancers that may be missed by ultrasound or digital breast tomosynthesis. However, its adoption is limited by factors such as high costs, limited access in rural areas, lengthy acquisition times, contraindications for patients with pacemakers or metal implants, allergies to gadolinium-based contrast agents, and reduced patient tolerance, particularly in those with claustrophobia. Efforts to shorten MRI acquisition times through abbreviated protocols (AB-MRI) have been successful in reducing scan duration but have not addressed challenges related to equipment costs, accessibility, or patient contraindications[1].

CEM, which uses a dual-energy approach with iodinated contrast to highlight malignancies, offers a lower-cost and easier-to-implement alternative that can help increase access to more patients. Due to these advantages, CEM is emerging as a viable alternative to MRI and AB-MRI for identifying contrast-visible lesions[2].

2.1.1 Breast MRI and abbreviated breast MRI (AB-MRI)

The conventional breast MRI protocol includes a dynamic contrast enhanced (DCE) series, which involves one pre contrast and several post-contrast T1-weighted sequences to capture the enhancement characteristics of breast lesions over time. This protocol often incorporates T2-weighted sequences with or without fat suppression, and additional planes. Sometimes a diffusion-weighted imaging (DWI) sequence is added to obtain additional functional information. These multi-parametric protocols provide comprehensive diagnostic data, which supports detailed lesion characterization, treatment planning, and monitoring[3,4].

Abbreviated breast MRI (AB-MRI) protocols are designed to enhance accessibility and reduce scan time compared to "full protocol" breast MRI while maintaining diagnostic accuracy. They typically include a T1-weighted pre-contrast and a single early postcontrast acquisition, with the possible addition of a T-2 weighted sequence[4,5].

In their meta-analysis of the diagnostic performance of AB-MRI and "full diagnostic protocol MRI" in breast cancer, Baxter et al. covered five screening (62/2,588 cancers/patients) and eight enriched cohort (540/1,432 cancers/patients) studies. The pooled sensitivity, specificity and AUC for screening studies was 0.90, 0.92, 0.94 for AB-MRI and 0.92, 0.95, 0.97 for breast MRI, respectively. The pooled sensitivity, specificity and AUC for enriched cohort studies was 0.93, 0.83, 0.94 for AB-MRI and 0.93, 0.84, 0.95 for breast MRI, respectively. There was no significant difference in sensitivity or specificity using AB-MRI or breast MRI (p=0.18 and 0.27, p=0.18 and 0.93, respectively). The meta-analysis concluded that that AB-MRI had an overall high diagnostic performance in the detection of breast cancer. The diagnostic performance was equivalent to that of a full protocol breast MRI amongst enriched cohorts and was lower but not significantly different in a screening setting[6].

2.1.2 Contrast-enhanced mammography (CEM)

CEM, also known as contrast-enhanced spectral mammography (CESM), as a mammography modality, has seen continued growth since it first received U.S. Food and Drug Administration (FDA) clearance in 2011 for diagnostic mammography as an adjunct following mammography and ultrasound exams to help localize a known or suspected lesion (K103485).

Eight meta-analyses and one systematic review on CEM have been published[7-15] along with 2 recent state-of-the art reviews[2,16]. Jochelson and Lobbes' state-of-the-art article on CEM in 2021[2] concluded that "CEM unit installations, examinations, and scientific publications have all increased. CEM is easy to perform in everyday clinical practice and is useful in indications including abnormal screenings, symptomatic patients". Kornecki published a comprehensive review of CEM in 2022[16], concluding that "Multiple studies point to the advantage of using CEM in the diagnostic setting of breast imaging". In a systematic review and meta-analysis of diagnostic performance of CEM performed by Cozzi et al. in 2022[7], a subgroup analysis of 10 studies on mammography-detected suspicious findings showed that CEM had a 92% pooled sensitivity (95% CI: 89%, 94%) and an 84% pooled specificity (95% CI: 73%, 91%).

The diagnostic performance of CEM vs. breast MRI was evaluated in 4 meta-analyses and 8 clinical studies published since January 2018[12-15]. The results of these publications are summarized in Section 5. In addition to these publications, the American College of Radiology (ACR) released the first version of the BI-RADS lexicon for CEM in 2022[17], as a supplement to ACR BI-RADS Mammography 2013[18], acknowledging that "Given that utilization is increasing, it is important that a lexicon be available to allow for consistency in reporting and also to allow for validation of standardized terms through studies looking at the performance of CEM in a variety of clinical settings".

2.2 Objectives

The aim of this whitepaper is to evaluate the most recent evidence comparing the diagnostic performance of GE HealthCare's CEM solution, SenoBright HD, with that of breast MRI.

Our analysis and conclusions are based on:

- A sub-analysis of a clinical study conducted in the United States: the CONTRRAST trial[1], which aimed to assess whether CEM is non-inferior to breast MRI or AB-MRI
- A targeted literature review of studies comparing GE HealthCare's CEM solution to breast MRI.

The CONTRRAST trial results showed that the breast cancer diagnostic performance of CEM, as measured by the area under the receiver operating curve (ROC AUC), is non inferior to breast MRI and to AB-MRI. The patient population of the study included both a screening population and a diagnostic population. As the SenoBright HD indications for use only covers the use of CEM for a diagnostic population, we performed a sub-analysis including only the diagnostic population. This sub-analysis included case sets obtained as part of a work-up for a finding detected during prior screening or before biopsy of a screening-detected abnormality. The sub-analysis of the CONTRRAST trial results, focused on the diagnostic patient population (Table 1) showed that CEM's breast cancer diagnostic performance, as measured by the ROC AUC, is comparable to AB-MRI and MRI. The statistical non-inferiority of CEM was demonstrated against AB-MRI, and CEM diagnostic performance fell short of non-inferiority vs. MRI (the lower limit of the 95% CI was –0.058 < -0.05 non-inferiority margin) as the study was not initially powered for the diagnostic population sub-group only.

Additionally, GE HealthCare conducted a TLR of recent publications comparing the diagnostic performance of GE HealthCare's CEM solution with both breast MRI and AB-MRI to confirm that the diagnostic performance of CEM is comparable to MRI in other clinical sites and countries.
This TLR showed that, apart from the CONTRRAST trial, all meaningful studies were conducted outside the United States (U.S.). Notably, the CONTRRAST trial was the only study that directly compared the diagnostic performance of CEM and AB-MRI. The TLR findings indicated that overall, the diagnostic accuracy (as defined by the ratio of "true positives + true negatives" / "total number of cases") and the ROC AUC of CEM and MRI are comparable, with majority of studies demonstrating higher sensitivity for MRI, and higher specificity for CEM (Table 7). These results confirm that the outcomes of the CONTRAST trial are consistent with the results of several other studies conducted in a variety of different patient population and clinical settings.

3. The CONTRRAST trial

An enriched reader study (CONTRRAST trial) used GE HealthCare's CEM solution and MRI data prospectively collected from asymptomatic patients at a single institution, Beth Israel Deaconess in Boston, Massachusetts, from December 2014 to March 2020, to determine whether CEM is non-inferior to breast MRI or AB-MRI and superior to low-energy (LE) CEM[1].

A total of 132 case sets were obtained from female patients at the time of screening (n=42), as part of the diagnostic work-up for a screening-detected finding (n=12) , or before biopsy (n=78). Amongst those 132 cases, 14 were negative, 74 were benign, and 44 were malignant (all female participants; mean age: 54 years ± 12 [standard deviation]). All images were anonymized, randomized, and read by 12 radiologists with varying experience reading CEM examinations (Table 4). The two readers without experience in CEM attended a pre-study lecture on CEM and completed a training set of 30 cases. To ensure consistency in interpretation and result recording, all readers underwent standardized training on an additional five cases. These training cases were excluded from the final set used in the reader study. Case sets included CEM and MRI that were performed within 3 months of each other and included all quality imaging required for standard clinical care. In addition, 2-year imaging or clinical follow-up or pathology results were available to confirm ground truthing. Cases were classified as negative, benign, or malignant at the case level.

The AB-MRI protocol arm of the CONTRRAST trial (Section 3) consisted of a selected number of sequences from the "full protocol" breast MRI exam that were used as a surrogate for the AB-MRI protocol. This included a pre-contrast T1-weighted fat-saturated sequence, T1-weighted fat-saturated first postcontrast sequence, subtraction sequence, and fluid-sensitive sequence (either T2-weighted with or without fat saturation or short tau inversion recovery). The "full protocol" breast MRI exam consisted of the AB-MRI sequences above, a delayed T1-weighted post-contrast sequence, early and late post-contrast sagittal sequences, and, if available, a non–fat-saturated sequence.

For CEM interpretation, readers were first shown low-energy images as a surrogate for digital mammography and asked to give a forced breast imaging reporting and data system (BI-RADS) score for up to 3 abnormalities. The highest score was used as the case score. Readers then reviewed the complete CEM examination and scored it similarly. After a minimum 1-month washout, the readers similarly interpreted AB-MRI and "full protocol" breast MRI examinations. Receiver operating characteristic analysis, powered to test CEM non-inferiority to "full protocol" breast MRI, was performed.

This study was powered to test the non-inferiority of CEM when compared with the "full protocol" breast MRI, with a negative margin of 0.05 based on a two-sided 95% confidence interval (CI) for the difference between the reader average areas under the receiver operating characteristic curve (AUCs). The receiver operating characteristic power and sample size calculations are based on the methods devised by Zhou et al[19].

Sensitivity was 75% for DM, 89% for CEM, 91% for AB-MRI, and 94% for full MRI. Specificity was 66% for DM, 71% for CEM, 65% for AB-MRI, and 63% for breast MRI. The mean AUCs for DM, CEM, AB-MRI, and breast MRI were 0.79, 0.91, 0.89, and 0.91, respectively. CEM was demonstrated to have superior AUC compared to DM ($p<0.001$). CEM was demonstrated to have non-inferior AUC compared to AB-MRI (lower limit of the 95% CI for the AUC difference was $-0.03 \geq -0.05$, non-inferiority margin), and to breast MRI (lower limit of the 95% CI for the AUC difference was $-0.05 \geq -0.05$, non-inferiority margin).

The CONTRRAST trial concluded that in an asymptomatic population, CEM was non-inferior to "full protocol" breast MRI and AB-MRI, and was superior to DM, in terms of ROC AUC.

4. The CONTRRAST trial sub-analysis comparing CEM, breast MRI, and AB-MRI for diagnostic use

A retrospective sub-analysis of the CONTRRAST trial was performed using GE HealthCare's CEM solution and breast MRI images from patients who had abnormal screening results or underwent imaging prior to biopsy, excluding screening patients. The reason to perform this sub-analysis was to be consistent with the SenoBright HD indications for use that only covers a use of CEM is diagnostic and not in screening of breast cancer. The same analyses performed for the CONTRRAST trial were conducted on this sub-group of patients.

4.1 Sub-analysis case collection

The sub-analysis included case sets of CEM and MRI images obtained either during the diagnostic work-up as part of routine clinical care (n=10, only including recalls from screening, excluding two cases from the annual exams of two different patients) or prior to biopsy for research purposes (clinical trial registration number NCT03482557; n=78). The same analyses as in the original CONTRRAST trial were conducted using the study data, excluding screening cases. Additional information regarding the case sets included in the sub-analysis is shown in Table 1.

Table 1: Breakdown of cases by origin, case type, and participant characteristics for the sub-analysis

	NCT03482557 (2018-2020)	Clinical cases (2016-2020)	Total
# of participants	78	10	88
Age (mean # SD)	54 ± 10	57 ± 18	55 ± 23
Source	Research and clinical	Clinical	
CEM indication	Before biopsy	Recall from screening	
Risk status	Any risk	Any risk	
Menopausal status			
Premenopausal	27	4	31
Post-menopausal	51	6	57
Case type			
Negative	0	1	1
Benign	38	6	44
Malignant	40	3	43
Participants features			
BRCA	1	0	1
Personal hx of cancer	7	2	9
Family hx of cancer	42	7	49
Lobular neoplasia	4	0	4
ADH	3	0	3
Chest radiation	1	0	1

4.2 Sub-analysis statistical methods

The sub-analysis aims to test the non-inferiority of CEM when compared with "full protocol" breast MRI and the non-inferiority of CEM when compared with AB-MRI, with a negative margin of 0.05 based on a two-sided 95% CI for the difference between the reader average areas under the receiver operating characteristic curve (AUCs).

In addition, a subset analysis was performed by comparing performance across modalities based on tissue density and background parenchymal enhancement (BPE). Tissue density was classified as non-dense (fat or scattered fibro glandular densities) and dense (heterogeneously dense or dense). BPE was categorized as low BPE (minimal or mild enhancement) and high BPE (moderate or marked enhancement).

Although a few cases had multiple cancers, only the case-level BI-RADS score was used for analysis. Negative and benign case sets were grouped together as noncancer examinations. Malignant case sets were used as the cancer examinations. The case-level sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated assuming that BI-RADS category 3 or higher indicates test-positive and BI-RADS 1 and 2 indicates test-negative. The true-positive designation corresponds to cancer cases with test-positive interpretations, whereas the false-positive designation corresponds to noncancer cases with test-positive interpretations.

The true-negative designation corresponds to noncancer cases with test-negative interpretations, whereas the false-negative designation corresponds to cancer cases with test-negative radiologist interpretations. The receiver operating characteristic analysis was based on the multi-reader multi-case method described by Gallas et al[20] and implemented with the iMRMC R package. The referenced method is not a complete case analysis and can handle data that are not fully crossed for any number of modalities, although only 2 of those modalities may be used at a time for variance analysis. One-way analysis of variance was used to compare reader AUC performance by years of experience for each separate modality. All analyses were performed using R statistical software (version 4.0.5; R Core Team), and $p<0.05$ indicates a statistically significant difference.

4.3 Sub-analysis results

Case set characteristics

A total of 88 case sets from 88 women were included (1 negative, 44 benign, and 43 malignant). The proportions of cases in different tissue density and BPE categories are described in Table 2.

Diagnostic performance

Overall AUCs across all readers for digital mammography, CEM, AB-MRI, and breast MRI were 0.76, 0.88, 0.87, and 0.88, respectively, showing that CEM had a significantly higher AUC than low energy CEM (difference: 0.12; $p<0.001$) (Table 3). The AUC of CEM is statistically non-inferior compared to AB-MRI (the lower limit of the 95% CI is –0.044 ≥ -0.05, the non-inferiority margin). The AUC of CEM is comparable to MRI, but fell short of demonstrating statistical non-inferiority, as the lower limit of the 95% CI is –0.058 < -0.05, the non-inferiority margin.

Diagnostic accuracy achieved with the 4 different imaging modalities, as measured with sensitivity, specificity, NPV, and PPV, is outlined in Table 3. The sensitivity of CEM was slightly lower than that of Breast MRI and similar to AB-MRI, and higher than that of digital mammography (2D MG) alone (Table 3). The specificity for CEM was higher than that of breast MRI, lower than digital mammography, and slightly lower than AB-MRI.

Table 2: Breakdown of cases by tissue density and BPE for the sub-analysis

	Benign or negative (n=45)	Malignant (n=43)	Total (n=88)
Tissue density			
Fat	0	0	0
SFGD	17	14	31
HD	20	24	44
Dense	8	5	13
BPE			
Min	14	16	30
Mild	15	14	29
Moderate	7	7	14
Marked	9	6	15

Note: BPE=background parenchymal enhancement, HD=heterogeneously dense, SFGD=scattered fibroglandular densities.

Table 3: Performance metrics and AUCs for the sub-analysis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	AUC difference with CEM	*P* Value	95% CI	Outcome
CEM	**88**	**65**	**72**	**86**	**0.875**				
2D MG	71	70	70	72	0.759	0.115	<0.001	0.052, 0.178	Superior
AB-MRI	88	66	73	87	0.868	0.007	0.803	-0.044, 0.058	Non-inferior
Full MRI	91	63	71	89	0.883	-0.008	0.748	-0.059, 0.043	Inconclusive

(The CONTRRAST trial used the LE CEM images as a surrogate for 2D digital mammography (DM or 2D MG))

When evaluating reader level AUCs, all readers improved when interpreting CEM as compared with digital mammography alone. AUC improved for 4 readers, decreased slightly for 7, and was unchanged for 1 when they interpreted CEM compared with AB-MRI. AUC improved for 3 readers and decreased for 9 when readers interpreted CEM compared with the Breast MRI. AUC per reader is included in Table 4.

Table 4: Reader AUCs for the sub-analysis

Reader	Years since training	CEM experience (yrs)	AUC			
			2D MG	CEM	AB-MRI	Full MRI
1	≥ 10	6	0.703	0.870	0.870	0.883
2	2-5	0	0.767	0.869	0.876	0.882
3	≥ 10	3	0.713	0.888	0.895	0.917
4	0-2	1	0.742	0.817	0.723	0.860
5	0-2	1	0.797	0.876	0.857	0.838
6	2-5	3	0.759	0.891	0.911	0.905
7	≥ 10	6	0.860	0.912	0.875	0.877
8	0-2	0.5	0.741	0.879	0.903	0.913
9	≥ 10	6	0.713	0.884	0.866	0.864
10	≥ 10	6	0.741	0.869	0.884	0.891
11	≥ 10	0	0.805	0.843	0.848	0.848
12	≥ 10	4	0.771	0.896	0.906	0.914

Subset analysis

The subset analysis comparing performance across modalities by tissue density revealed that CEM had a significantly higher AUC compared with digital mammography for examinations of both non-dense and dense tissue (p=0.03 and p=0.002, respectively) (Table 5). In both dense and non-dense tissue cases, CEM showed a similar AUC to both AB-MRI and MRI (0.85 vs. 0.83 and 0.85 for dense tissue and 0.92 vs. 0.93 and 0.94 for non-dense tissue, respectively) (Table 5).

In the comparison of AUC by BPE, there was no evidence of a difference in performance between CEM and AB-MRI or breast MRI (Table 5).

Table 5:
Subset analysis of AUCs by tissue density and BPE for the sub-analysis

Feature	AUC	AUC difference with CEM	*P* value	95% CI
Non-dense tissue				
CEM	0.922			
2D MG	0.875	0.047	0.031	0.004, 0.09
AB-MRI	0.928	-0.006	0.755	-0.043, 0.031
Full MRI	0.939	-0.017	0.306	-0.051, 0.016
Dense tissue				
CEM	0.846			
2D MG	0.709	0.137	0.002	0.05, 0.224
AB-MRI	0.832	0.014	0.720	-0.062, 0.09
Full MRI	0.849	-0.003	0.944	-0.079, 0.073
Low BPE				
CEM	0.888			
AB-MRI	0.882	0.006	0.868	-0.061, 0.072
Full MRI	0.893	-0.005	0.866	-0.068, 0.057
High BPE				
CEM	0.843			
AB-MRI	0.828	0.015	0.753	-0.078, 0.108
Full MRI	0.853	-0.010	0.855	-0.113, 0.093

4.4 CONTRRAST trial sub-analysis conclusions

A retrospective sub-analysis of the CONTRRAST trial enriched reader study was conducted, which excluded cases obtained at screening and included only CEM and MRI exams performed during diagnostic work-up or prior to biopsy. CEM demonstrated diagnostic performance, as measured by the AUC, comparable to AB-MRI, meeting the non-inferiority criterion. Although the diagnostic performance of CEM is comparable to MRI, the statistical non-inferiority is not demonstrated (the lower limit of the 95% CI was –0.058 < -0.05 the non-inferiority margin). Furthermore, a subset analysis across different tissue densities and BPE levels showed no differences in diagnostic performance between CEM, AB-MRI, and breast MRI.

5. Targeted literature review (TLR)

A TLR was conducted to assess the diagnostic performance of GE HealthCare's CEM solution compared to magnetic resonance imaging (MRI) in diagnostic breast exams (as per the ACR definition).

5.1 Methodology

The TLR consisted of 3 phases: 1) comprehensive literature search, 2) study selection, and 3) data extraction from the identified studies.

5.1.1 Bibliographic literature search

In addition to the database searches, a manual review of reference lists from pertinent articles was conducted. This included frequently cited or historically significant articles and bibliographies from relevant SLRs, which matched closely to the study objectives. This approach validated the database search results and ensured the inclusion of additional relevant studies.

Potentially relevant publications were reviewed and assessed to compile a final set of studies for the main results summary.
All retrieved studies were evaluated against the predefined criteria specified in Table 8 of the Appendix, and a final set of studies was identified for summarization.

Inclusion and exclusion criteria, such as study design, population characteristics, intervention types, and outcome measures, were applied to determine eligibility. These criteria included parameters like study type (e.g., randomized controlled trials, observational studies), population characteristics (e.g., age, gender, health condition), types of interventions, specific outcomes of interest and CEM vendors used. The TLR excluded studies that did not include any exams performed with a CEM solution by GE HealthCare or studies performed in a non-diagnostic population only.

5.1.2 Comprehensive targeted literature review (TLR)

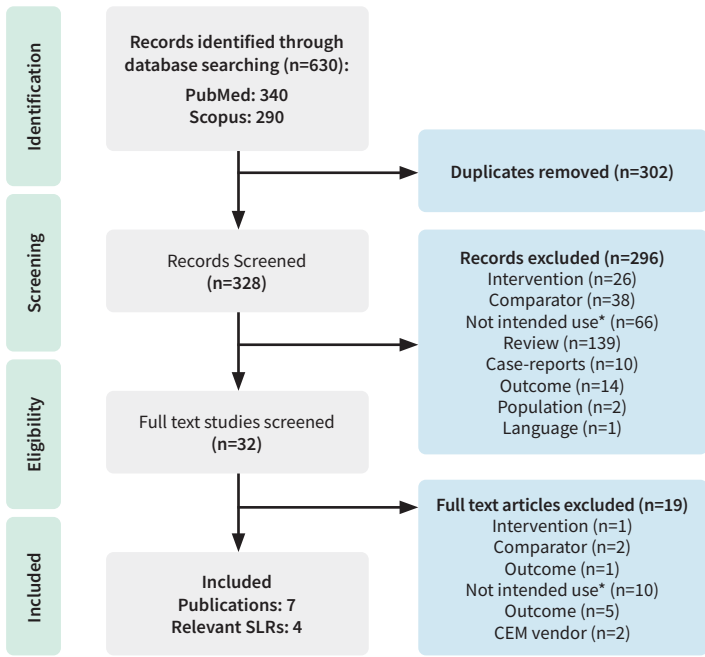
The initial phase involved identifying relevant articles that evaluate the diagnostic performance of CEM vs. breast MRI. This was achieved through systematic searches of the following electronic databases:
1. PubMed
2. Scopus

The search strategies were designed to capture a broad range of studies relevant to the objectives. Keywords and search terms were selected based on the scope of the study, including specific medical terms, intervention names, and population descriptors (Table 9 and Table 10 in the Appendix). The time horizon defined for the search (starting 1 January 2018) aimed to provide overlap with previous peer-reviewed systematic literature reviews (SLRs) comparing CEM with breast MRI (see Section 5.2) to validate our search strategy and to identify more recent publications (last published SLR search date was May 2022).

5.1.3 PRISMA flow chart

Figure 1 shows the PRISMA flow of studies included in the current review. Searches of literature databases yielded 630 separate references. Due to the overlap of coverage between the databases, 302 references were found to be duplicates and were excluded. Following a detailed examination of the remaining 328 references, 296 references were excluded leading to the inclusion of 32 references for full-text screening. Detailed screening of the references led to the exclusion of 21 references and inclusion of 11 publications. A total of 11 studies were included in the current review, of which 7 publications were prioritized for reporting purposes and the remaining 4 relevant SLRs were summarized separately.

Figure 1: PRISMA flow chart



*Not intended use was defined for the following patient populations / clinical indications: screening, high-risk patient follow-up, extent of disease assessment and therapy follow up.

5.2 Summary of bibliographic literature search comparing diagnostic performance of CEM vs. MRI

Four meta-analyses of the diagnostic performance of GE HealthCare's CEM solution compared to MRI have been reported[12-15] which are based on systematic reviews of published literature up to May 2022. Across these four SLRs there were 27 unique studies of which 11 studies were conducted in a diagnostic patient population. The pooled estimates for CEM across these 4 meta-analyses ranged from 91% to 98% for sensitivity and 43% to 77% for specificity compared to 95% to 97% for sensitivity and 30% to 77% for specificity for MRI (Table 6).

Xiang et al.[12] included 13 studies comparing CEM with MRI in 918 patients. Of these 13 studies, only 3 studies included patients with suspicious lesions / abnormalities or symptoms (N=315; 34% of total). Four of the studies included in the meta-analysis were conducted in the U.S. The estimated pooled sensitivity and specificity of CEM were 0.97 (95% CI: 0.95%, 0.98%) and 0.66 (95% CI: 0.59%, 0.71%), respectively, and 0.97 (95% CI: 0.95%, 0.98%) and 0.52 (95% CI: 0.46%, 0.58%), respectively, for MRI. For the diagnostic odds ratio (DOR), the pooled results of CEM were 60.15 (95% CI: 24.72%, 146.37%) and 31.34 (95% CI: 19.61%, 50.08%) for MRI. The AUC of the summary receiver operating characteristic curve (SROC) was 0.9794 for CEM and 0.9157 for MRI.

Pötsch et al.[13] included 7 studies with 582 patients and 1137 lesions comparing CEM with CE-MRI. Of the 7 studies, 6 included patients with suspicious lesions / symptoms / BI-RADS 4 or 5 (N=427, 73% of total). One study included patients in a staging and assessment of additional lesions in a BI-RADS 6 setting. Across all 7 studies, the pooled sensitivity was 91% (95% CI: 77%, 97%) for CEM and 97% (95% CI: 86%, 99%) for MRI (p<0.001). The pooled specificity was 74% (95% CI: 52%, 89%) for CEM and 69% (95% CI: 46%, 85%) for MRI (p=0.09).

Gelardi et al.[14] included 15 studies with 1315 patients comparing CEM with CE-MRI. Seven studies were in patients for differential diagnosis of suspicious lesions from screening (N=802; 61% of the total) and 8 studies were for pre-operative staging. Four studies were conducted in the U.S. Meta-analysis of diagnostic performance was conducted at the per-lesion level. Across all detected lesions, the pooled sensitivity of CEM was 96% (95% CI: 93%, 99%) and for CE-MRI was 96% (95% CI: 93%, 98%) and the pooled specificity of CEM was 43% (95% CI: 25%, 63%) and for CE-MRI was 30% (95% CI: 11%, 52%). A sub-group analysis of the 7 studies in patients (N=802) for differential diagnosis of suspicious lesions from screening improved diagnostic performance with a pooled sensitivity of CEM of 98% (95% CI: 0.93%, 1.00%) and for CE-MRI of 95% (95% CI: 0.91%, 0.98%); the pooled specificity of CEM was 58% (95% CI: 0.32%, 0.82%) and for CE-MRI 55% (95% CI: 0.26%, 0.82%).

Neeter et al.[15] included 6 studies with 607 patients comparing CEM with MRI in patients with suspicious breast lesions on prior imaging or clinical examination. The pooled sensitivity of CEM was 96% (95% CI: 90%, 99%) and 97% (95% CI: 92%, 99%) for MRI. Pooled specificity was 77% (95% CI: 53%, 91%) for CEM and 77% (95% CI: 57%, 89%) for MRI. The pooled diagnostic odds ratio estimates indicate a higher overall diagnostic performance of MRI compared to CEM (122.9 vs. 79.5).

Note that of the 27 unique studies included in these 4 published SLRs, 11 of them were identified in the TLR. Fifteen studies pre-dated the time horizon of the TLR search, and 1 study was not found in PubMed. The TLR identified 3 more recent publications[1,21,22]; from 2022 onwards).

5.2.1 Summary of studies included in the TLR

Seven studies matched the inclusion criteria described in Section 5.1.1. The characteristics of the selected studies comparing CEM and MRI are described in Table 11 and the diagnostic performance results are summarized in Table 12 and Table 13 provides details on the experience of image readers in these studies.

Phillips et al.[1] evaluated the diagnostic performance of CEM vs. breast MRI and AB-MRI, and compared these modalities to conventional digital mammography in the «CONTRRAST trial» (Section 3 and 4 contain a more detailed presentation of this study and the subsequent sub-analysis). The authors concluded that CEM was non-inferior to both AB-MRI and breast MRI in terms of AUC (statistically significant).

Rudnicki et al.[23] compared the diagnostic performance of CEM vs. 1.5T breast MRI in a retrospective study that involved 121 patients with abnormalities detected on ultrasound or mammography. The reference histopathological examination revealed 81 malignant and 40 benign lesions. Breast anatomy type of the patients was categorized as «predominantly glandular» (53%), «mixed» (32%), and «fatty» (23%). These patients subsequently underwent both CEM and MRI within a 2-month interval. Images were interpreted by a radiologist with at least 5 years of experience in CEM and MRI. Sensitivity was 100% for both CEM and MRI. Specificity was 33% for CEM and 23% for MRI. Accuracy was 77% for CEM and 74% for MRI. Similar analysis was performed considering only dense breasts and resulted in equal sensitivity on CEM and MRI and «negligibly lower specificity» on CEM vs. MRI.

Yasin and El Ghany[24] compared the diagnostic performance of CEM vs. 1.5T breast MRI in a prospective study that included 50 patients with BIRADS 4 breast lesions detected by mammography and ultrasound. Histopathological assessment was the gold standard and revealed 34 malignant and 22 benign lesions. CEM and MRI images were evaluated by 2 experienced radiologists with 15 years of experience in CEM and breast MRI. CEM was found to have lower sensitivity (94.1%) than MRI (100%), but CEM had higher specificity (100%) than MRI (95.5%). The accuracy of CEM was 96.4%, while the accuracy of MRI was 98.2% with no statistical significance (p=0.827). The authors concluded that CEM had proven to be a sensitive diagnostic tool for breast cancer, demonstrating higher specificity, but slightly lower sensitivity, compared to CE-MRI.

Açar et al.[21] compared the diagnostic performance of CEM vs. 1.5T breast MRI. The prospective study included 116 patients and evaluated a total of 219 lesions, of which 125 were malignant and 94 benign. Images were interpreted by 2 observers. Observer 1 was a radiology specialist with 32 years of experience in breast imaging. Observer 2 was a fourth-year radiology resident. For CEM, the sensitivity, specificity, accuracy, and AUC were calculated to be 98.40%, 81.91%, 91.32%, and 0.902, respectively. For MRI, the sensitivity, specificity, accuracy, and AUC was 100%, 75.53%, 89.49%, and 0.878, respectively. When breasts were divided into 2 groups as dense (type C and D) and non-dense (type A and B), the sensitivity for lesions in dense breasts was found to be 98.27%, specificity was 85.21%, and the AUC was 0.917 with CEM and the sensitivity for lesions associated with dense breast tissue was 100%, specificity was 79.62%, and the AUC was 0.898 with MRI. The authors also noted that the differences in specificity and sensitivity of CEM vs. MRI were not statistically significant.

Table 6: Summary of published meta-analyses on CEM vs. MRI diagnostic performance

Publication	Number of studies included in meta-analysis	Total number of patients included in meta-analysis	Patient population description	CEM Estimated pooled sensitivity	MRI Estimated pooled sensitivity	CEM Estimated pooled specificity	MRI Estimated pooled specificity	Study conclusion
Xiang 2020	13	918	Cases with a confirmed diagnosis of breast cancer	97%	97%	66%	52%	In conclusion, CESM is reported to have a higher degree of accuracy in the diagnosis of breast cancer. Compared with MRI, it has a higher specificity and diagnostic performance, and can be used as an effective tool in the screening and diagnosis of breast cancer.
(CEM vs. MRI)				(95% CI: 0.95-0.98)	(95% CI: 0.95-0.98)	(95%CI: 0.59-0.71)	(95% CI: 0.46-0.58)	
Potsch 2022	7	605	Women undergoing CEM and CE-MRI due to indeter-minate or suspicious findings at conventional imaging (ie, U.S. and/or mammography, digital breast tomosynthesis)	91%	97%	74%	69%	In conclusion, while contrast-enhanced mammography (CEM) and contrast-enhanced MRI (CE-MRI) show comparable diagnostic performance, CE-MRI was superior regarding the most clinically relevant metrics of sensitivity, negative predictive value, and negative likelihood ratio. The limited amount of currently available data is inconsistent with the intense discussion on the topic. Thus, it is as of yet unclear how clinically relevant the diagnostic performance differences are between CEM and CE-MRI. This calls for further, large-scale, and setting-specific prospective research that will also focus on cost-effectiveness.
(CEM vs. CE-MRI)				(95% CI: 0.77-0.97)	(95% CI: 86, 99)	(95% CI: 0.52-0.89)	[95% CI: 46, 85]	
Gelardi 2022	15	1315	Detection, diagnosis and pre-operative assessment of breast cancer	All studies: 96% (95% CI: 0.93-0.99)	All studies: 96% (95% CI: 0.93-0.98)	All studies: 43% (95% CI: 0.25-0.63)	All studies: 30% (95% CI: 0.11-0.52)	Our findings confirm the potential of CEM as a supplemental screening imaging modality, even for intermediate-risk women, including females with dense breasts and a history of breast cancer. Both CE-MRI and CEM exhibit a high sensitivity, whereas CE-MRI exhibits a lower specificity compared with CEM for diagnosing breast lesions. The lower specificity of CE-MRI mainly related to the high number of false positives encountered suspicious lesions among the secondary lesions might result in a high number of unnecessary invasive biopsies. CEM is a viable screening method because ofits lower costs, higher availability, shorter acquisition times, and higher patient tolerance.
(CEM vs. CE-MRI)	7	802	Sub-group: differential diagnosis (DD) of suspicious lesions at screening	Sub-group: DD suspicious lesions at screening 98% (95% CI 0.93-1.00)	Sub-group: DD suspicious lesions at screening 95% (95% CI: 0.91-0.98)	Sub-group: DD suspicious lesions at screening 58% (95% CI: 0.32-0.82)	Sub-group: DD suspicious lesions at screening 55% (95% CI: 0.26-0.82)	
Neeter 2023	6	607	Women with suspicious breast lesions on prior imaging (e.g., full-field digital mammography, (ultrasound) or clinical examination	96%	97%	77%	77%	In conclusion, we showed that sensitivity was high and specificity moderate for both CEM and breast MRI. The higher pooled DOR estimates for breast MRI indicate a higher overall diagnostic performance compared to CEM. Nevertheless, it seems premature to discard CEM as alternative for breast MRI due to the limited number of studies included in this review. Future studies that are directly comparing CEM and breast MRI for various indications are much needed.
(CEM vs. MRI)				(95% CI: 90%-99%)	(95% CI: 92%-99%)	(95% CI: 53%-91%)	(95% CI: 57%-89%)	

Ferranti et al.[22] evaluated the diagnostic accuracy of CEM and 3T MRI compared to FFDM plus ultrasound.
The prospective study included 118 women with unresolved or suspicious findings after digital mammography and ultrasound. Cytological/histological assessment was the gold standard and ultimately revealed breast cancer in 88 of the enrolled patients. Two experienced breast radiologists with a minimum of 10 years of experience in breast imaging, interpreted the cases. Sensitivity was 100% for CEM and 99% for MRI. Specificity was 50% for CEM and 47% for MRI. Accuracy was 93% for CEM and 88% for MRI.

Kamal et al.[25] evaluated the diagnostic performance of CEM vs. 1.5T breast DCE-MRI in the assessment of indeterminate lesions (BIRADS 3 and 4). The study included 82 patients with 171 lesions. 120 lesions were proven to be malignant with histological analysis. The calculated DCE-MRI sensitivity, specificity, and diagnostic accuracy were 100%, 68.63%, and 90.64%, respectively. The CEM sensitivity, specificity, and diagnostic accuracy were calculated as 94.17%, 64.71%, and 85.38%, respectively. The authors reported that that DCE-MRI sensitivity was slightly, yet significantly, higher than that of CEM (p=0.014). The specificity and overall accuracy of DCE-MRI was slightly better than that of CEM; however, no statistically significant difference could be detected (p=0.674 and 0.134, respectively).

Xing et al.[26] evaluated the diagnostic performance of CEM vs. 3T breast MRI on 235 patients, who were suspected of having breast abnormalities by clinical examination or mammography or ultrasound. Histopathological analysis was used as the reference and confirmed 177 of the 263 lesions as malignant. CEM and MRI exams were performed on all patients and the images were interpreted by 3 radiologists with 10-year working experience in breast imaging. Calculated sensitivity, specificity, accuracy, and AUC for CEM was 91.5%, 89.5%, 81.0%, and 0.950, respectively. Sensitivity, specificity, accuracy, and AUC for MRI was 91.5%, 80.2%, 71.7%, and 0.939, respectively. There was no statistically significant difference in AUC between CEM and MRI (Z=0.701, p>0.05). Overall, CEM demonstrated better accuracy, specificity, and false-positive rate in breast cancer detection compared to MRI.

5.3 Conclusions of the TLR

The TLR evaluated the diagnostic performance of CEM vs. breast MRI in evaluating concerns or findings prior to biopsy. Following the methodology described in Section 5.1.1 four meta-analyses and seven articles were included in this TLR report.

The four meta-analyses are based on 27 unique studies that were conducted across 10 countries, covering a diverse set of patient populations and clinical settings. Two out of four meta-analyses[12,14] included studies conducted in the U.S. The pooled estimates for CEM across the meta-analyses we surveyed ranged from 91% to 98% for sensitivity and 43% to 77% for specificity compared to 95% to 97% for sensitivity and 30% to 77% for specificity for MRI.

In addition to the 4 meta-analyses surveyed, seven studies matched the inclusion criteria described in Section 5.1.2. The results of these studies are summarized in Table 7 showing absolute values for sensitivity, specificity, AUC, and accuracy where reported. Among the seven studies, only the CONTRRAST trial[1] (described in detail in Section 3) was conducted in the U.S. and was the only study to include AB-MRI as a comparator in addition to conventional breast MRI. Among the seven studies included in the TLR, four demonstrated better sensitivity for breast MRI compared to CEM, while six reported higher specificity for CEM versus breast MRI. Regarding the area under the curve (AUC), two out of three studies that measured it favored CEM, with one study showing equal AUC between CEM and breast MRI. Of the six studies reporting accuracy, four found CEM to be more accurate, while two favored breast MRI.

Table 7: Summary of diagnostic performance results of studies included in the TLR (absolute values in %)

	Sensitivity (Se)			Specificity (Sp)			Arear Under Curve (AUC)			Accuracy (Acc)		
	CEM Se	MRI Se	AB-MRI Se	CEM Sp	MRI Sp	AB-MRI Sp	CEM AUC	MRI AUC	AB-MRI AUC	CEM Acc	MRI Acc	AB-MRI Acc
Phillips 2023	89%	94%	91%	71%	63%	65%	91%	91%	89%	NR	NR	NR
Rudnicki 2021	100%	100%	NR	33%	23%	NR	NR	NR	NR	77%	74%	NR
Yasin 2019	94%	100%	NR	100%	96%	NR	NR	NR	NR	96%	98%	NR
Acar 2024*	98%	100%	NR	82%	76%	NR	90%	88%	NR	91%	89%	NR
Ferranti 2022*	100%	99%	NR	50%	47%	NR	NR	NR	NR	93%	88%	NR
Kamal 2020*	94%	100%	NR	65%	69%	NR	NR	NR	NR	85%	91%	NR
Xing 2019*	92%	92%	NR	90%	80%	NR	95%	94%	NR	81%	72%	NR

* Diagnostic performance reported per lesion; NR - not reported.

The meta-analyses and studies included in the TLR broadly concluded that CEM has comparable performance to MRI. These results highlight CEM as a valuable imaging modality, particularly in diagnostic scenarios or clinical settings where breast MRI is unavailable or contraindicated.

6. Summary and discussion of results

The retrospective sub-analysis of the CONTRRAST trial enriched reader study[1] evaluated the diagnostic performance of SenoBright compared to AB-MRI and "full protocol" conventional breast MRI. The sub-analysis excluded cases obtained at screening and included only CEM and breast MRI exams performed during diagnostic work-up or prior to biopsy.

The TLR focused on publications that compared the performance of CEM vs. breast MRI and was based on four published meta-analyses[12-15] and seven studies published after January 1, 2018[1,21-26]. Only the CONTRRAST trial[1] described in detail in Section 3 included AB-MRI as a comparator in addition to "full protocol" breast MRI.

6.1 Discussion

The CONTRRAST trial showed that the breast cancer diagnostic performance of CEM, as measured by the ROC AUC, is non inferior to breast MRI and to AB-MRI.

The sub-analysis of the CONTRRAST (Section 4) trial focused on the diagnostic patient population and showed that CEM's breast cancer diagnostic performance, as measured by the ROC AUC, is non inferior to AB-MRI. Moreover, it also showed that AUC for CEM and Breast MRI are comparable but fell short of demonstrating statistical non-inferiority with a lower limit of the 95% CI of –0.059 < - 0.05, the non-inferiority margin.

The targeted literature review (Section 5) included results from studies conducted across diverse countries, patient populations, and clinical settings, demonstrating that CEM has comparable diagnostic performance to breast MRI, with a slight advantage of MRI in terms of sensitivity compensated by an advantage of CEM in terms of specificity.

These findings collectively support CEM as a viable alternative to MRI and AB-MRI for diagnostic purposes, providing comparable accuracy while potentially offering a more accessible breast imaging option in clinical practice.

6.1.1 Applicability of analysis to a U.S. diagnostic population

The CONTRRAST trial[1] sub-analysis was conducted on a U.S.-based population. The TLR was based on four published meta-analyses[12-15] (a total of 41 studies and 3445 patients) and seven studies published after January 1, 2018[1,21-26] (a total of 854 patients), and concluded that CEM has overall comparable performance to MRI.

Two of the four meta-analyses[12,14] included in our TLR incorporated studies conducted in the U.S., with 8 of the 41 total studies included in the meta-analyses originating from the U.S. Of the seven studies included in our TLR, only the CONTRRAST trial1 was conducted in the U.S., comprising 132 U.S. patients out of a total of 854. The CONTRRAST trial served as the basis for the sub-analysis focused on a diagnostic population (n=88).

Both the CONTRRAST trial, including its sub-analysis, and the studies included in the TLR demonstrate a consistent pattern, confirming that CEM's diagnostic performance is comparable to MRI across a broad range of countries. This analysis concluded that the CONTRRAST trial, sub analysis, and TLR together provide substantially robust and diverse samples of data that reasonably reflect the diagnostic population in the U.S.

6.1.2 Applicability of analysis to SenoBright HD

By design, the TLR excluded studies that did not include any exams performed with a CEM solution by GE HealthCare. Consequently, the conclusions of the TLR and the CONTRRAST Trial subanalysis are applicable to SenoBright HD, and do not extend to the CEM devices of other manufacturers.

7. Conclusion

The retrospective sub-analysis of the CONTRRAST trial, which was conducted in the U.S. using subjects in the target population, included CEM and breast MRI exams performed during diagnostic work-up or prior to biopsy (Section 4). T**he results showed that the diagnostic performance of CEM, as measured by ROC AUC, is comparable to AB-MRI and "full protocol" breast MRI.** However, the statistical non-inferiority was demonstrated only against AB-MRI, and it falls short against "full protocol" breast MRI (the lower limit of the 95% CI is –0.058 < - 0.05 non-inferiority margin).

Additionally, the TLR (Section 5), which included results from studies conducted inside and outside of the U.S., diverse patient populations and clinical settings, demonstrated that **CEM offers comparable diagnostic performance to breast MRI.** This suggests CEM as a valuable alternative in diagnostic imaging. Although the majority of the TLR studies indicated that breast MRI had better sensitivity, CEM generally had better specificity with similar AUC values between CEM and breast MRI.

In conclusion, the authors conclude that the sub-analysis of the CONTRRAST trial data, along with supporting evidence from the TLR, strongly indicates that SenoBright HD's diagnostic performance, as measured by ROC AUC, is comparable to breast MRI and AB-MRI.

8. References

1. Phillips J, Mehta TS, Portnow LH, et al. Comparison of Contrast-enhanced Mammography with MRI Utilizing an Enriched Reader Study: A Breast Cancer Study (CONTRRAST Trial). Radiology. 2023;309(2):e230530.

2. Jochelson MS, Lobbes MBI. Contrast-enhanced Mammography: State of the Art. Radiology. 2021;299(1):36-48.

3. ACR Practice Parameter for the Performance of Contrast- Enhanced Magnetic Resonance Imaging (MRI) of the Breast. Revised 2023. Available from: https://www.acr.org/-/media/acr/files/practice-parameters/mr-contrast-breast.pdf

4. Mann RM, Cho N, Moy L. Breast MRI: State of the Art. Radiology 2019; 292:520–536. https://doi.org/10.1148/radiol.2019182947

5. Kuhl CK. Abbreviated Breast MRI: State of the Art. Radiology. 2024 ; 310(3):e221822.

6. Baxter GC, Selamoglu A, Mackay JW, Bond S, Gray E, Gilbert FJ. A Meta-analysis Comparing the Diagnostic Performance of Abbreviated MRI and a Full Diagnostic Protocol in Breast Cancer. Clinical Radiology. 2021 Feb;76(2):154.e23-154.e32.

7. Cozzi A, Magni V, Zanardo M, et al. Contrast-enhanced Mammography: A Systematic Review and Meta-Analysis of Diagnostic Performance. Radiology. 2022;302(3):568-81.

8. Tagliafico AS, Bignotti B, Rossi F, et al. Diagnostic performance of contrast-enhanced spectral mammography: Systematic review and meta-analysis. Breast. 2016;28:13-9.

9. Zhu X, Huang JM, Zhang K, et al. Diagnostic Value of Contrast-Enhanced Spectral Mammography for Screening Breast Cancer: Systematic Review and Meta-analysis. Clin Breast Cancer. 2018;18(5):e985-e995.

10. Zanardo M, Cozzi A, Trimboli RM, et al. Technique, protocols and adverse reactions for contrast-enhanced spectral mammography (CESM): a systematic review. Insights Imaging. 2019;10(1):76.

11. Suter MB, Pesapane F, Agazzi GM, et al. Diagnostic accuracy of contrast-enhanced spectral mammography for breast lesions: A systematic review and meta-analysis. Breast. 2020; 53:8-17.

12. Xiang W, Rao H, Zhou L. A meta-analysis of contrast-enhanced spectral mammography versus MRI in the diagnosis of breast cancer. Thorac Cancer. 2020;11(6):1423-32.

13. Pötsch N, Vatteroni G, Clauser P, et al. Contrast-enhanced Mammography versus Contrast-enhanced Breast MRI: A Systematic Review and Meta-Analysis. Radiology, 2022. 305(1):94-103.

14. Gelardi F, et al. Contrast-Enhanced Mammography versus Breast Magnetic Resonance Imaging: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2022;12(8):1890.

15. Neeter LMFH, Robbe MMQ, van Nijnatten TJA, et al. Comparing the Diagnostic Performance of Contrast-Enhanced Mammography and Breast MRI: a Systematic Review and Meta-Analysis. J Cancer. 2023 Jan 1;14(1):174-82.

16. Kornecki A. Current Status of Contrast Enhanced Mammography: A Comprehensive Review. Canadian Association of Radiologists Journal. 2022;73(1):141-56.

17. ACR. ACR BI-RADS® Contrast Enhanced Mammography, a supplement to ACR BI-RADS® Mammography 2013. 2022. Available from: https://www.acr.org/-/media/ACR/Files/RADS/BI-RADS/BIRADS_CEM_2022.pdf, accessed 06/29/2022.

18. ACR. ACR BI-RADS® ATLAS — MAMMOGRAPHY. II. REPORTING SYSTEM. 2013 (1). Available from: https://www.acr.org/-/media/ACR/Files/RADS/BI-RADS/Mammography-Reporting.pdf

19. Zhou XH, Obuchowski NA, McClish DK. Statistical methods in diagnostic medicine. 2nd ed. Hoboken, NJ: Wiley, 2011.

20. Gallas BD, Bandos A, Samuelson F, Wagner RF. A framework for random-effects ROC analysis: biases with the bootstrap and other variance estimators. Commun Stat A-Theory 2009;38(15):2586–260.

21. Açar ÇR, Orguc S. Comparison of Performance in Diagnosis and Characterization of Breast Lesions: Contrast-Enhanced Mammography Versus Breast Magnetic Resonance Imaging. Clin Breast Cancer. 2024;S1526-8209(24):00107-1.

22. Ferranti FR, Vasselli F, Barba M, et al. Diagnostic Accuracy of Contrast-Enhanced, Spectral Mammography (CESM) and 3T Magnetic Resonance Compared to Full-Field Digital Mammography plus Ultrasound in Breast Lesions: Results of a (Pilot) Open-Label, Single-Centre Prospective Study. Cancers (Basel). 2022;14(5):1351.

23. Rudnicki W, Piegza T, Rozum-Liszewska N, et al. The effectiveness of contrast-enhanced spectral mammography and magnetic resonance imaging in dense breasts. Pol J Radiol. 2021;86:e159-e164.

24. Yasin R, El Ghany EA. BIRADS 4 breast lesions: comparison of contrast-enhanced spectral mammography and contrast-enhanced MRI. Egypt J Radiol Nucl Med. 2019;50:34.

25. Kamal RM, Hanafy MM, Mansour SM, et al. Can contrast-enhanced mammography replace dynamic contrast-enhanced MRI in the assessment of sonomammographic indeterminate breast lesions? Egypt J Radiol Nucl Med. 2020;51:66.

26. Xing D, Lv Y, Sun B, et al. Diagnostic Value of Contrast-Enhanced Spectral Mammography in Comparison to Magnetic Resonance Imaging in Breast Lesions. J Comput Assist Tomogr. 2019;43(2):245-51.

9. Appendix

Acronym	Definition
2D MG	Two-dimensional digital mammography
AB-MRI	Abbreviated Breast MRI
Acc	Accuracy (defined as the ratio of “true positives + true negatives” / total number of cases)
ACR	American College of Radiology
ADH	Atypical ductal hyperplasia
AUC	Area under ROC curve
BI-RADS	Breast Imaging Reporting and Data System
BPE	Background Parenchymal Enhancement
BRCA	BReast CAncer gene, that refers to BRCA1 and BRCA2, the two genes associated with a higher risk of breast and ovarian cancer when mutated
CEM	Contrast-Enhanced Mammography
CESM	Contrast-Enhanced Spectral Mammography
CE-MRI	Contrast-Enhanced MRI
CI	Confidence Interval
DCE MRI	Dynamic Contrast-Enhanced MRI
DM	Digital Mammography
DOR	Diagnostic Odds Ratio

Acronym	Definition
DWI	Diffusion-Weighted Imaging
FDA	Food and Drug Administration
GEHC	GE HealthCare
FFDM	Full field digital mammography
FN	False Negative
FP	False Positive
LE-CEM	Low Energy Contrast Enhanced Mammography (low energy image acquired during the CEM procedure)
MG	Mammography (FFDM)
MRI	Magnetic Resonance Imaging
Mx	Mammography (FFDM)
NPV	Negative Predictive Value
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROC	Receiver Operating Curve
SLR	Systematic Literature Review
TLR	Targeted Literature Review
TP	True Positive
TN	True Negative

9.2 Bibliographic literature search: inclusion – exclusion criteria and review Steps

Potentially relevant publications were reviewed and assessed to compile a final set of studies for the main results summary discussion. Inclusion and exclusion criteria were applied to determine the studies eligible for review. The criteria included factors such as study design, population characteristics, intervention types, and outcome measures. All retrieved studies were evaluated against the eligibility criteria specified in Table 8, and a final set of studies were identified for summarization.

Primary screening (Level 1 – abstract and title)

Primary screening was conducted by a single reviewer, who examined each reference (title and abstract) identified in the literature search. Basic selection criteria (population, intervention, and study design) were applied to decide on the inclusion or exclusion of each study reference. A quality check of the records followed this process to ensure consistency and accuracy.

Secondary screening (Level 2 – full-text)

Full-text articles were obtained for potentially relevant studies identified during Level 1 screening. These were independently reviewed against the eligibility criteria by a single reviewer. The secondary screening involved a more detailed assessment of the studies, considering the methodology, sample size, the CEM vendor used and the relevance to the research objectives. A quality check of the records followed this process to ensure the robustness of the selection process.

A meticulous record of included and excluded articles, along with the reasons for these decisions, was maintained and summarized in a PRISMA flow chart (Figure 1) This record included details such as the reason for exclusion (e.g., irrelevant intervention, not intended use) and was crucial for transparency and reproducibility.

Data extraction

A standardized evidence data extraction template was developed in Microsoft Excel per the project objectives. Data was extracted by one reviewer, who systematically recorded details such as study design, population demographics, intervention specifics, outcomes measured, and key findings. A quality check was performed by another independent reviewer to ensure data accuracy and reliability.

Reporting

The review methods and results were detailed comprehensively. This included the findings of the literature search presented in a Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart to illustrate the selection process, the study selection methodology, a list of included studies, and a summary of the final included studies. The final report provided a thorough analysis of the included studies, discussing the implications of the findings in the context of the research objectives, and identifying any gaps or limitations in the existing literature.

Table 8: Study inclusion and exclusion selection criteria

Descriptor	Inclusion criteria	Exclusion criteria
Population	Adult female patients ≥18 years of age (under 60, 60-75 and over 75)	• Studies focusing solely on children and adolescents. • Pregnant and lactating women • Studies performed in a non-diagnostic population only. (including screening, women with known breast cancer (e.g., extent of disease evaluation, pre-operative assessment)) • Follow-up therapy • Therapy response prediction • CEM after biopsy
Interventions	Contrast enhanced mammography [CEM] (also referred to as CESM, CEDM)	• No direct comparison with MRI • CCRF-CEM (human leukemia cell)
Comparisons	MRI; CE-MRI; DCE-MRI; Abbreviated MRI	
Reference Standard	Use of an acceptable reference standard (results of histopathology (for malignant and benign lesions), and follow-up or additional imaging (for benign lesions)) to determine true disease state	NA
Outcomes	Diagnostic accuracy performance metrics: True Positive (TP), True Negative (TN), False Positive (FP), False Negative (FN), Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV)accuracy, ROC/AUC	Outcomes other than those listed if diagnostic accuracy not reported
Study design	Evidence from randomized controlled trials, single-arm trials, case-control studies, observational studies (retrospective, prospective and cohort studies), SLRs/meta-analysis (SLRs will be only used to validate the included evidence and summarized separately)	• Case study • Case series • Case report • Reviews • Comments • Editorials
Duration	6 years (1 January 2018-current)	Studies before 2018
Language	English	Non-English
CEM vendor	Interventions include exams performed on CEM solutions by GE HealthCare (SenoBright HD, SenoBright, or CEM on Senographe Essential)	Interventions do not include any exams performed on CEM solution by GE HealthCare

9.3 Comprehensive literature search queries in PubMed and Scopus databases

Table 9: PubMed search query (Time period for final search: 1st January 2018 to 5th July 2024)

Search number	Query	Results
Total no. hits	167 + 173	**340**
1	"Contrast enhanced spectral mammography"[Title/Abstract] OR "contrast-enhanced spectral mammography"[Title/Abstract] OR "contrast-enhanced mammography"[Title/Abstract] OR "contrast enhanced mammography"[Title/Abstract] OR "CESM"[Title/Abstract] OR "dual energy mammography"[Title/Abstract] OR "dual-energy mammography"[Title/Abstract] OR "dual-energy subtraction mammography"[Title/Abstract] OR "dual energy contrast enhanced digital mammography"[Title/Abstract] OR "contrast-enhanced digital mammography"[Title/Abstract] OR "contrast enhanced digital mammography"[Title/Abstract]	**692**
2	"Contrast-enhanced magnetic resonance imaging"[Title/Abstract] OR "Contrast enhanced magnetic resonance imaging"[Title/Abstract] OR "Contrast-enhanced breast magnetic resonance imaging"[Title/Abstract] OR "Contrast enhanced breast magnetic resonance imaging"[Title/Abstract] OR "Dynamic Contrast-enhanced MRI"[Title/Abstract] OR "DCE-MRI"[Title/Abstract] OR "CE-MRI"[Title/Abstract] OR "Contrast-enhanced MRI" [Title/Abstract] OR "contrast enhanced MRI" [Title/Abstract] OR "breast magnetic resonance imaging"[Title/Abstract] OR "Breast MRI"[Title/Abstract] OR "Breast-MRI"[Title/Abstract]	**14178**
3	Magnetic resonance imaging [MESH]	**5,52,081**
4	#2 OR #3	**5,55,798**
5	#1 AND #4	**207**
6	#1 AND #4; Publication limit 2018 - current	**167**
7 (Additional combined search including CEDM terms)	#1 OR «contrast media»[MeSH Terms] OR («contrast»[All Fields] AND «media»[All Fields]) OR «contrast media»[All Fields] OR «contrast»[All Fields] OR «contrasted»[All Fields] OR «contrasting»[All Fields] OR «contrastive»[All Fields] OR «contrastively»[All Fields] OR «contrastiveness»[All Fields] OR «contrastivity»[All Fields] OR «contrasts»[All Fields]) AND («enhance»[All Fields] OR «enhanced»[All Fields] OR «enhancement»[All Fields] OR «enhancements»[All Fields] OR «enhancer»[All Fields] OR «enhancer s»[All Fields] OR «enhancers»[All Fields] OR «enhances»[All Fields] OR «enhancing»[All Fields]) AND («spectral»[All Fields] OR «spectrally»[All Fields]) AND («mammography»[MeSH Terms] OR «mammography»[All Fields] OR «mammographies»[All Fields] OR «mammography s»[All Fields])) OR («contrast enhanced»[All Fields] AND «dual-energy»[All Fields] AND («mammography»[MeSH Terms] OR «mammography»[All Fields] OR («digital»[All Fields] AND «mammography»[All Fields]) OR «digital mammography»[All Fields]))))) AND («contrast enhanced magnetic resonance imaging»[Title/Abstract] OR «contrast enhanced magnetic resonance imaging»[Title/Abstract] OR «contrast enhanced breast magnetic resonance imaging»[Title/Abstract] OR «contrast enhanced breast magnetic resonance imaging»[Title/Abstract] OR «Dynamic Contrast-enhanced MRI»[Title/Abstract] OR «DCE-MRI»[Title/Abstract] OR «CE-MRI»[Title/Abstract] OR «contrast enhanced mri»[Title/Abstract] OR «contrast enhanced mri»[Title/Abstract] OR «breast magnetic resonance imaging»[Title/Abstract] OR «breast mri»[Title/Abstract] OR «breast mri»[Title/Abstract])))) AND (2018:2024[pdat])	**173**

Table 10: Scopus search query (Duration: 1st January 2018 to 5th July 2024)

Search number	Query	Results
1	((TITLE-ABS-KEY («Contrast-enhanced magnetic resonance imaging» OR «Contrast enhanced magnetic resonance imaging» OR «Contrast-enhanced breast magnetic resonance imaging» OR «Contrast enhanced breast magnetic resonance imaging» OR «Dynamic Contrast-enhanced MRI» OR «DCE-MRI» OR «CE-MRI» OR «Contrast-enhanced MRI» OR «contrast enhanced MRI» OR «breast magnetic resonance imaging» OR «Breast MRI» OR «Breast-MRI») OR TITLE-ABS-KEY (magnetic AND resonance AND imaging OR mri))) AND (TITLE-ABS-KEY («contrast enhanced spectral mammography» OR «contrast-enhanced spectral mammography» OR «contrast-enhanced mammography» OR «contrast enhanced mammography» OR «CESM» OR «dual energy mammography» OR «dual-energy mammography» OR «dual-energy subtraction mammography» OR «dual energy contrast enhanced digital mammography» OR «contrast-enhanced digital mammography» OR «contrast enhanced digital mammography»)) AND PUBYEAR > 2017 AND PUBYEAR < 2025 AND (LIMIT-TO (SUBJAREA , «MEDI»)) AND (LIMIT-TO (DOCTYPE , «ar») OR LIMIT-TO (DOCTYPE , «re»)) AND (LIMIT-TO (LANGUAGE , «English»))	**290**

Table 11: Characteristics of selected studies comparing diagnostic performance of CEM to MRI (n=7)

Publication [Author Year]	Study design	Study location (Country)	Intervention	CEM equipment	Comparator(s)	Reference standard	Patient population	Patient sample size	Number malignant lesions	Number benign lesions
Phillips 2023	Prospective reader [Single centre; multireader (n=12)]	USA	CEM	GE HealthCare	2D mammo-graphy MRI (Abbreviated and Full)	Patients where 2-year imaging or clinical follow-up or pathology results were available.	CEM and MRI were performed in asymptomatic individuals who presented initially for breast cancer screening. These women then underwent a diagnostic evaluation if an imaging finding was detected at their screening examination. - Case sets were obtained at the time of screening (as part of a prior research study comparing screening CEM and MRI [ClinicalTrials.gov identifier NCT02275871]; n=42), - as part of work-up for a screening-detected finding (as part of clinical care, n=12), - or before biopsy of a screening-detected abnormality (as part of research for the purposes of collecting cases for this reader study [NCT03482557]; n=78).	132	44	74
Rudnicki 2021	Retrospective reader study	Poland	CEM	GE HealthCare (CEM on Senographe Essential)	MRI	Histopathology report.	Patients with abnormalities found on basic examinations: ultrasound (US) or/and digital mammography (DM). Subsequently, CESM or MRI examinations were performed. Two imaging methods were used when one of them did not give sufficient clinical information and the clinical risk of cancer was high. All of the patients had to undergo both CESM and MRI followed by histological examination of the lesions to be included in the study group.	121	81	40
Yasin 2019	Prospective, single centre study	Egypt	CEM	GE HealthCare (CEM on Senographe Essential with SenoBright upgrade)	MRI	Histopathology by core biopsy or excision biopsy.	All patients had previously undergone mammography (MG) and ultrasound and had a breast lesion of BIRADS 4.	50	34	22
Acar 2024	Prospective, single centre study	Turkey	CEM	GE HealthCare (Senographe Pristina™)	MRI	Histopathology and at least 2 years of imaging follow-up.	Patients who were clinically suspected of malignancy and/or had suspicious findings detected by mammography or ultrasound.	116	125	94
Ferranti 2022	Prospective, single centre study	Italy	CEM	GE HealthCare (SenoBright)	MRI	Histopathology of samples obtained by biopsy/surgery.	Women with unresolved/suspicious findings after FFDM and ultrasound (ULS) underwent a diagnostic workup that included baseline (FFDM and ULS) reassessment, plus CESM and 3T MRI after being informed.	118	CEM:46 MRI:49	CEM:10 MRI:17
Kamal 2020	Prospective, single centre study	Egypt	CEM	GE HealthCare (CEM on Senographe Essential)	DCE-MRI	Histopathology analysis of postoperative pathology, biopsy samples, fine-needle aspiration cytology or close follow up for 1 year.	Patients with at least a single indeterminate lesion (BIRADS 3 and 4).	82	120	51
Xing 2019	Prospective study	China	CEM	GE HealthCare (CEM on Senographe Essential)	MRI	Histopathology report.	Patients suspected with abnormal breast lesions by clinical examination or ultrasonography.	235	177	86

Table 12: Diagnostic performance results for CEM compared to MRI from literature review

Publication [Author Year]	Patient sample size (n)	Comparator	Sensitivity (%)			Specificity (%)			Diagnostic accuracy (%)			Area Under Curve (AUC)			
			CEM	MRI	P-Value for difference in sensitivity	CEM	MRI	P-Value for difference in specificity	CEM	MRI	P-Value for difference in diagnostic accuracy	CEM	MRI	P-Value for difference in AUC	
Phillips 2023	132	MRI	89%	94%	NR	71%	63%	NR	NR	NR	NR	0.91	0.91	*p*=0.85	In an asymptomatic study sample, CEM was noninferior to full MRI and AB-MRI and was superior to digital mammography.
		AB-MRI		91%	NR		65%	NR	NR	NR	NR		0.89	*p*=0.58	
Rudnicki 2021	121	MRI	100%	100%	NR	33%	23%	NR	77%	74%	NR	NR	NR	ROC curves provided but data not reported - not possible to indicate the more effective method, *p*=0.32	CESM can be used with confidence instead of MRI for cancer detection in patients with dense breast. It provides the same sensitivity as MRI, but with negligibly lower specificity than MRI. More studies are needed to confirm the obtained results.
Yasin 2019	50	MRI	94.1%	100%	NR	100%	95.5%	NR	96.%	98.2%	NR	NR	NR	NR	CESM is a sensitive diagnostic tool for breast cancer with higher specificity and less sensitivity as compared to contrast-enhanced breast MRI. CESM has shorter examination time, thus a more accessible alternative to MRI, and has the potential to be an important diagnostic tool in breast cancer detection and staging.
Acar 2024*	116	MRI	98.4%	100%	NR	81.9%	75.5%	NR	91.3%	89.5%	NR	0.902	0.878	NR	In the diagnosis of breast lesions, CEM and MRI were evaluated, and it was found that MRI had higher sensitivity, while CEM had higher specificity. However, there was no significant statistical differ- ence between the 2 methods. Considering this, CEM can be consid- ered as an alternative to MRI in the characterization and classification of breast lesions.
Ferranti 2022*	118	MRI	100%	99%	NR	50%	47%	NR	93%	88%	NR	NR	NR	NR	CESM may represent a valuable alternative and/or an integrating technique to MRI in the evaluation of breast cancer patients.
Kamal 2020*	82	DCE-MRI	94.2%	100%	0.014	64.7%	68.6%	0.674	85.4%	90.6%	0.134	NR	NR	NR	Contrast-enhanced mammography and dynamic contrast-enhanced MRI improved the characterization of breast lesions. CEM showed slightly lower sensitivity and accuracy compared to MRI; however, because of being relatively easy, available, cheap, and acceptable by women, CEM can replace DC-MRI as a problem-solving tool in the characterization of indeterminate breast lesions.
Xing 2019*	235	MRI	91.5%	91.5%	NR	89.5%	80.2%	NR	81%	71.7%	NR	0.95	0.939	$p > 0.005$	Contrast-enhanced spectral mammography, a combination of HE image and LE image, can well display breast lesions and has the diagnostic efficacy equivalent to MRI. Importantly, CESM imaging shows higher specificity, positive predictive value, and diagnostic conformance rate than MRI. Combined with those benefits, CESM has such advantages as convenient and fast examination, strong applicability, and low costs; thus, it can be popularized as a useful tool in breast disease.

*Diagnostic performance reported per lesion; NR - not reported.

Table 13: Summary of experience of image readers in studies comparing CEM with MRI

Publication [Author year]	Study design	No. of patients	No. of readers	Mammography reading experience	Radiologists with prior CEM reading experience (Yes/No/NR)	For multi-reader studies, diagnostic accuracy reported for individual readers? (Yes/No)
Phillips 2023	Prospective reader [Single centre; multireader (n=12)]	132	12	Years since training: 0-2 years N=3 2-5 years N=2 ≥ 10 years N=7	Yes [10/12 with prior experience] The two readers without experience in CEM (previously interpreted <30 cases) received a prestudy CEM lecture and completed a training set of 30 cases.	Yes
Rudnicki 2021	Retrospective reader study	121	Not clear [1 reader for CEM; 1 reader for MRI]	≥ 5 yrs experience in CEM and MRI.	Yes	No
Yasin 2019	Prospective, single centre study	50	2	15 yrs experience in breast imaging, including mammography, CEM, and breaswt MRI.	Yes	No
Acar 2024	Prospective, single centre study	116	2	Observer 1 was a radiology specialist with 32 years of experience in breast imaging. Observer 2 was a fourth-year radiology resident.	Yes	No
Ferranti 2022	Prospective, single centre study	118	2	NR	Unclear	No
Kamal 2020	Prospective observational	82	NR	NR	NR	NR
Xing 2019	Prospective study	235	3	10 years experience in breast imaging.	NR	No

Notes

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GE HealthCare is a trusted partner and leading global healthcare solutions provider, innovating medical technology, pharmaceutical diagnostics, and integrated, cloud-first AI-enabled solutions, services and data analytics. We aim to make hospitals and health systems more efficient, clinicians more effective, therapies more precise, and patients healthier and happier. Serving patients and providers for more than 125 years, GE HealthCare is advancing personalized, connected and compassionate care, while simplifying the patient's journey across care pathways. Together, our Imaging, Advanced Visualization Solutions, Patient Care Solutions and Pharmaceutical Diagnostics businesses help improve patient care from screening and diagnosis to therapy and monitoring. We are a $19.7 billion business with approximately 53,000 colleagues working to create a world where healthcare has no limits.

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