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Contrast-enhanced breast imaging: Current status and future challenges

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ABSTRACT

Background: Contrast-enhanced breast MRI and recently also contrast-enhanced mammography (CEM) are available for breast imaging. The aim of the current overview is to explore existing evidence and ongoing challenges of contrast-enhanced breast imaging.
Methods: This narrative provides an introduction to the contrast-enhanced breast imaging modalities breast MRI and CEM. Underlying principle, techniques and BI-RADS reporting of both techniques are described and compared, and the following indications and ongoing challenges are discussed: problem-solving, high-risk screening, supplemental screening in women with extremely dense breast tissue, breast implants, neoadjuvant systemic therapy (NST) response monitoring, MRI-guided and CEM- guided biopsy.
Results: Technique and reporting for breast MRI are standardised, for the newer CEM standardisation is in progress. Similarly, compared to other modalities, breast MRI is well established as superior for problem-solving, screening women at high risk, screening women with extremely dense breast tissue or with implants; and for monitoring response to NST. Furthermore, MRI-guided biopsy is a reliable technique with low long-term false negative rates. For CEM, data is as yet either absent or limited, but existing results in these settings are promising.
Conclusion: Contrast-enhanced breast imaging achieves highest diagnostic performance and should be considered essential. Of the two contrast-enhanced modalities, evidence of breast MRI superiority is ample, and preliminary results on CEM are promising, yet CEM warrants further study.

1. Introduction

In women with a normal breast cancer risk, full-field digital mammography (FFDM) is currently the recommended primary (screening) modality which can be supplemented by ultrasound (US) if indicated [1]. Digital breast tomosynthesis (DBT) as adjunct to FFDM moderately increases cancer detection rates: the pooled risk ratio for the detection of invasive cancer using FFDM with and without DBT is 1.3 (95 % confidence intervals 1.2–1.5), demonstrating superiority of FFDM with DBT [2]. However, in breast imaging contrast-enhancement is the most important tool to enable differentiation between benign and malignant breast lesions [3–5]. At this time, two different techniques are able to provide such contrast-enhanced information: (contrast-enhanced) breast MRI and contrast-enhanced mammography (CEM).

This narrative review starts with the underlying principle and techniques of contrast-enhanced breast imaging followed by descriptions of standardized breast MRI and CEM reporting according to the fifth edition of Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology. Finally, it concludes with a discussion on using both modalities for different indications to tackle current challenges: problem-solving, screening high-risk women, supplemental screening in women with extremely dense breast tissue, breast implants, neoadjuvant systemic therapy response monitoring and interventional techniques (MRI-guided and CEM-guided biopsy).

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2. Underlying principle

Contrast-enhanced differentiation of benign and malignant lesions is possible due to tumour angiogenesis: all tumours induce blood vessel growth, but whereas benign tumours have little angiogenesis and slow vessel growth, malignant tumours (in particular invasive carcinomas of no special type) have intense angiogenesis and rapid blood vessel growth resulting in leaky vessels. Leaky vessels allow contrast leakage into interstitial space, which can then be visualized with the imaging modalities breast MRI and CEM [6]. Once should be aware of weak or no enhancement in the case of invasive lobular cancer and mucinous carcinomas, potentially resulting in false negative cases [7,8].

3. Techniques

The core of a breast MRI study is a dynamic T1-w-GRE sequence before and after injection of a macrocyclic gadolinium-based contrast agent, usually covering about 5 min after contrast injection. Additional T2w- and DWI should be used for further classification of enhancing lesions to improve specificity. The contrast agent is administered at a standardized dose of 0.1 mmol/kg bodyweight, i.e. involves injection of 5 mL to 7 mL of contrast agent for patients with a body weight of 50 to 70 kg [9]. There is no breast compression involved. An adequate breast immobilization is necessary to avoid motion artifacts.

Detection of breast cancer on CEM relies on the same general principle as breast MRI: after intravenous administration of an iodinated contrast agent, low- and high energy images are performed. These images are used to create a recombined image that highlights contrast-enhancing regions [10–12]. An iodinated contrast agent is administered at 1.5 mL/kg bodyweight at a rate of 3 mL/sec, i.e. involves an injection of 75 mL – 100 mL for patients with a body weight between 50 and 75 kg. The breast must be compressed as for a regular mammogram; ionizing radiation is used at a dose comparable within limits specified by the European regulatory agencies [12,13].

4. BI-RADS lexicon reporting and decision rules

Standardized interpretation and reporting of breast MRI became part of the BI-RADS lexicon in its fourth edition. In the current fifth edition, besides enhancement of a mass or non-mass enhancement, shape, margin, distribution, internal enhancement pattern, and signal-intensity time curve type also determine the probability of a malignant lesion [14]. Type 1 signal-intensity curves include a continuous signal increase ('persistent'), and gives the lowest probability of a malignant lesion; type 2 is a steady signal over time ('plateau'); and type 3 includes a signal drop from initial to delayed phase ('wash-out'), giving the highest probability of a malignant lesion [9]. Diffusion Weighted Imaging (DWI) is a quantitative technique that allows to determine the risk of enhancing lesions to be malignant by means of the quantitative Apparent Diffusion Coefficient (ADC). DWI is not currently incorporated into the BI-RADS lexicon, despite being highly recommended by the European Society of Breast Imaging to improve lesion determination [15]. T2-features are currently only included as additional features in BI-RADS.

The BI-RADS lexicon does not provide clinical decision rules to guide diagnostic decision making. In order to improve standardized reporting in breast MRI, decision rules can be envisaged. Previous studies suggest that the use of decision rules that combine morphological and kinetic BI-RADS features into an evidence-based score (Kaiser Score, KS) provides objective guidance in the interpretation of breast MRI [9,16].

In 2022, a supplement was added to the BI-RADS lexicon detailing standardized interpretation and reporting for CEM [17]. CEM imaging findings are divided into three categories: findings seen on low energy images only (which can be considered comparable in diagnostic performance to FFDM [18]), enhancement seen on recombined images only, and findings detected on low energy images in combination with corresponding enhancement seen on recombined images. The enhancement characteristics of suspicious findings on recombined images of CEM should be defined: mass (including shape, margin and internal enhancement), non-mass enhancement, enhancing asymmetry (i.e. abnormal enhancement observed in one view only) and lesion conspicuity.

5. Problem-solving

There is general consensus and empirical evidence to use breast MRI as problem-solving tool in situations such as discordant FFDM and US findings [19,20]. Breast MRI has been demonstrated to avoid additional workup including biopsies in screening recalls and may avoid a large proportion of unnecessary biopsies in suspicious mammographic calcifications, depending on pre-test probability and patient setting (screening, symptomatic or follow-up) [21]. Next, breast MRI can also be considered in cases of nipple discharge with inconclusive findings on conventional imaging [22]. However, one should be aware of the definition of problem-solving, since it might be interpreted differently and therefore can be used diversely among studies [23].

With regard to CEM, there is also evidence as problem-solving tool to reduce biopsies, among other indications [24–27]. In addition, a study by Migliaro et al., subgroup analysis found that 6 out of 28 women (21.4 %), who underwent CEM as problem-solving examination and presented with enhancing asymmetry on CEM, were considered malignant [28].

6. Screening high-risk women

According to the current guidelines, breast MRI should be used in the screening or women at a high risk of developing breast cancer (lifetime risk equal to or higher than 20 %), for instance because of gene mutation carriers [1,20,29]. The recommended starting age for undergoing screening using breast MRI in this subgroup of women depends on the risk indication and the specific guideline, but most often starts at the age of 30 years [30]. Guidelines base their recommendations on studies that found using breast MRI as part of the screening of high-risk women was superior, in terms of improved diagnostics, to FFDM, US and DBT [31,32].

The first pilot study investigating the use of CEM versus breast MRI in a cohort of 307 women with an intermediate to high-risk for developing breast cancer demonstrated that two out of three mammographically occult breast cancers were detected with CEM, while breast MRI detected all three cancers. According to this study it was suggested that CEM should be considered in those women who do not meet the criteria for MRI or in the case of limited MRI access [33]. A second study on CEM by this same research group found superior diagnostic performance of CEM when compared to FFDM in women with an increased risk of breast cancer [34].

Due to increased radiation exposure, there is no evidence to support the use of CEM in high-risk women, especially because screening in this group of women starts at a young age [35].

7. Supplemental screening in women with extremely dense breast tissue

A recent multicentre study of over 40,000 women with extremely dense breast tissue on FFDM, found offering breast MRI as supplemental screening tool to be beneficial: the reported cancer detection rate of supplemental breast MRI was 16.5/1000 women with a normal FFDM [36]. As a result, the European Society of Breast Imaging now recommends supplemental breast MRI every 2–4 years for women age 50–70 years with extremely dense breast tissue [37]. Moreover, full-protocol breast MRI for screening in women with extremely dense breast tissue is cost effective. More recently, abbreviated breast MRI protocols have been proposed to further improve the cost effectiveness of breast MRI [38,39]. The equivalent diagnostic performance of abbreviated versus

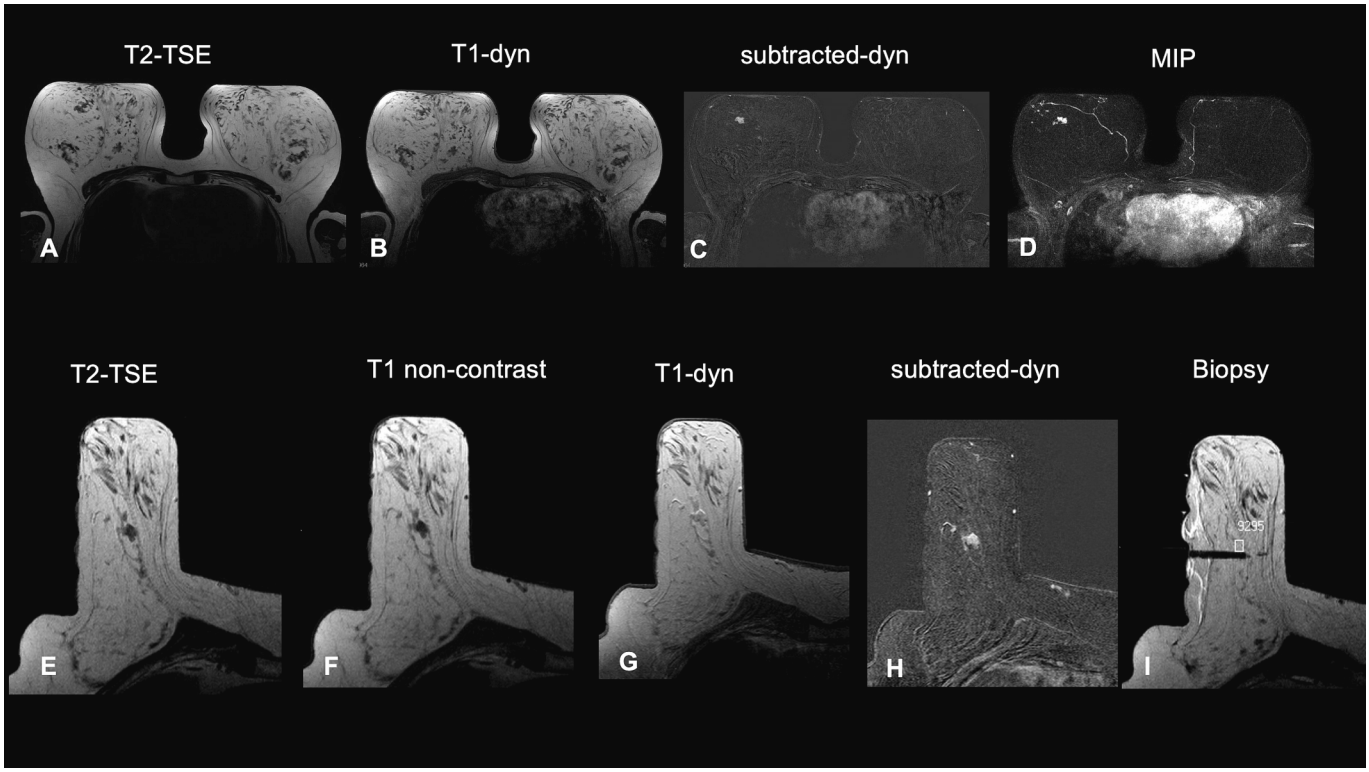

Fig. 1. A 41-year-old woman with a palpable lump in the left breast was newly diagnosed with a luminal B breast cancer (Ki67: 80 %). On MRI, the carcinoma exhibited features of a highly proliferative and biologically aggressive breast cancer, including a relatively high T2-signal, early intense enhancement, and rapid washout. The tumour had a size of 3,3 cm (A-D). The patient received neoadjuvant chemotherapy consisting of 4 cycles of EC and 12 cycles of Paclitaxel. On the following restaging MRI, the carcinoma was no longer distinguishable. Only a T1- and T2-isointense area with but discrete contrast enhancement was observed, most likely indicative of absorptive findings (E-H). The radiological findings were confirmed by histopathology, which finally revealed tumour sclerosis and a mild absorptive inflammation without residual evidence of malignancy, corresponding to a complete remission.

full protocol breast MRI is increasingly accepted by the community [40–42]. In addition, a recent preliminary study already indicated an increased patient throughput at the MR unit when using abbreviated breast MRI protocols, despite the fact that the full potential of abbreviated protocols will only be used when dedicated magnets are available that support high patient throughput [43].

Although there is as yet no evidence on the screening performance of CEM, trials are currently ongoing to investigate the potential non-inferiority of CEM versus breast MRI in this setting with estimated completion dates from mid-2025 to 2026: The Breast Screening – Risk Adaptive Imaging for Density Trial (BRAID, NCT04097366) and The Contrast Enhanced Mammography Screening Trial (CMIST, NCT05625659).

8. Breast implants

The increasing prevalence of breast augmentations or reconstructions presents a challenge for imaging. Breast implants necessitate individually-customized imaging that not only focuses on cancer detection, but also on the detection of implant-related complications [44]. Women who underwent breast augmentation do not carry to an elevated risk of breast cancer [45,46]. However, mammography exhibits decreased sensitivity in this population, attributed to the implants and postoperative scarring [44,47]. Breast MRI, in particular contrast-enhanced breast MRI, is not affected by implants or postoperative scarring and is therefore considered the preferred imaging modality in this setting [46,48]. Furthermore, breast MRI is also the most accurate modality for implant rupture detection [23].

The first few studies on the ability to perform CEM in women with breast implants have been published [49,50]. A small retrospective study including 17 women with newly diagnosed breast cancer found concordant findings between CEM and breast MRI regarding tumour size measurements [49]. Both modalities detected all cancers, but one additional lesion of uncertain malignant potential was detected using breast MRI (atypical ductal hyperplasia) [49]. The second retrospective study, including in 198 CEM exams in 104 women, confirmed the ability to use CEM in women with implants [50]. A potential limitation of CEM compared to breast MRI may lie in its limited field of view, which may incur the risk of missing far posterior located lesions [49,51].

9. Neoadjuvant systemic therapy response monitoring

Neoadjuvant systemic therapy (NST) plays a pivotal role in the therapeutic management of both early-stage aggressive subtypes and locally advanced invasive breast cancers. NST allows to downstage tumours, increasing the rate of successful breast-conserving surgeries and avoiding extensive axillary surgery [52–55]. Monitoring the response to NST is of crucial importance to guide further therapeutic interventions, particularly in terms of surgical treatment management [1]. FFDM, breast and axillary US, and breast MRI can be considered to monitor NST response. Currently, breast MRI is considered to be the most accurate imaging modality for monitoring early response to NST, exhibiting the highest sensitivity for breast cancer detection [56–59]. Furthermore, breast MRI findings demonstrate a high degree of concordance with pathology findings, only rarely over- or underestimating residual lesion extent [60] (Fig. 1). However, breast MRI has limitations as its diagnostic accuracy and specificity are influenced by tumour molecular and histological subtypes, various NST-regimes, and therapy response patterns [61,62]. Therefore, breast surgery cannot be avoided yet after completion of NST, because radiologic complete response on breast MRI is not always in accordance with pathologic complete response.

Recent studies suggest similar performance of CEM for the

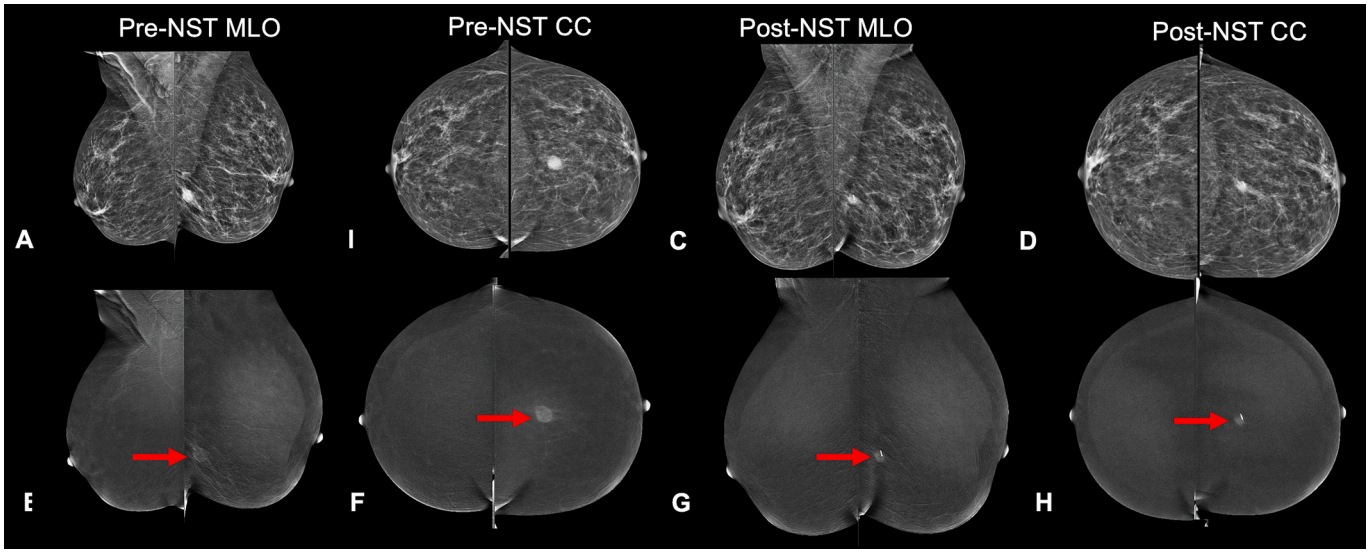

Fig. 2. A 48-year old woman with a palpable lump in her left breast that corresponded with a 1.5 cm triple negative breast cancer on the CEM in her lower outer quadrant After completion of neoadjuvant chemotherapy (consisting of 8 cycles of doxorubicin, cyclofosfamid and paclitaxel) the patient underwent CEM prior to surgery. On CEM, a persisting mass enhancement of 0,9 cm on the anterior part of the iodine seed can be seen (red arrow, D). After breast-conserving surgery, a residual triple negative breast cancer of 0,8 cm was observed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

evaluation of residual disease after NST compared to breast MRI [63–69]. The results of these studies on CEM demonstrate are highly consistent, finding high correlations for breast MRI and CEM in lesion size measurements, and a tendency of both modalities to overestimate the lesion size [63,68]. Remarkably, sensitivity for pathologic complete response (pCR) and residual disease prediction was predominantly higher using breast MRI compared to CEM (breast MRI 77–100 %; CEM 72–81 %) [63,67,68]. All studies concur that, at the very least, CEM represents an acceptable and promising alternative to breast MRI in monitoring NST response where MRI is contraindicated or unavailable [63,68] (Fig. 2).

10. Interventional techniques: MRI-guided versus CEM-guided biopsy

Image-guided biopsy is a crucial step in histopathologic evaluation of a suspicious breast lesion. Several image-guided techniques are available, including US-guided, stereotactic/DBT-guided, and MRI-guided [70]. The method of choice is determined based on the visibility of the target lesion in the corresponding modality [70]. MRI-guided biopsy is a safe and accurate procedure performed when the initial MR-detected finding cannot be identified on subsequent target examinations including second-look ultrasound, stereotactic mammography or DBT [70,71]. Several independent studies have demonstrated technical success rates ranging between 90 and 99 % [71,72]. Therefore, MRI-guided biopsy can be considered a reliable technique with low long-term false negative rates [73]. On the other hand, the availability of MRI-guided biopsy is limited and the procedure is expensive [20,74].

CEM-guided biopsy represents a promising alternative to MRI-guided biopsy, particularly due to its organisational advantages [75,76]. The first CEM-guided biopsy study reported a technical success rate of 95.4 % for 66 CEM-guided biopsy procedures, and low complication rates [77]. A second, preliminary, CEM-guided biopsy study including 51 CEM-guided biopsy procedures reported a cancellation rate of 9.8 %, due to non-visibility of the target lesion, with a mean biopsy time of 16.6 min [78]. Further studies, directly comparing MRI-guided and CEM-guided biopsy procedures, are therefore needed.

Table 1
Overview of breast MRI and contrast-enhanced mammography (CEM) characteristics.

	Breast MRI	CEM
Contrast agent	Gadolinium-based	Iodine-based
Concentration of the contrast agent	0.1 mmol/kg bodyweight [7]	1.5 mL/kg bodyweight [10]
BI-RADS lexicon	Extensive chapter on breast MRI reporting, including kinetic curve analysis [14]	Supplement lexicon present, interpretation using low energy and recombined image [17]
Problem-solving tool	Empirical evidence supports the use of breast MRI as problem-solving tool [19–23]	Evidence available, for instance to reduce biopsies [24–28]
High-risk screening	Breast MRI is a recommended part of high-risk screening [1,20,26]	No scientific evidence available
Supplemental screening in extremely dense breast tissue	Increased cancer detection rate of 16.5/1.000 women [36] Breast MRI is recommended [37]	Prospective trials currently ongoing (results expected 2025–2026)
Imaging breast implants	Preferred imaging modality, both for cancer detection and implant evaluation [23,46]	CEM is feasible in women with implants [49,50]
Neoadjuvant systemic therapy monitoring	High correlation lesion size measurement [66] Sensitivity ypT + prediction: 88–92 % [62,65]	High correlation lesion size measurement [66] Sensitivity ypT + prediction: 76–81 % [62,65]
Interventional	Technical success rates 90–99 % [71,72] Numerous independent studies	Technical success rate 95.4 % [77] Cancellation rate 9.8 % [78]

Abbreviation: ypT+ = residual disease after completion of neoadjuvant systemic therapy.

11. Summary

Contrast-enhanced breast imaging using breast MRI is the most powerful breast cancer screening method and offers superior cancer detection regardless of breast density (Table 1). CEM is a relatively new

technique. CEM can be considered superior to unenhanced breast imaging and though preliminary results are encouraging evidence on its performance is limited.

Current challenges for contrast-enhanced breast imaging techniques include evaluating the potential cost-benefit gains of substituting breast MRI with shortened breast MRI protocols or CEM, especially in the setting of screening women with extremely dense breast tissue on FFDM. The introduction of CEM-guided biopsy might reduce the necessity for MRI-guided biopsy in near future.

Editor conflict of interest statement

Given his role as editor-in-chief prof. dr. P.A.T. Baltzer had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

CRediT authorship contribution statement

T.J.A. van Nijnatten: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization. **S. Morscheid:** Conceptualization, Methodology, Investigation, Writing – original draft, visualization.. **P.A.T. Baltzer:** Conceptualization, Methodology, Writing – review & editing, Supervision. **P. Clauser:** Conceptualization, Methodology, Writing – review & editing, supervision. **R.Alcantara:** Conceptualization, Methodology, Writing – review & editing, supervision. **C.K. Kuhl:** Conceptualization, Methodology, Writing – review & editing, Supervision. **J.E. Wildberger:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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