Editorial Commentary

The emerging role of contrast-enhanced mammography

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"Do not fear to be eccentric in opinion, for every opinion now accepted was once eccentric."—Bertrand Russell.

Breast imaging across three decades

In the last 25 years, breast imaging has undergone a profound transformation, driven by four main trends.

First, large-scale implementation of screening mammography for breast cancer reached huge volumes in the early 2000s (1), both in Europe (2) and in the United States (1). As already postulated in the 1960s, breast cancer screening—combined with improved treatments—is effectively able to reduce breast cancer mortality (1,3).

Second, needle biopsy progressively replaced surgical breast biopsy which had shown various technical and clinical shortcomings (4). While fine-needle aspiration was initially widely employed, needle caliper steadily increased, as in core-needle biopsy and ultimately vacuum-assisted biopsy (5). This currently allows to collect larger tissue samples that provide the pathologist more ease to elaborate a diagnosis (6).

Third, established breast imaging modalities went through relevant technical improvements. Breast ultrasound—already known to be fast, readily available and cost-effective—has been enriched by multiparametric approaches (Doppler techniques and elastography) and supplemented by contrast-enhanced ultrasound (7,8). Automated breast ultrasound was also developed to address the poor reproducibility of conventional hand-held breast ultrasound (7). However, the real clinical impact of all these technical innovations remains limited and only partially demonstrated. In X-ray based imaging, screen-film mammography—while still widely used globally—has been replaced in high-income countries by digital mammography (9), which offers radiation exposure reduction, easier integration with modern radiology information systems, higher workflow efficiency, and lower running costs, also boosting detection rates in young women and in women with dense breasts (9,10). The yet ongoing implementation of digital breast tomosynthesis (DBT) represented a further turning point. DBT is a digital evolution of mammography and is able to significantly improve cancer detection rates in various age groups, regardless of breast density (11,12). At least in some studies, DBT use also led to a reduction in recall rates, in particular when recall rates are relatively high (13). However, the evidence of a significant reduction in interval cancer rates—which would robustly substantiate the use of DBT for breast cancer screening in the general population—has yet to be demonstrated (11,14).

Fourth, contrast-enhanced breast magnetic resonance imaging (CE-MRI) has seen extensive introduction in clinical practice (15). International guidelines began to recommend its use in a wide range of settings (16), namely in three paramount situations of the breast cancer diagnostic pathway: screening of high-risk women, pre-treatment staging, evaluation of the response to neoadjuvant therapy (15,16). While mammography and ultrasound

only generated a morphological evaluation, CE-MRI offered a comprehensive assessment of morphologic and functional properties of breast tissues (15), with an insight on *in-vivo* pathophysiological conditions tightly linked to carcinogenesis. Tumoral neoangiogenesis invariably occurs when breast cancer grows larger than 2 mm, but is incapable of producing architecturally sound vessels (17). Permeable ones are created instead, allowing for the extravasation of gadolinium-based contrast agents and for their accumulation in the cancer stroma (18). This results into modifications of local T1 properties recognizable on T1-weighted sequences (15), allowing to assess the wash-in and wash-out curve and its correlations with different tissue properties (18). Contrast enhancement explains the steep increase in sensitivity of CE-MRI compared to ultrasound and mammography. CE-MRI sensitivity often approaches 95–100%, as demonstrated by large-scale multicenter trials employing CE-MRI to screen high-risk women (19). The introduction of breast CE-MRI represented a breakthrough into a previously uncharted territory, de facto inaugurating a new combined morphofunctional approach, identifiable as "contrast-enhanced breast imaging".

The rise of contrast-enhanced mammography (CEM)

The combined morphofunctional approach underpins the rationale of CEM (20), which was developed by translating into an X-ray modality the same physio-pathological principles that allowed for the development of CE-MRI. CEM exploits the preferential uptake of iodinated contrast agents (ICAs) by breast tumors, observed both in computed tomography and in subtraction angiography (21). At first, the visualization of contrast uptake in the breast against fibroglandular tissue and fat was attempted with a temporal subtraction technique (21). However, since technical drawbacks made this procedure highly impractical, a digital recombination of low- and high-energy images acquired after intravenous injection of ICA was adopted (22). This recombination is generated by vendor-specific algorithms that gave rise to different denominations of the same technique: contrast-enhanced digital mammography (CEDM), contrast-enhanced spectral mammography (CESM), contrast-enhanced dual-energy mammography (CEDEM).

Notwithstanding the still persisting lack of technical and procedural standardization (23), across the last 16 years CEM has been experimentally introduced in various breast imaging settings, such as the diagnostic work-up of symptomatic women and screening recalls, problem-solving of specific mammographic findings, pre-operative local staging, post-operative surveillance, neoadjuvant therapy monitoring, and screening of women at increased risk or with dense breasts (20,24). Due to the morphofunctional nature of its images, in all these applications CEM consistently improved diagnostic performance when compared to digital mammography, ultrasound, and DBT, frequently matching CE-MRI overall performance (24).

Another relevant advantage of CEM was also observed considering patient experience and preferences: two surveys pitching CEM against CE-MRI in high-risk women screening (25) and in the problem-solving setting (26) found that shorter examination time and globally less taxing procedure made CEM much better tolerated by patients.

Screening by CEM

In this context, an article by Sung *et al.* (27)—assessing the diagnostic performance of CEM as a screening tool for women at increased risk of breast cancer—was recently published in *Radiology*. Several valuable points highlighted by its results deserve to be discussed. First, to the best of our knowledge (23), this is—by sheer number of performed CEM examinations, 1,069—the second largest study yet published. It is surpassed only by an institutional practice review by Bhimani *et al.* (28), who performed over 2,300 CEMs on various clinical indications. It is therefore the "overall first" according to the number of screening CEMs performed [1,069], largely surpassing the retrospective study by Klang *et al.* (29) which declared that 725 CEMs out of its total 953 examinations were performed for screening purposes. As acknowledged by the authors, the study by Sung *et al.* (27) is moreover the first to describe CEM application on such a large—and essentially quite homogeneous—group of women at increased risk of breast cancer, incorporating a previous study from their own research group (30) with 307 patients. The authors ultimately included 904 baseline CEM examinations, performed in a time-frame of little more than 3 years [2012–2016] with technical and procedural choices partly shared by other research groups around the world (23). Of note, the authors chose to initiate image acquisition slightly later (2.5–3 minutes after contrast injection) than most other centers (exactly 2 minutes after contrast injection). This was presumably done to maximize ICA circulation and extravasation in breast lesions prior to breast compression, without extending the examination over 10 minutes, i.e.,

the upper threshold of the time frame in which ICA wash-out and increasing background parenchymal enhancement do not hinder CEM interpretation (31,32). Moreover the acquisition order, one of the most controversial details of CEM technique (23), was left by Sung *et al.* (27) at the discretion of the radiographer, in accordance with one of their previous studies that found diagnostic equivalence between different sequences (31).

The second point regards adverse reactions to ICAs, which in this study were 15 in 904 patients (1.7%). This value is over two times the pooled value of 0.82% (95% confidence interval. 0.64–1.05%) we recently obtained in a meta-analysis of 14,012 patients from 84 studies up to January 2019 (23). We already envisaged how that pooled rate could probably be underestimated due to sporadic reporting of the vast number of mild adverse reactions that resolve without any medical intervention, as were 13 out of 15 (87%) adverse reactions reported by Sung *et al.* (27).

A third point worth discussing concerns the diagnostic performance reported by this study. Considering that repeated low-dose radiation exposure leads to an increased risk of radiation-induced breast cancer in high-risk women, particularly young carriers of deleterious mutations (33), these women could be screened with CE-MRI alone, as suggested in Australia (34) and some European countries such as Italy (35) and Germany (36). However, the most recent national guidelines in the United States (37) still recommend screening high-risk women with both CE-MRI and mammography, which are performed either concurrently or at a six months interval. In this framework – since CEM low-energy images have been demonstrated to be equivalent to plain digital mammography images (38)—Sung *et al.* (27) were able to compare the diagnostic performance of routine mammography interpretation (i.e., interpretation limited to low-energy images) with that of "integral" CEM interpretation (low-energy and recombined images). In accordance with previous studies, CEM provided a higher cancer detection rate (15.5/1,000) than low-energy images alone (8.8/1,000). Since however 51 CEM-observed lesions were biopsied, versus only 23 low-energy-observed lesions, CEM resulted in a lower positive predictive value (PPV) than low-energy images, with 29.4% and 34.8% respectively. While these values do not overstep specific PPV thresholds for mammography and CE-MRI defined in the Breast Imaging Reporting and Data System (BI-RADS) (39), they indeed represent a drawback for CEM. This can indeed be explained by the fact that a number of benign lesions, or even normal gland tissue, may occasionally display conspicuous contrast enhancement (40). Diagnostic performance data obtained by Sung *et al.* (27) from 858 women with at least 1-year follow up further confirmed CEM trends toward a higher cancer detection rate and a lower PPV. Aside from 14 women with cancers already detected with CEM, two women with a previous negative CEM ultimately developed interval cancer: in one woman, CE-MRI detected an invasive ductal carcinoma contralateral to an equally CE-MRI-detected ductal carcinoma in situ (DCIS), while the other patient had an asymptomatic DCIS detected at ultrasound ten months after a negative CEM. As expected, also in this reduced cohort, CEM showed a statistically significant higher sensitivity compared to low-energy images (87.5% versus 50.0%, P=0.03) with a significant increase for the negative predictive value too (99.7% versus 99.0%, P=0.02). Moreover, while performance metrics for low-energy images showed 24 false positives, this number grew to 53 for CEM, resulting in a statistically significant (P<0.001) 3.4% cutback for specificity (97.1% and 93.7% for low-energy images and CEM, respectively) mirrored by a non-significant (P=0.39) PPV reduction (from 25% to 20.9% for low-energy images and CEM, respectively). However, CEM specificity reported by this study is comparable to the ones of CE-MRI and of combined applications of digital mammography and screening ultrasound found in other studies that have targeted the same increased-risk category of women (19,41,42). It should also be noted that the creation and implementation of a CEM-specific BI-RADS lexicon would help to refine lesion characterization. Studies aiming to explore this possibility resulted both in improvements of CEM specificity and more appropriate biopsy referral (30,43).

A fourth and final point regards CEM performance in the "very-high-risk" echelons of the high-risk category, such as in *BRCA/TP53* mutation carriers and women who underwent thoracic radiation therapy. Sung *et al.* (27) reported to have performed 100/904 CEM examinations (11.1%) in such women, 82 of them being *BRCA* mutation carriers (9.1%). As already mentioned, and as acknowledged by the authors themselves, their strategy is surely beneficial in countries, such as the United States, where these women would be subjected to mammography screening techniques. The morphofunctional information provided by CEM should be preferred to purely morphological information garnered from mammography, to create a screening schedule in which a high-sensitivity contrast-enhanced breast imaging study is performed every six

Table 1 Main technical, procedural, and diagnostic features of contrast-enhanced breast MRI and contrast-enhanced mammography

Features	Contrast-enhanced breast MRI	Contrast-enhanced mammography
Images	Three-dimensional	Two-dimensional
Multiparametric technique	Yes	No
Radiation exposure	No	Yes
Contraindications	Several	Very few
Contrast-related health issues	Yes	Yes
Kinetic contrast analysis	Yes	No
Ease of interpretation	Low	High
Accessibility	Low to intermediate	Intermediate to high
Cost	High	Low
Diagnostic performance	High	High
Patient preference	Lower	Higher

MRI, magnetic resonance imaging.

months. Conversely, we would suggest—especially when CE-MRI alone is used to screen high-risk women—the more cautionary approach in which CEM-based breast cancer screening of high-risk women is performed only when CE-MRI is unavailable or when a woman has major contraindications to MRI, as aptly implemented by Sung *et al.* (27). As a notable exception, a specific indication in favor of CEM as a one-stop alternative to the combination of CE-MRI and mammography could be the annual screening of previously irradiated women, who have a higher incidence of DCIS with possible low neoangiogenesis that may be missed at CE-MRI (44). However, since these DCIS display microcalcifications, they could be detected with low-energy images of CEM. This is a subgroup of high-risk women who would probably most benefit from CEM-based screening. Finally, we remark that large-scale extension of CEM-based breast cancer screening to the whole increased-risk cohort—or to even larger cohorts such as the intermediate or average risk ones—would need to be substantiated by studies demonstrating a reduction in interval cancer rates compared to mammography screening. As already mentioned for DBT (11,14), we can also observe how a recently published study by Wernli *et al.* (45) comparing CE-MRI and digital mammography for breast cancer screening in over 13,000 women with previous breast cancer history did not display any statistically significant difference in the interval cancer rate, albeit showing an increased cancer detection rate for CE-MRI.

Perspectives

We are witnessing how CEM is challenging the hitherto uncontested CE-MRI dominance in crucial aspects of breast imaging (15,20,24) such as pre-operative staging, post-operative surveillance, identification of occult primary breast cancer, problem solving for equivocal findings at first-level examinations, and neoadjuvant therapy response monitoring. CEM is able to offer an immediately available work-up option for recalled suspicious findings (20,24) and also to easily solve one of the most irksome shortcomings of CE-MRI by providing a direct parallel visualization of microcalcifications in low-energy images and in their eventually associated contrast enhancement area (46). The article of Sung *et al.* (27) gave a valuable demonstration of CEM versatility in previously neglected tasks, once more highlighting the diagnostic superiority of the combined morphofunctional assessment provided by contrast-enhanced breast imaging. Competition between CE-MRI and CEM is therefore wide open: *Table 1* summarizes and compares each modality's major characteristics.

Another turning point could eventually be represented by a response to concerns on gadolinium-based contrast agents and ICAs. Indeed, since 2014 the use of gadolinium-based contrast agents in CE-MRI has come under close scrutiny, due to its retention in various structures of the central nervous system (47). While gadolinium retention in the brain has yet to display any pathological effect subsequently detectable at neurologic examination (47), this unresolved issue stimulated

research into unenhanced MRI protocols, such as those based on diffusion-weighted imaging (48). Exploiting different MRI multiparametric properties these sequences still grant a morphofunctional assessment of the breast, which is of utmost importance in a screening setting (48). Similarly, the combined application of radiomics and of spectral X-ray-based material decomposition to contrast-free dual-energy digital mammography recently paved the way for the extension of quantitative image analysis to X-ray-based techniques (49). These advancements allow for systematic tissue characterization without ICA administration (49,50). Paradoxically, the quest for an ever-easier access to in-deep breast tissue characterization may exit the terrain of contrast-enhanced breast imaging, only to swiftly open a new competition between MRI and mammography in their contrast-free quantitative applications.

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Footnote

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