Contrast Enhanced Mammography (CEM) in the evaluation of breast calcifications: preliminary experience

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This article summarizes the results of a recent study evaluating the role of CEM in the detection and characterization of breast calcifications. We used CEM to evaluate the presence of contrast enhancement at the site of calcifications and obtained histopathological results from vacuum-assisted biopsy (VAB) samples. In order to assess disease aggressiveness in malignant lesions, we then examined the association of lesion size with immunohistochemical characteristics. We found that CEM has the ability to recognize neoplasms larger than 5mm, with high a proliferative index (Ki-67 > 20%) and frequently HER2 positive. These findings suggest that CEM could detect aggressive malignancies.

The widespread use of mammography and screening programs has resulted in a considerable increase in the detection of non-palpable infra-clinical lesions, in particular ductal carcinoma in situ (DCIS) [1].
The typical early manifestation of DCIS is calcifications, whose interpretation is one of the greatest challenges for the breast radiologist. There are specific and appropriate radiological symptomatology to describe calcifications, as indicated in the Breast Imaging Reporting and Data System (BI-RADS) lexicon, developed by the American College of Radiology to standardize terminology [2]. Various studies have been carried out to determine whether features of calcifications can be used to predict malignancy [3] and whether descriptors of calcifications could help to stratify the risk of malignancy [4].
The BI-RADS Fifth Edition atlas subdivides suspicious calcifications into two-categories: category 4B (amorphous, coarse heterogeneous, and fine pleomorphic) and category 4C (fine linear/fine linear branching calcifications) [2].
The majority of biopsies carried out for suspected calcifications detected in mammography turn out to have a benign histology [5]. It is therefore evident that the use of radiological symptoms alone for the characterization of calcifications is no longer sufficient. For years we have been looking for new imaging techniques that could increase diagnostic accuracy in the presence of calcifications.
Contrast-enhanced mammography (CEM) is an emerging breast imaging technique that uses contrast-enhanced recombined images for the assessment of neoangiogenesis [6]; CEM combines the relative ease, low cost and availability of mammography with a high sensitivity resulting from the use of contrast medium [7].
The aim of our study was to evaluate the presence or absence of enhancement, to investigate correspondence between enhancement at the site of calcifications and underlying pathology, and to determine the extent of calcifications and histochemical signs of disease aggressiveness in malignant lesions.

MATERIALS AND METHODS

Between May 2018 and July 2019, 34 patients with 36 lesions were enrolled for CEM examinations before scheduled vacuum assisted biopsy (VAB) for suspicious calcifications (BI-RADS 4).
The inclusion criteria were: patients with ACR BI-RADS 4 calcifications on mammograms; no related mass lesions at physical examination and breast ultrasound. The exclusion criteria were: renal function impairment or history of an allergic reaction to contrast medium.
A Selenia Dimensions Mammography System (Hologic, Marlborough, Massachusetts, USA) was used with the appropriate software to perform "Dual Energy" subtractions. CEM images were analyzed by a radiologist with more than twenty years of experience in breast imaging, but with a less developed experience in CEM evaluation.
About one week after CEM, patients had their pre-scheduled stereotactic VABiopsy carried out. The procedures were performed with the Affirm Prone Breast Biopsy System (Hologic, Marlborough, Massachusetts, USA).

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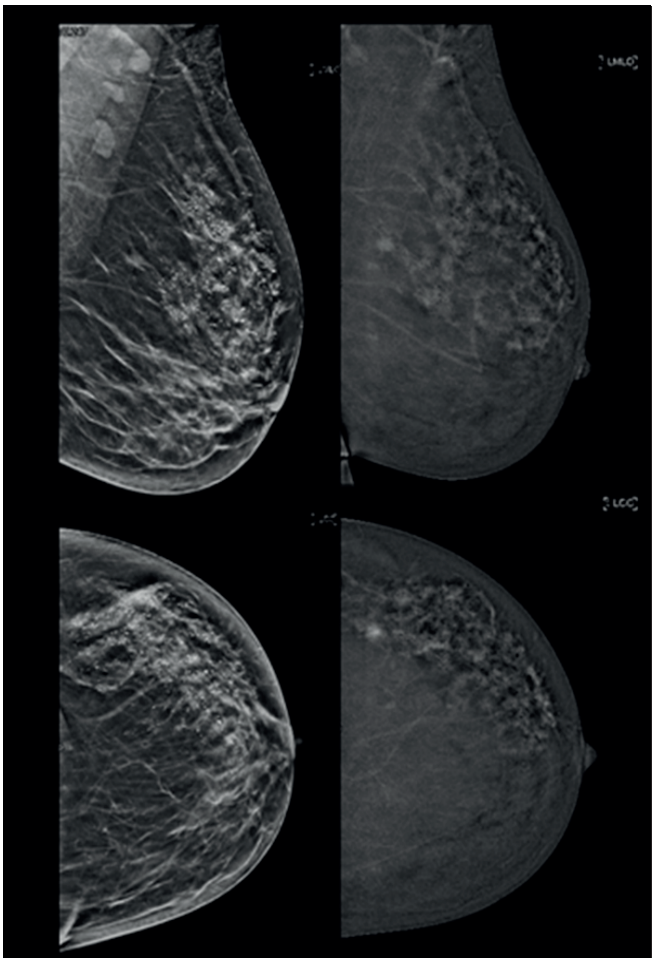

Figure 1: Suspicious calcifications of the left breast that entirely occupy the upper outer quadrant. In CEM there is a diffuse non-mass enhancement (DCIS) and, in the deep seat, a centimeter long mass enhancement that corresponds to the infiltrating component.

In the case of malignancy (B5), patients were referred for breast surgery. The size of lesions and the results of immuno-histochemical evaluation were available in most cases after definitive surgery. In the case of B2 or B3 results, patients underwent a 6-months follow up with digital mammography (B2) or CEM (B3). For all malignant lesions, we evaluated either the presence or absence of CEM enhancement and the size of lesions, their immuno-histochemical results and proliferation index (Ki-67). Arbitrarily, we set a cut-off of 5 mm for lesion size (based on the TNM AJCC 2017 classification [8]) and 20% for Ki-67, according to AIOM guidelines [9] and our oncologists' interpretation of aggressive disease.

RESULTS

Our preliminary results are based on 36 lesions consisting of suspicious calcifications at mammography in 34 patients who then had CEM carried out CEM and subsequently biopsy sampling.

The calcifications were BI-RADS 4b in 14 cases (39%) and BI-RADS 4c in 22 cases (61%). The extent of calcifications was on average 26,3 mm.

Based on results of histology at VAB, lesions were classified as B5 in 15/36 (42%), B3 in 7/36 (19%), B2 in 14/36 (39%). B5 lesions went to surgery, whereas B3 and B2 went to 6-month follow up.

The 15 malignant cases comprised 11 DCIS, 2 IDC and 2 IDC+DCIS.

At CEM examination, 10 cases (27.8%) showed contrast enhancement corresponding with the site of calcifications [Figures 1 and 2]; in 26 cases (62.3%) no enhancement was observed. Out of the 10 cases with enhancement 7 were malignant (B5) and 3 benign (B2). Out of the 26 cases without enhancement, 8 were malignant (B5) and 18 were benign (B3 and B2).

However, we must take into consideration that currently there is no codified system to evaluate enhancement and therefore there may be errors of interpretation.

Data on lesion size, immunohistochemical and Ki-67 were not available for all 15 malignant lesions but only for those 11 already treated at our Institute (4/15 patients have not undergone surgery yet) [Table 2].

Looking at the presence of enhancement, tumor size and Ki-67 values of the 11 malignant lesions, we noted that the five enhancing lesions had a size greater than 5 mm (for 4/5 patients ≥1cm) and a Ki-67 value higher than the cut-off of 20%. The six no-enhancing lesions, instead, had low degrees of cell proliferation (Ki-67 < 20%) and size less than 5 mm (3/6 patients had microfocal disease —our pathologist categorizes single or multiple foci with DCIS <1 mm or a single focus of IDC < 1mm as "microfocal").

CEM enhancement occurred more frequently in IDC lesions (4/5) while absence of enhancement occurred mostly in DCIS lesions (5/6) and in a microfocal IDC.

CEM enhancement occurred mainly in HER2 positive and Basal-like carcinomas (4/5) and only in one Luminal A IDC 10 mm in size; besides the very small lesion size, non enhancing lesions were prevalently Luminal A DCIS.

DISCUSSION

Breast calcifications continue to be a major challenge for the breast radiologist in terms of detection, characterization, radiological-histological correlation and the correspondence of those signs with the extent of the underlying pathology.

DCIS is associated with calcifications in 90% of cases [10]. BI-RADS morphology and distribution descriptors have been introduced to standardize the terminology and suggest different degrees of suspicion [2]. Due to non-continuous proliferation of DCIS inside the lobar ducts, it is possible that malignancies may exceed the extent of visible calcifications and remain occult when surgery is planned, leading to subsequent wider resections and relapse occurrence in the follow-up [11]. Apart from any possible interpretative errors by radiologists, a non-negligible part of DCIS may remain totally occult at routine breast imaging examination. Breast examinations using contrast media may improve disease detection and preoperatively suggest the supposed real extent of the disease, thus improving its management [12].

CEM is a emerging diagnostic technique that combines the morphological features of standard 2D mammography with the functional features of MRI because it uses a conventional, non-ionic iodinated contrast media. It has numerous advantages, in particular, it is not influenced by breast density, it has relatively low costs, being based on the use of mammographic equipment with a wide availability. Moreover, most patients usually consider the procedures quite comfortable because of the short time of examination and the closeness of the operators. [13]

One of the most interesting aspects of CEM is that it allows the calcifications to be seen in the low energy image and the possible enhancement in the recombined image, thus allowing an adequate and precise spatial localization. In case of enhancement, it is possible to carry out a precise stereotactic biopsy procedure instead

B5 lesions	Enhancement	Histology	Molecular subtype	Histological size (mm)	Ki-67%
1	✓	DCIS G3	Her-2	21	37
2	✓	IDC G3	Basal Like	27	58
3	✓	IDC G3	Basal Like	13	60
4	✓	IDC G3	Her-2	7	80
5	✓	IDC G3	Luminal A	10	22
6	×	DCIS G2	Luminal A	4	20
7	×	DCIS G3	Her-2	Microfocal	7
8	×	DCIS G3	Luminal B	Microfocal	10
9	×	DCIS G2	Luminal A	Microfocal	15
10	×	DCIS G2	Luminal A	Microfocal	12
11	×	IDC G3	Luminal A	Microfocal	5

Table 1 Features of the 11 malignances

of attempting a more complicated MRI-guided breast biopsy.

CEM has almost the same sensitivity of MRI in the detection of invasive cancers [14] but only a few authors have evaluated the performance of CEM for lesions that are represented only by calcifications without an associated mass, i.e. prevalently pre-neoplastic or *in situ* disease [7]. In this context, neoangiogenesis is probably not so developed as in the case of invasive cancers, and even breast compression during the examination may limit the contrast media flow and enhancement [15].

Unlike studies published in the literature [7], we had some malignant cases without CEM enhancement. These studies reported a weak enhancement in the presence of all DCIS, without, however, adequately stratifying the disease (low grade versus high grade) or evaluating the size of lesions.

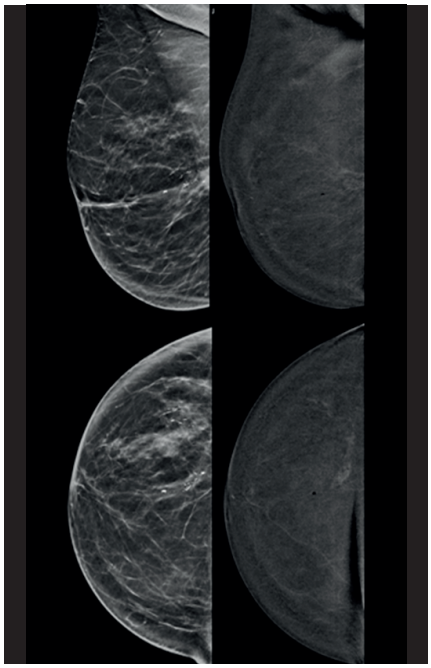

Figure 2. Surgical scar in the centre of the right breast. There are two clusters of calcifications: the external ones, linear branching calcifications, are suspicious. In contrast, the central ones, pericicatricial, seem to be liponecrotic. In CEM we see that both clusters have enhancement and are therefore both suspicious.

We found 5 cases of DCIS with enhancement (lesion size ranging from 7 to 27 mm, average 15.6 mm) and 6 DCIS without enhancement (all less than 5 mm). Our preliminary results therefore seem to show that suspicious calcifications with enhancement indicate a more extensive (> 5 mm) disease. These data could allow the selection of calcifications for biopsy. This is part of the attempt to reduce overdiagnosis and consequent overtreatment which represent the great challenge of modern breast radiology. We also evaluated the biological features of these malignances through the analysis of Ki-67 in order to look for a possible explanation of false negative CEM results. Several studies have shown that the expression of Ki-67 in malignant tumors is related to pathological grade [16]. Ki67-positive tumor cells grow fast, have high invasion and poor prognosis [17]. As there are many discrepancies between laboratories in assays for Ki-67, these scores should be determined in the light of established local laboratory values [17]. We applied a cut-off of 20% as used by our oncologists to define more proliferative lesions.

As Kuhl *et al.* said for pure DCIS at MRI, CEM looks promising for finding high-grade disease [12]. CEM enhancement occurred more frequently in IDC lesions (4/5) with high Ki-67 values, while absence of enhancement occurred mostly in DCIS lesions (5/6) and in a microfocal IDC, all of them with low Ki-67 values.

Moreover, CEM enhancement occurred mainly in HER2 positive and Basal-like carcinomas (4/5) and only in one Luminal A IDC of 10 mm in size. In addition, the very small size, non-enhancing lesions were predominantly Luminal A DCIS.

CONCLUSIONS

In conclusion, our preliminary study seems to show that in CEM the presence of enhancement in correspondence with suspicious calcifications indicates a disease with a high proliferative index and with dimensions > 5 mm. This could be useful to distinguish indolent tumors from more aggressive neoplasms worthy of treatment, with a consequent reduction of overdiagnosis and overtreatment. We consider our preliminary findings as a starting point for the development of further studies with large number of patients.

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