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Review

Contrast-Enhanced Mammography: Bridging the research gaps and defining the future

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ABSTRACT

Contrast-enhanced mammography (CEM) has emerged as a promising breast imaging technique offering morphological and functional information through the use of dual-energy mammography and intravenous iodinated contrast agents. Despite increasing clinical use, its implementation remains heterogeneous, and several technical and clinical questions stay unanswered.

This review aims to highlight the major research gaps related to CEM technique, safety, interpretation, and clinical applications. We examined key areas requiring standardization, including acquisition protocols, contrast agent dosing, and interpretation of background parenchymal enhancement. Safety concerns regarding radiation exposure and contrast media reactions were addressed, along with a comparison between CEM and breast MRI in terms of diagnostic performance. New applications such as CEM-guided biopsies and supplemental screening in high-risk women were critically reviewed and the integration of artificial intelligence and radiomics into CEM interpretation was also considered and discussed. Finally, we briefly summarized the main ongoing multicenter trials investigating the clinical utility and implementation of CEM across different healthcare settings.

1. Introduction

In the last two decades new breast imaging techniques have been developed, in an attempt to overcome magnetic resonance imaging (MRI) limitations, such as high cost and patchy access, among others.

Contrast-enhanced mammography (CEM) is the newest addition to breast imaging. Through a dual-energy technique along with the administration of intravenous iodinated contrast agents, CEM produces low-energy (LE) images, resembling conventional digital mammography, and recombined images, allowing the visualization of enhancing areas, in a morphological and functional approach. The clinical advantages of CEM are particularly evident in dense breast tissue, where conventional mammography shows limited sensitivity for lesion identification; moreover, CEM provides a valuable alternative for patients who cannot undergo MRI due to contraindications such as claustrophobia.

Since its approval by the U.S. Food and Drug Administration in 2011, the adoption of CEM has progressively increased worldwide, as well as the number of researches on the topic.

CEM is a promising breast imaging technique: it seems surprisingly easy to learn [1] and has some advantages over breast MRI, including fewer contraindications, a better availability, reduced procedural time and costs, and an overall patient preference [2,3], meanwhile keeping a comparable diagnostic performance [4–6].

Despite growing clinical adoption, CEM is still unevenly performed across different centers, both in terms of contrast agent employed and acquisition protocol, and several critical research gaps remain that warrant further investigation.

In addition, along with established indications for CEM examination, such as pre-operative breast cancer staging, monitoring the response to neoadjuvant chemotherapy, problem solving for inconclusive findings on conventional breast imaging, further indications are emerging, and there is a growing interest in CEM-guided biopsies as an alternative to MRI-guided biopsies as well as in AI and radiomics applied to CEM images interpretation.

This review aims to explore the main gaps in the research on CEM, regarding technique, safety and main clinical applications, and to present updated data on ongoing trials.

2. CEM technology: From physics to practice

Originally, two different techniques using contrast agents in

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mammography had been developed, the temporal subtraction technique and the dual-energy technique, the former consisting of the acquisition of high-energy (HE) images before and after contrast agent injection, the latter of the acquisition of both LE and HE images after contrast agent injection. In the temporal subtraction technique, the mask image (pre-contrast) was subtracted from the post-contrast series, to allow the visualization of areas of contrast enhancement, in a similar fashion to breast contrast-enhanced MRI (CE-MRI), with a main limitation linked to motion artifacts. The dual-energy technique lacks of kinetic information of tumor enhancement but allows the acquisition of multiple projections of the same breast and is better tolerated by patients, since breast compression duration is reduced [7].

The currently employed dual-energy technique can be performed using standard mammography units implemented with dedicated filters and software upgrades to allow dual-energy imaging. HE and LE images are obtained in quick succession, during a single breast compression (see Fig. 1).

CEM makes use of the photoelectric effect of iodine. This physical phenomenon consists in the emission of an electron from a material due to an incident radiation, and depends on the energy of the X-ray beam and the k-edge of the material. The absorption k-edge of iodine (33 keV) falls within the average range of the X-ray beam in mammography. LE images are acquired below the K-edge of iodine; therefore, despite the presence of intravenous iodine-based contrast, the attenuation from contrast agent is minimal and the resulting LE image appears remarkably similar to a full-field digital mammography (FFDM) image and equivalent in terms of diagnostic quality [8]. On the contrary, during the acquisition of HE images the energy of the X-ray beam falls above the K-edge of iodine, and a photoelectric effect occurs, causing the ejection of an electron from the inner shell of an iodine atom, consequently increasing the attenuation of iodine. HE images, not interpretable to the human eye, will be used to construct the recombined images in post-processing, showing exclusively areas of enhancement.

3. Protocol optimization: Timing and sequence challenges

In a typical acquisition workflow, the patient is positioned for mammographic imaging within 2 min from the intravenous injection of an iodinated contrast agent, to allow the uptake of contrast into the breast, and the study should be completed within 10 min, before the substantial wash-out of contrast agent from tissues. Such timing is reported in the main reviews concerning CEM technique [8–10].

Anyway, the optimal timing for image acquisition following contrast administration remains an area of ongoing investigation. In a recent work, Convington et al. [11] stated that the ideal interval for performing CEM imaging should be between 2–8 min following contrast injection, to allow an optimal perfusion of contrast material into breast tissues. Lately, a Chinese prospective study [12] aiming to understand whether delayed-phase imaging performed at 7–9 min after the injection of iodinated contrast agent improved the diagnostic performance of CEM in distinguishing malignant and benign lesions, suggested that the delayed phase's addition did not reach significant diagnostic improvement. Further investigation is required to verify whether delayed-phase imaging could aid in the characterization of certain breast cancers (e.g. invasive lobular carcinoma − ILC or ductal carcinoma in situ − DCIS).

For what concerns the imaging protocol, the acquisition order of CEM images is currently undefined, with different Institutions varying widely in their clinical practice. As highlighted by the comprehensive systematic review by Zanardo et al. [13], examining 84 studies from 22 countries (totaling more than 14,000 patients), there is significant variability in technical parameters and acquisition protocols across Institutions worldwide. The sequence of image acquisition lacks consensus, with Zanardo et al. [13] reporting that the order of image acquisition was documented in only 53 % of the studies. The sequence adopted was mainly based on the presence of suspicious or clearly pathologic findings, starting from the suspected/affected side, even if there is no scientific evidence currently available to support this approach. Despite some Authors have demonstrated the irrelevance of the acquisition order [14], prospective studies comparing different approaches and evaluating the impact of acquisition order on diagnostic performance would provide valuable evidence for protocol optimization.

4. Contrast agents: dose, type, and rationale

Iodinated-based contrast agents administration represents another area of inconsistency.

Accepted guidelines for CEM recommend the administration of 1.5

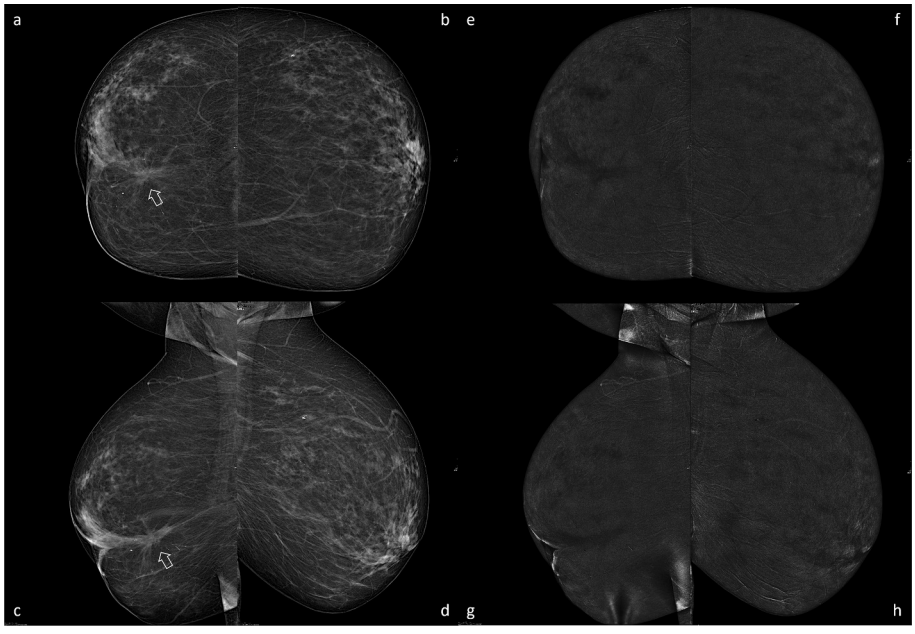

Fig. 1. Complete CEM examination in a 77-year-old patient with history of right breast cancer and suspected recurrence in the site of the surgical scar at conventional imaging. (a-d) LE images (white arrows marking the suspicious area). (e-h) Recombined images showing no areas of pathological enhancement.

mL/kg body weight of iodinated contrast medium (not exceeding a maximum volume of 150 mL), with an iodine concentration ranging from 300 to 370 mgI/mL, delivered via an automated power injector at a rate of 2–3 mL/sec [9]. Notably, despite the widespread implementation of these parameters in the clinical practice, formal studies evaluating optimal contrast administration protocols specific for CEM examinations are still not available.

The currently adopted contrast administration parameters seem to have been empirically extrapolated from computed tomography (CT) protocols, as explicitly acknowledged by early investigators [15], without a clear scientific rationale or justification. However, CEM is predominantly performed in otherwise healthy individuals undergoing breast cancer screening or diagnostic work-up, while contrast-enhanced CT examinations are frequently conducted in patients with significant underlying medical conditions, including critical conditions requiring urgent intervention. This significant difference in baseline patient characteristics requires a careful reassessment of contrast protocols empirically adapted from CT imaging, as risk–benefit considerations may differ substantially between these populations.

According to the abovementioned review by Zanardo et al. [13] six different molecules were used in the available studies, with Iohexol being the most frequently employed (53 % of the studies), followed by Iopromide (23 %), while Iobitridol, Iomeprol, Iopamidol and Ioversol were administered in a smaller number of cases. Both Iohexol and Iopromide were administered at two different concentrations: 350 and 300 mg iodine/mL, and 370 and 300 mg iodine/mL, respectively. To our knowledge, neither dose-finding nor comparative studies about different contrast iodine concentration and flow rate are currently available, and no investigations have systematically evaluated minimum effective doses or alternative dosing strategies, particularly in patients with renal impairment or other contraindications to standard dosing.

A recent two-center exploratory retrospective study by Pediconi et al. [16] employing high concentration iodinated contrast media (400 mg iodine/ml) administered at 1.0 mL/kg, has demonstrated that increasing iodine concentration guarantees the benefits of CEM while allowing a reduction of the volume injected and a consequent iodine saving (Fig. 2).

In contemporary medical practice, optimization of iodinated contrast media dosage should represent not only a clinical imperative but also an environmental responsibility, from the perspective of sustainable imaging.

5. Background parenchymal enhancement (BPE) in CEM

As CEM implies the use of intravenous contrast media, also normal breast tissue may demonstrate enhancement, known as BPE. According to CEM supplement to the 2013 ACR BI-RADS Mammography [17] BPE is not necessarily directly related to the amount of fibro-glandular tissue and should be described in a four-level scale.

Physiological, benign BPE can be detected in CEM examinations similarly to that observed in breast MRI. Since the physical principles of CEM and CE-MRI are different, it is uncertain whether the influence of hormone levels and breast density on MRI-detected BPE is applicable to CEM too. The existing literature examining this relationship [18–24] have yielded heterogeneous outcomes, but most studies have demonstrated that BPE is associated with mammographic breast density [18–24] and is lower in post-menopausal women [19,20,21,23,24].

It was demonstrated that BPE on MRI represents a biomarker associated with increased breast cancer risk [25]. However, the potential analogous significance of BPE on CEM examinations remains incompletely characterized. Further prospective studies with standardized assessment methodologies are needed to elucidate the relevance of CEM-detected BPE as a breast cancer risk indicator.

Furthermore, the impact of menstrual cycle timing on CEM interpretation accuracy remains undetermined, since no clear pattern in variation of BPE across the menstrual cycle has yet been demonstrated.

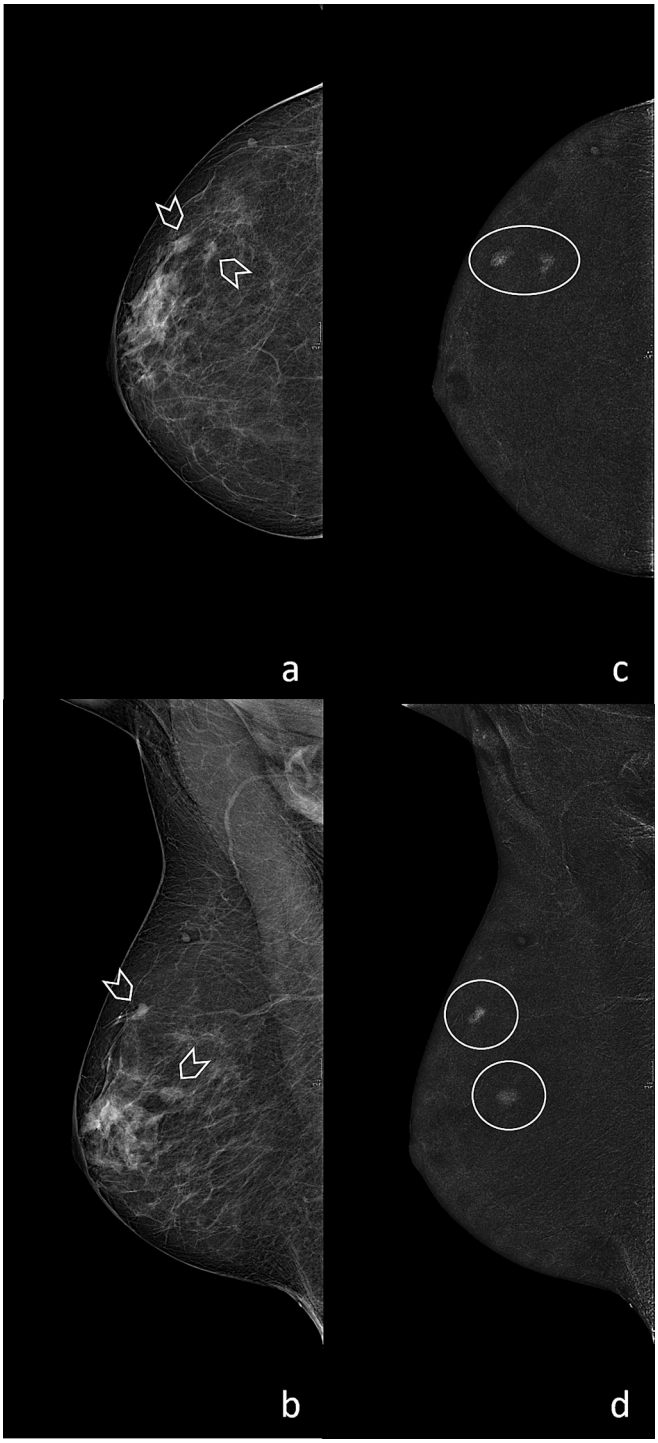

Fig. 2. Two FFDM-detected suspicious irregular masses in the upper-outer quadrant of the right breast of a 71-year-old woman, clearly visible on LE CC (craniocaudal) and MLO (mediolateral oblique) views (arrows) (a-b). (c-d) Recombined images obtained after the administration of high concentration iodinated contrast media (Iomeprol 400 mgI/ml at 1.0 mL/kg bodyweight) showing two corresponding enhancing masses with irregular shape and margins, classified as BI-RADS 4 (circles). Pathology: invasive breast carcinoma of no special type + DCIS.

6. Safety profile: Dose and allergies

Radiation exposure represents a fundamental concern for every imaging technique that employs ionizing radiation, needing risk–benefit analysis and dose optimization strategies in the routine clinical practice.

Multiple studies [26–31] have evaluated CEM radiation dose in comparison with FFDM and digital breast tomosynthesis (DBT), demonstrating an increased absorbed dose for CEM (though remaining within safety thresholds established by the Mammography Quality Standards Act guidelines [32]), but the magnitude differs, presumably due to differences in the device employed, the system settings, and the patient characteristics, in particular breast thickness. Zanardo and colleagues in their review [13] revealed that only 14 % of studies documented the per-view average glandular dose, with reported measurements ranging from 0.43 to 2.65 mGy. This substantial variability in dose values and the paucity of systematic documentation underscore the urgent need to implement standardized protocols for dose reporting and optimization strategies. Attempts to reduce radiation exposure have been undertaken [33] and further are under development, but additional research is needed.

For what concerns contrast agent safety, adverse reactions were

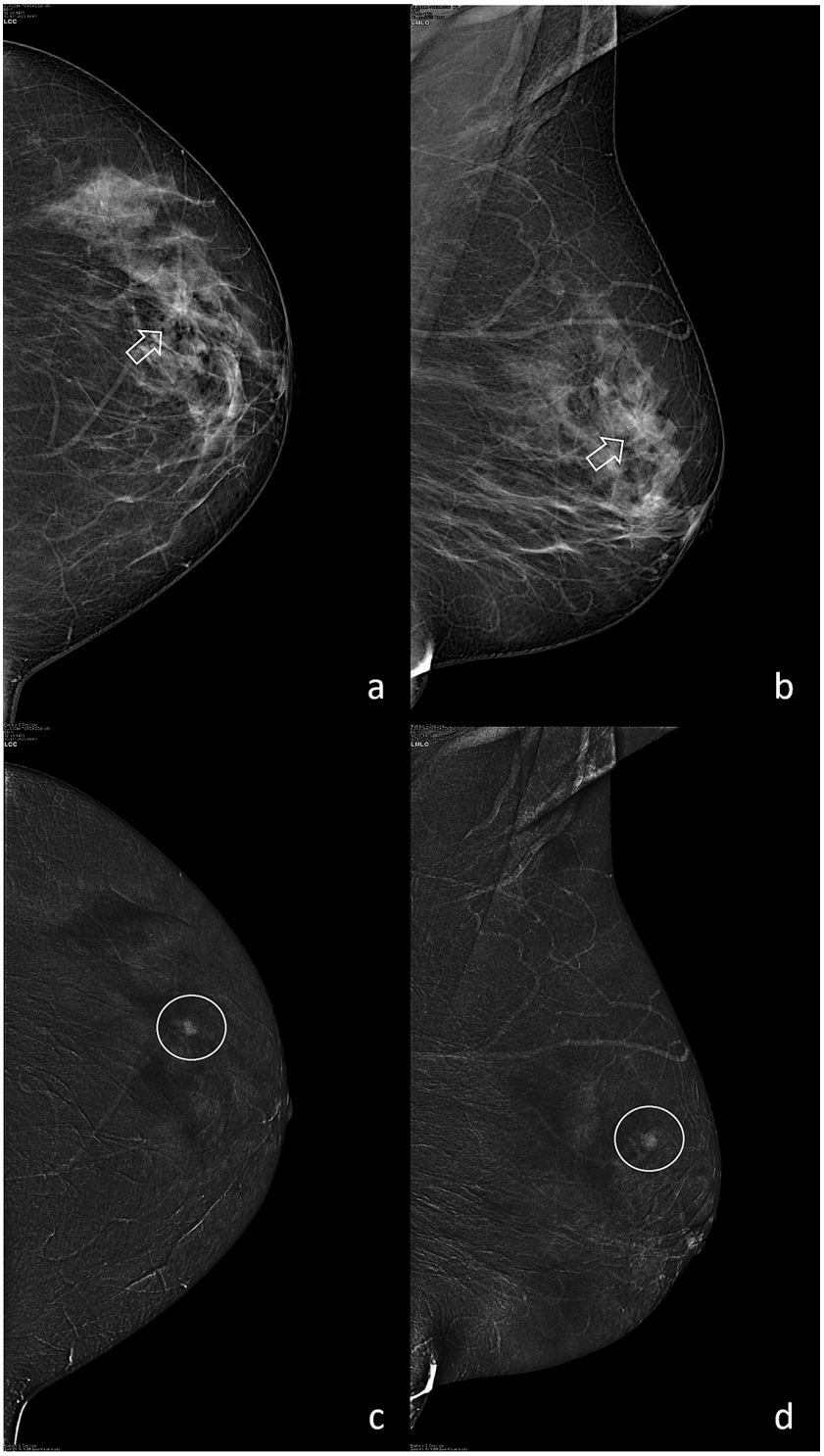

Fig. 3. 55-year-old women with recent detection of a subtle architectutal distortion in the left breast on FFDM, without a clear correspondence during second-look US. (a-b) LE CC and MLO view showing a small area of architectutal distortion in the left upper-outer quadrant (arrows). (c-d) Recombined images showing a corresponding 8 mm enhancing mass with irregular shape and margins, classified as BI-RADS 4 (circles). Pathology: invasive breast carcinoma of no special type.

reported by 17 % studies (0.007 % patients) included in the systematic review by Zanardo et at. [13], with a pooled rate of 0.82 %. While most reactions were mild (87 %), there were 10 % moderate reactions controlled with oral treatment and 3 % severe reaction requiring intensive care. These findings suggest that even if CEM appears relatively safe, systematic data collection on contrast agent safety in patients undergoing CEM is fundamental, especially considering their outpatient nature.

7. Current indications and comparison with breast CE-MRI

According to some recently published reviews [9,11], the currently established main indications for CEM are the evaluation of symptomatic breast, the pre-surgical staging of breast cancer, the assessment of the response to neoadjuvant therapy, the evaluation of indeterminate findings on conventional diagnostic breast imaging, and the presence of contraindications to breast CE-MRI (Fig. 3).

A 2023 cross-sectional survey among 434 European Society of Breast Imaging (EUSOBI) members about CEM implementation and current and future indications [34] revealed a 50 % adoption rate of CEM, predominantly in academic settings with high breast imaging workloads. Most CEM users (71.4 %) reported performing fewer than 200 examinations annually, with high protocol heterogeneity observed. The perceived absence of clinical necessity (65.0 %) and resource constraints (37.3 %) constituted the primary barriers to implementation. In the current clinical practice, CEM seems to be used mainly in patients with MRI contraindications (80.6 %) and for preoperative staging (68.7 %).

CEM has demonstrated a significantly higher sensitivity than conventional breast imaging, including FFDM, breast ultrasound (US), and a combination of both, particularly in patients with dense breasts [35–37] and an overall diagnostic performance comparable to that of CE-MRI of the breast [38].

A recent comprehensive systematic review and *meta*-analysis encompassing 60 studies with 10,605 patients [39] documented CEM's robust performance with an area under the receiver operating characteristic curve (AUC) of 0.94, and a reported overall sensitivity and specificity of 95 % and 81 %, respectively, when considering both enhancement characteristics and morphologic features patterns from both LE and recombined images. Notably, some researches have also demonstrated that CEM reached a higher positive predictive value than breast MRI [38].

Beyond the established indications, new applications for CEM are emerging (see Table 1), involving primarily its potential role as a screening modality for women at an increased risk of breast cancer (intermediate/high risk), in consideration of its excellent diagnostic performance, approaching that of breast CE-MRI, lower costs, higher availability, and potential patients' preference [2,40].

Undergoing an annual breast CE-MRI is the current recommendation for women with a calculated lifetime risk of 20 % or more and the EUSOBI now recommends supplemental screening through CE-MRI also in women with dense breasts [41].

Many researchers have investigated the role of CEM in the screening setting [5,27,37,42], including supplemental screening of dense breasts, demonstrating that CEM represents a promising cost-effective alternative to breast MRI, especially when its accessibility is limited. Nevertheless, the radiation dose increase may be clinically significant among young high-risk populations, particularly BRCA1 gene mutation carriers, who present increased chromosomal radiosensitivity and radiation-induced breast cancer risk [37].

Unfortunately, the number of patients included in the current literature is too small for an adequate subgroup analysis, while identifying specific subpopulations of women who may benefit from CEM screening seems to be a priority.

The BRAID (Breast Screening – Risk Adaptive Imaging for Density) trial is a UK randomized controlled large-scale trial including more than 9300 women (enrollment closed in march 2024) which aimed to determine the value of supplementary imaging including CEM and abbreviated breast MRI in diagnosing breast cancer in women with dense breast tissue and a negative screening mammogram. Interim results have demonstrated that supplemental contrast imaging facilitate earlier cancer detection in women with dense breasts, without significant differences between breast MRI and CEM, but the effective health benefit of the additional cancer detection was not established [43].

A second clinical trial, currently underway, is the USA multi-centre Contrast Enhanced Mammography Imaging Screening Trial (CMIST), comparing DBT and CEM in the screening setting of women with dense breasts.

There is a critical need for further prospective multicenter trials that directly compare cancer detection rates and other metrics of CEM with those of conventional screening modalities and breast CE-MRI.

A significant recent innovation is the introduction of CEM-guided biopsy as an alternative to MRI guidance in the characterization of enhancing-only breast lesions. It was developed to reach enhancing lesions without a clear matching on LE images or targeted US. The main advantages of CEM-guided biopsy consist in a substantially shorter time procedure (about 15 min vs. 60–70 min) and considerable cost saving, while keeping an excellent success rate (up to 95 % in a recent study including 66 lesions [44]). Although no comparative studies are available at the moment, it can be reasonably affirmed that CEM-guided biopsy would probably be preferred by patients, given the less discomfort linked to the procedure.

The main limitations linked to CEM-guided biopsy include the reduced availability (even though this is also true for MRI-guided biopsy and CEM-guided biopsy is way easier to implement), technical challenges in maintaining compression and patient positioning during the procedure and the possible difficulty in reaching certain lesion sites (peripheral lesions or near to the chest wall), the risks associated with iodine-based contrast agents, and the radiation exposure, even if it falls within safe limits [45]. In this context, the prone table approach might probably be preferable, since it seems to reduce the stress linked to the procedure and the risk of fainting [46].

To date, CEM-guided biopsy has demonstrated significant potential for providing time-saving, cost-effective, and accurate tissue sampling, even if there is still limited experience and standardization. Larger case series are required to confirm the results achieved. Furthermore, the need for a comprehensive evaluation of radiation dose metrics associated with the procedure and of the impact of BPE on CEM-guided biopsy outcomes warrants additional investigation.

Artificial intelligence (AI) is emerging as a transformative tool in all breast imaging techniques, including CEM. Early studies have demonstrated promising results in the application of AI algorithms for automated lesion detection, enhancement pattern classification, and differential diagnosis, particularly in distinguishing benign from malignant findings. Radiomics applied to CEM, which involves extracting large amounts of quantitative imaging features, has also shown potential in improving risk stratification, predicting treatment response, and

Table 1
Main emerging applications for CEM (modified from [11]).

Screening of women at an increased risk of breast cancer
CEM-guided biopsy
Artificial intelligence and radiomics applied to CEM
CEM as an alternative to breast CE-MRI beyond contraindications

reducing inter-reader variability. Furthermore, AI may support workflow efficiency by assisting in triaging cases or highlighting suspicious areas for radiologist review.

However, most of these applications remain at the experimental stage, with evidence largely derived from retrospective or single-center studies. For example, Beuque et al. [47] developed a deep learning model for lesion classification in CEM, achieving AUCs up to 0.95. Fusco et al. [48] applied textural radiomics combined with machine learning classifiers like support vector machines (SVM), yielding AUCs up to 0.90. Liu et al. [49] integrated clinical data with CEM radiomic features to predict biopsy outcomes and reduce unnecessary procedures. Similarly, Wang et al. [50] have demonstrated an AUC of 0.96 in distinguishing benign from malignant lesions using a combined clinical-radiomic model. Even though these results are promising, none of these tools have yet achieved regulatory approval (e.g., FDA or CE marking), and their generalizability across different imaging platforms and patient populations remains unproven.

The correlation between morpho-functional characteristics observed on contrast-enhanced breast imaging, including CEM, and underlying histopathological features represents a critical challenge in breast imaging interpretation and risk stratification. Over the past couple of years, various studies have investigated the relationship between lesion morphology, enhancement patterns, and tumor biology including the most recent by Ventura et al. [51], who have identified significant relationship between imaging features and histopathological characteristics, particularly the degree of enhancement of biologically aggressive lesions.

In this scenario, AI and machine learning technologies could substantially improve CEM's diagnostic and prognostic performance by identifying subtle imaging patterns beyond human visual perception.

Currently, only a few AI tools for breast imaging – mostly for conventional mammography – have obtained regulatory clearance, and none specific to CEM is in widespread clinical use. Regulatory hurdles include the need for rigorous clinical validation, explainability of algorithm decisions, and reproducibility across diverse datasets. Furthermore, the integration into clinical workflows poses challenges such as interoperability with PACS/RIS systems, IT infrastructure demands, and potential resistance from clinicians wary of opaque "black-box" systems. Larger, multicenter prospective validations and a clearer regulatory pathway are essential to bridge the gap between research and routine clinical implementation and to establish AI's real benefit and broad applicability.

8. Cost-effectiveness considerations and economic implications

Even if a comprehensive economic analysis falls outside the scope of this review, preliminary cost-effectiveness considerations seem to indicate that CEM may offer substantial economic advantages over breast MRI.

A recent international survey on CEM reimbursement strategies among twenty leading CEM centers in Europe, North and South America, Oceania, and Asia [52] indicated that CEM is cheaper than breast MRI, with a price difference between the two ranging from 100 to 300€.

It is also worth considering that most existing mammography units can be implemented with specific filters and a dedicated software to perform CEM, thereby avoiding resource waste and significantly reducing equipment costs compared to complete system replacement. This option allows healthcare facilities to expand their diagnostic capabilities while using existing equipment. In addition, compared to breast MRI, CEM offers lower operational costs, due to shorter examination times, lower maintenance, and minimal infrastructure requirements. Finally, although no head-to-head studies exist, it is plausible to affirm that CEM requires less training for both radiologists and radiographers familiar with mammography, compared to breast MRI.

The economic accessibility of CEM may be particularly valuable in resource-constrained healthcare environments and could facilitate broader implementation of advanced breast imaging techniques, but formal cost-benefit analyses are necessary.

9. Ongoing clinical trials and future research

A growing number of prospective clinical trials are currently assessing the role of CEM in both the screening and the diagnostic setting. These studies mainly aim to clarify CEM's diagnostic performance, its utility across risk profiles, and its potential to complement or replace established imaging modalities such as DBT and breast MRI.

Major ongoing or recently completed trials include: the above-mentioned CMIST and TOCEM in North America, which have evaluated the performance of CEM in women with dense breasts and in those with a personal history of breast cancer, respectively; the European RACER trial, that aimed to study the diagnostic impact of CEM in patients recalled from breast cancer screening, and whose results were recently published; the cited BRAID trial in the UK, which compared risk-adapted screening strategies using CEM and abbreviated MRI. Other large-scale investigations, such as C-MERIT, focus on integration with biomarkers, lesion-specific evaluation (e.g., microcalcifications), and optimization of protocols. Ongoing or recently completed clinical trials including $>$ 500 patients, available at https://clinicaltrials.gov (searching "contrast enhanced mammography") were summarized in Table 2.

The diversity of these trials in terms of design, population, and geography reflects a growing consensus on the need for robust data to define CEM's place in routine breast cancer screening and diagnostics. Their results are expected to shape future guidelines and clinical practice.

10. Conclusion

The diagnostic accuracy of CEM has been established in multiple studies, demonstrating superior sensitivity compared to FFDM and comparable performance to breast CE-MRI. However, standardization of acquisition protocols, contrast agent dosing, and timing remain inconsistent across Institutions. Multicenter trials employing standardized methodologies are needed to establish optimal technical parameters.

Safety considerations, particularly regarding radiation dose and allergic reactions, require additional investigation. Even though the risk of severe adverse reactions to iodinated contrast media is low, systematic data collection about contrast agent safety specifically applied to the breast imaging population would be valuable.

The cost-effectiveness of CEM as a screening or diagnostic tool represents another understudied area. Current evidence suggests that CEM may reduce unnecessary biopsies and follow-up imaging, but comprehensive economic analyses accounting for equipment costs, contrast media, interpretation time, and downstream consequences are lacking.

Finally, AI integration with CEM represents an emerging area with significant potential. Early research demonstrates promising results for automated lesion detection and characterization, but validation among large populations and different clinical settings is needed.

In conclusion, CEM is a promising technique but its strengths and weaknesses are still underdefined (Fig. 4). Addressing the cited research gaps through rigorous multicenter trials will be essential to define its optimal role in breast cancer screening and diagnosis. The next five years will likely determine whether CEM remains a promising innovation or becomes a new standard of care in breast imaging.

11. Summary

CEM shows comparable diagnostic accuracy to breast MRI, with potential advantages in terms of availability, cost, and patient preference. However, widespread adoption is limited by the lack of standardized protocols and prospective validation studies. Ongoing clinical

Table 2
Main ongoing or recently completed clinical trials including > 500 patients.

Study Name	NCT ID/ Reference	Objective	Population & Country	Status
RACER	NL6413/ NTR6589	To assess CEM as a diagnostic tool after recall from screening	529 women, Netherlands	Completed (results published in *Lancet Reg Health Eur 2024* [53])
TOCEM	NCT04764292	To evaluate the added value of CEM in patients with a personal history of breast cancer	1647 women, USA	Active, not recruiting (interim results published in *Radiology 2024* [54])
BRAID	NCT04097366	To evaluate risk-adapted screening with CEM/ Abb-MRI/ABUS vs standard screening	6305 women with dense breasts, UK	Active, not recruiting (interim results published in *Lancet May 2025* [43])
SCEMAM	NCT04764292	To compare DBT + CEM as an alternative to screening MRI	601 women, USA	Active, not recruiting (interim results published in *Radiology June 2025* [55])
CMIST	NCT05625659	To compare CEM vs DBT in women with dense breasts (cancer detection and false positives)	2032 women aged 45–74, USA	Recruiting (results expected 2025)
C-MERIT	NCT05667532	To compare cancer detection rate between CEM and FFDM	1000 women with dense breasts, USA	Recruiting
DENSE-2 Trial	NCT06636370	To compare CEM and Abb-MRI in a population-based screening program	36,000 (estimated) women with extremely dense breasts, Netherlands	Recruiting
Con-Trust	NCT06629896	To compare CEM as an alternative to DM + MRI in high-risk women (detection)	2200 (estimated) high-risk women, Italy	Recruiting
CEM to Reduce Biopsy Rates for Less Than Highly Suspicious Breast Abnormalities	NCT05206331	To improve the accuracy of radiologists' decisions for need to biopsy lesions classified as 4A or 4B (with FFDM, DBT or US)	1855 (estimated), USA	Recruiting
Outcome of Biennial Screening CEM in Women with a Personal History of Breast Cancer	NCT06105749	To determine if biennial DBT + CEM improves cancer detection, in women with a personal history of breast cancer.	1500 (estimated), USA	Recruiting

Abb-MRI = Abbreviated breast MRI; ABUS = automated breast ultrasound; US = breast ultrasound.

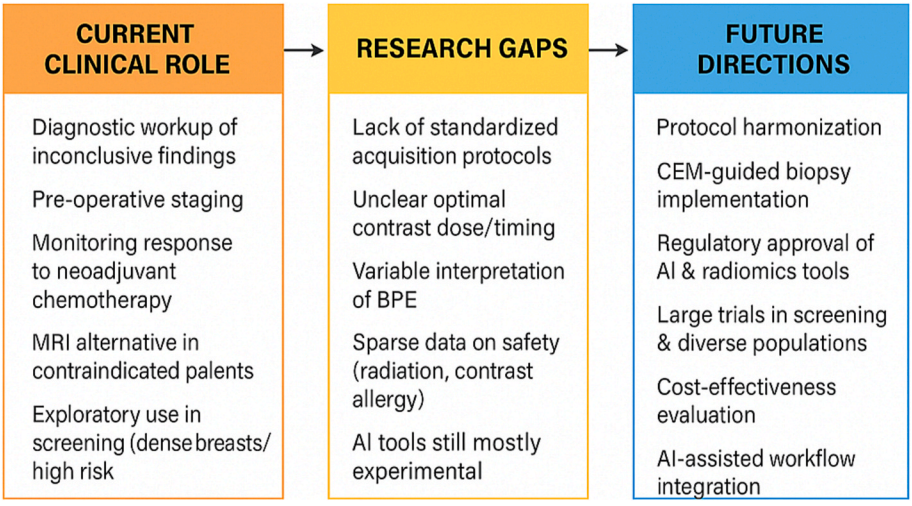

Fig. 4. Current clinical applications, main research gaps, and key directions for future development of CEM.

trials and AI-based tools are expected to play a crucial function in defining the future clinical role of CEM.

CRediT authorship contribution statement

Federica Pediconi: Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Giuliana Moffa:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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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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