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FULL PAPER

Comparison between second-look ultrasound and second-look digital breast tomosynthesis in the detection of additional lesions with presurgical CESM

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Objectives: To compare second-look ultrasound (SL-ultrasound) with second-look digital breast tomosynthesis (SL-DBT) in the detection of additional lesions (ALs) with presurgical contrast-enhanced spectral mammography (CESM).
Methods: We retrospectively included 121 women with 128 ALs from patients who underwent CESM for presurgical staging at our centre from September 2016 to December 2018. These ALs underwent SL-ultrasound and a retrospective review of DBT (SL-DBT) performed 1–3 weeks prior to CESM to evaluate the performance of each technique individually and in combination. ALs in CESM images were evaluated according to enhancement type (focus, mass, or non-mass), size (<10 mm or >10 mm) and level of suspicion (BI-RADS 2, 3, 4 or 5). Our gold-standard was post-biopsy histology, post-surgical specimen or >24 month negative follow-up. McNemar's test was used for the statistical analysis.
Results: Out of the 128 ALs, an imaging correlate was found for 71 (55.5 %) with ultrasound, 79 (61.7%) with DBT, 53 (41.4 %) with DBT and ultrasound, and 97 (75.8%) with ultrasound and/or DBT. SL-DBT demonstrated a higher detection rate *vs* SL-ultrasound in non-mass enhancement (NME) pattern (p: 0.0325) and ductal carcinoma in situ histological type (p: 0.0081). Adding SL-DBT improved the performance *vs* SL-ultrasound alone in the overall sample (p: <0.0001) and in every subcategory identified; adding SL-ultrasound to SL-DBT improved the detectability of ALs in the overall sample and in every category except for NME (p: 0.0833), foci (p: 0.0833) and B3 lesions (p: 0.3173).
Conclusion: Combined second-look imaging (SL-DBT+ SL-ultrasound) for CESM ALs is superior to SL-DBT alone and SL-ultrasound alone. In B3 lesions, NME, and foci, the analysis of a larger sample could determine whether adding SL-ultrasound to SL-DBT is necessary or not.
Advances in knowledge: Thanks to its high sensitivity, CESM is a useful tool in presurgical staging to detect the extent of the disease burden and identify ALs not detected with conventional imaging. Since CESM-guided biopsy systems are still scarcely available in clinical practice, it is necessary to look for other approaches to histologically characterize ALs detected with CESM. In our study, combined second-look imaging (SL-DBT + SL-ultrasound) showed better performance in terms of detectability of ALs, than either SL-DBT or SL-ultrasound alone, and allowed us to identify 91.2% of ALs that turned out to be malignant at final histology; for the remaining 8.8% it was still necessary to perform MRI or MRI-guided biopsy. However, this issue could be solved once CESM-guided biopsies spread in clinical practice. SL-DBT demonstrated a higher detection rate than SL-ultrasound in NME and ductal carcinoma in situ histology.

INTRODUCTION

Contrast-enhanced spectral mammography (CESM) is a new breast imaging diagnostic technique which highlights areas of tumoral neoangiogenesis via an injection of iodinated contrast media.[1] CESM demonstrated a high sensitivity in the detection of breast cancer (BC), up to 85–97% in two recent meta-analyses,[2,3] with a diagnostic performance similar to contrast-enhanced MRI (CE-MRI).[4] Thanks to its high sensitivity, it is a useful tool in presurgical staging to detect the extent of the disease burden and identify additional lesions (ALs) not detected with conventional imaging.[5] In a recent study, CESM performed as

pre-operative staging gave rise to additional biopsies in 17.5% and changed the type of surgery in 18.4% of patients, showing an overall sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 93%, 98%, 90%, 98% and 97% respectively.[6] Previous studies have confirmed these results with similar detection percentages of ALs that led to necessary changes in surgical plans, confirmed by histologic post-surgical specimens.[7,8]

Since CESM-guided biopsy systems are still scarcely available in clinical practice, it is necessary to look for other approaches to histologically characterize ALs detected with CESM. Several studies have already demonstrated that CESM sensitivity is as high as CE-MRI,[4,5,9] so a choice could be to perform CE-MRI and MR-guided biopsy on ALs. However, this procedure is highly time-consuming and costly and not always feasible depending on the location of the ALs, as confirmed in literature.[10,11]

As with MRI,[12,13] second-look ultrasound (SL-ultrasound) targeting CESM findings is surely one of the most important alternatives, since ultrasound-guided core biopsies are widely available, and quick and easy to perform. To our knowledge, there are no studies on the detection rate of SL-ultrasound for ALs with CESM, but a previous study reported a lack of correlate for MRI additional findings of up to 53%.[14]

Since their introduction in clinical practice, digital breast tomosynthesis (DBT) and DBT-guided-biopsy systems have demonstrated an improvement in the detection rate of breast lesions, reducing false-positive recall rates in screening due to superimposition of normal glandular tissue.[15,16] Clauser et al, in their study evaluated the role of SL-DBT in ALs found with presurgical MRI and reported that when SL-DBT was combined with SL-ultrasound the detection rate for clinically relevant ALs increased from 52 to 75%, with MR-guided biopsy being necessary for the remaining 25%.[17]

The purpose of our study was to compare second-look ultrasound (SL-ultrasound) and second-look DBT (SL-DBT) in terms of performance in the overall sample and in every subcategory identified, and whether, and in which cases, the combination of both (SL-ultrasound + SL-DBT) could significantly improve the detectability of CESM ALs *vs* SL-ultrasound alone and SL-DBT alone.

Methods and materials

From the CESMs performed as presurgical staging from September 2016 to December 2018, we retrospectively screened those with evidence of ALs on recombined images not detected with conventional imaging [full-field digital mammography (FFDM) + whole-breast ultrasound] in the ipsilateral or contralateral breast. We reported and classified ALs according to the MRI BI-RADS reporting system[18] with distinct levels of suspicion: BI-RADS 2, BI-RADS 3, BI-RADS 4 and BI-RADS 5. Every AL underwent second-look ultrasound after CESM (SL-ultrasound) and review of DBT images that had been acquired 1–3 weeks prior to CESM (SL-DBT).

Among ALs with a correlate detected by SL-ultrasound and/or SL-DBT, those classified as BI-RADS 2 and/or 3 with CESM underwent a follow-up when the level of suspicion was confirmed with second-look imaging. Conversely, when SL-ultrasound and/or SL-DBT upgraded the level of suspicion to BI-RADS 4 or 5, we performed ultrasound-guided biopsy or tomo-guided biopsy, depending on the imaging technique showing the higher level of suspicion. In cases of ALs with the same level of suspicion in both SL-ultrasound and SL-DBT, we chose to perform ultrasound-guided biopsy.

Every AL reported as BI-RADS 4 and 5 with CESM with an imaging correlate detected by SL-ultrasound and/or SL-DBT underwent biopsy, regardless of the level of suspicion of the two SL techniques.

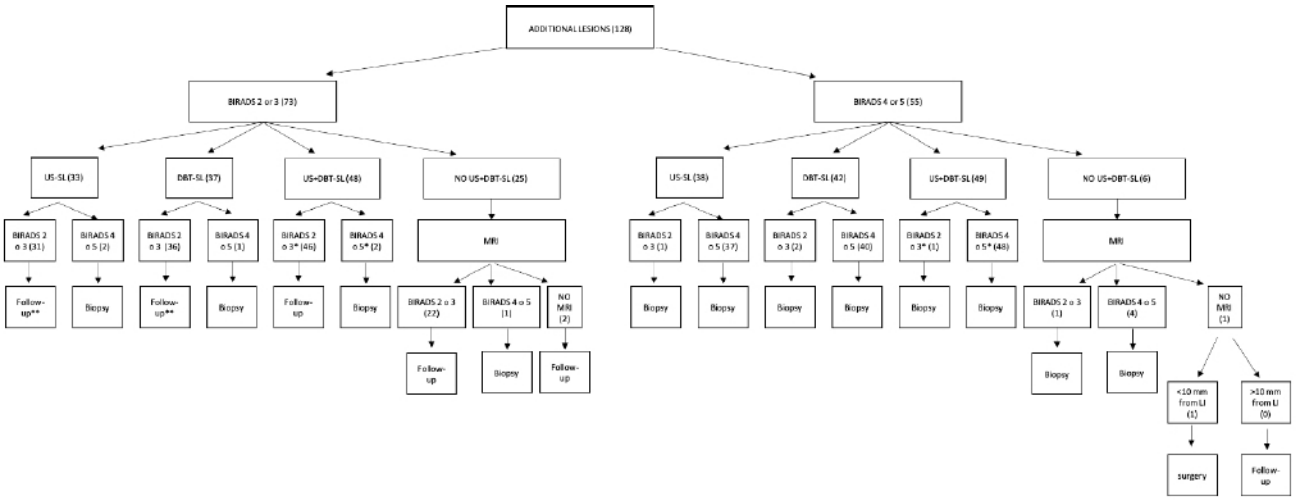
Every AL with a negative second-look underwent CE-MRI, whatever the level of suspicion identified in CESM. In this group, BI-RADS 3 CESM ALs without an imaging correlate in CE-MRI or with the same level of suspicion, underwent a follow-up. BI-RADS 4 and 5 CESM ALs with an imaging correlate in CE-MRI underwent MR-guided biopsy, regardless of the MRI level of suspicion, while those without an imaging correlate underwent short-term follow-up with CESM, since CESM-guided biopsy systems are not yet available in Italy. When ALs with negative CE-MRI were at a distance of <10 mm from the index lesion, we added the overall size of the enhancing area (index lesion + AL + intralesional distance) on our reports and recommended that the surgeon widen the surgical margin to include the ALs in the surgical excision (Figure 1).

All patients underwent whole-breast ultrasound, bilateral FFDM and DBT performed in the standard craniocaudal (CC) and mediolateral oblique (MLO) views using a full-field digital mammography unit with tomosynthesis (Selenia Dimensions, Hologic), between 1 and 3 weeks before CESM; in females of premenopausal age, CESM was performed during the second week of the menstrual cycle.

CESM was executed with a commercial mammography system (Selenia Dimensions, Hologic, Marlborough, MA), after an intravenous administration of 1.5 cc/kg of body weight of iodine-based contrast agent (Iopromide 370 mg ml^{-1}; Bayer HealthCare, Whippany, NJ or Iopamidol 370 mg ml^{-1}; Bracco Imaging S.p.A., Milan, Italy) at 3 cc/s followed by 20 ml of saline flush using an automated power injector. The first acquisition began 2 min after the injection. Standard mammographic views of each breast (CC and MLO images) were obtained in sequence within 5 min. After 8 min, a "delayed image" of each breast was acquired to permit a qualitative assessment of the enhancement kinetics. No issue was raised by our institutional ethics committee about radiation dose since our population was composed by females with a proven breast cancer and CESM was performed as pre-surgical staging and not as screening programme, so a minor increase in radiation dose was tolerated.

For each CESM view, a low-energy (LE) image and a high-energy image were performed serially, at 26–31 kVp with

Figure 1. Flowchart of diagnostic management of CESM ALs; * depending on the higher level of suspicion out of the two imaging techniques (SL-ultrasound and/or SL-DBT); ** follow-up or biopsy if level of suspicion is confirmed by the other SL imaging technique. LI: index lesion; SURGERY: explained in text. ALs; arterial lesion; CESM, contrast-enhanced spectral mammography; SL-DBT, second-look digital breast tomosynthesis.



rhodium and silver (Rh and Ag) filters and at 45–49 kVp with a copper filter, respectively. A recombination algorithm was used to subtract the unenhanced breast tissue and provide a recombined image for highlighting the areas of relative contrast enhancement. All the mammographic views were used for our analysis.

CESM images were reviewed in consensus by three experienced breast radiologists with 4–27 years' experience in breast imaging.

The radiologists, not blinded to other imaging methods (ultrasound, FFDM and DBT), described the index lesions in terms of localization, size, and type of enhancement.

Every measurable enhancing finding at a distance >5 mm from the index lesion or on the contralateral breast was considered an AL. In order to distinguish ALs from background parenchymal enhancement (BPE) when present, the radiologists evaluated the symmetry, distribution and intensity of the enhancing findings, since BPE is more often symmetric and with a stronger intensity in the delayed recombined images acquired after 8 min than in the early recombined images acquired after 2 min. ALs were described and classified as mass, non-mass and focus according to the MRI BI-RADS lexicon, since a standardized lexicon for CESM does not yet exist.[18]

Both whole-breast bilateral ultrasound and targeted SL-ultrasound were performed using handheld ultrasound by a radiologist of our institution with a 10–13 MHz transducer and an ultrasound unit (ESAOTE, MyLab 70 XVG).

Target SL-ultrasound was performed after 3–7 days by a breast radiologist of our institution who retrospectively evaluated the CESM images, looking for the ALs' correlate, such as masses or distortions; when a correlate was found, we performed 14G CNB.

DBT images acquired 1–3 weeks prior to CESM were re-evaluated retrospectively in separate sessions by a breast radiologist of our institution; when a correlate with suspicious imaging characteristics (masses, architectural distortions, microcalcifications and asymmetries) and lesion size and localization correspondence with CESM ALs was found, we performed 8G tomo-VAB.

Lesions classified as benign (B2) were: B2 lesions confirmed by post-biopsy histology; lesions with at least a 2-year negative follow-up; lesions B1 or B2 after surgical excision in case of ALs with negative SL-ultrasound, SL-DBT and CE-MRI, and at a distance of <10 mm from the index lesion.

Lesions classified as having uncertain malignancy potential (B3) were: B3 lesions confirmed after surgical excision in case of ADH, papilloma, LN and phyllodes tumour, B3 lesions confirmed by post-biopsy histology for the remaining categories that did not undergo surgical excision.

Lesions were classified as malignant if confirmed by final histology after surgical excision.

We then divided the overall sample into subcategories according to histology (malignant, B3, benign lesion), and when malignant, also the cancer histological type [IDC, ILC, ductal carcinoma in situ (DCIS)], type of enhancement in CESM [focus, mass, non-mass enhancement (NME)], and maximum diameter (≤10 mm; >10 mm).

Following, we evaluated the performance of SL-ultrasound, SL-DBT and the combination of both in terms of detectability of ALs identified in CESM recombined images in the overall sample and in every subcategory identified.

Table 1. Side-distribution of 128 benign, high-risk (B3), and malignant additional lesions detected in patients who underwent pre-operative breast CESM

Additional lesions	n	Benign		High-risk lesions (B3)		Malignant	
Total	128	61	47.7%	10	7.8%	57	44.5%
Ipsilateral	68	26	38.2%	5	7.4%	37	54.4%
Contralateral	60	35	58.3%	5	8.3%	20	33.3%

CESM, contrast-enhanced spectral mammography.

Statistical analysis

Using McNemar's test, we compared SL-ultrasound and SL-DBT performances for the whole sample and the subcategories to discover which SL-technique was more effective and when. Then, we verified whether and when the combination of SL-ultrasound and SL-DBT was better than SL-ultrasound or SL-DBT alone. The analyses were performed using IBM SPSS Statistics 23.0 (IBM SPSS Inc., Chicago, IL) and Microsoft Excel (Microsoft Corporation, Redmond, WA).

RESULTS

In 304 CESMs carried out as pre-surgical staging, 128 ALs were found which were either ipsilateral or contralateral to the index lesion in 121 patients: among these, 57/128 (44.5%) were confirmed as malignant, 10/128 (7.8%) as B3 lesions, and 61/128 (47.7%) as benign (Table 1).

ALs found on SL-DBT were masses in 40 cases, microcalcifications in 22, distortions in 16, and 1 focal asymmetry.

Out of 57 malignant Als, 30 (52.6%) showed as mass enhancement in CESM, 18 (31.6%) as NME, and 9 (15.8%) as foci.

CESM NME ALs were observed in SL-DBT as 12 microcalcifications, 3 masses, 6 distortions and 1 focal asymmetry; mass-like ALs were observed in SL-DBT as 30 masses, 10 distortions and 4 microcalcifications; foci ALs were observed in SL-DBT as 7 masses and 6 microcalcifications.

SL-ultrasound detected an imaging correlate in 71/128 CESM ALs: 39/57 (68.4%) malignant lesions, with a significant decrease in performance in the DCIS histological type (3/11; 27.3%); 27/61 (44.2%) benign lesions, and 5/10 (50.0%) B3 lesions.

SL-DBT detected an imaging correlate in 79/128 CESM ALs: 41/57 (71.9%) malignant lesions; 29/61 (47.5%) benign lesions, and 9/10 (90.0%) B3 lesions.

The histologic characteristics of CESM ALs with and without a SL-detected correlate are reported in Table 2.

The combination of both techniques (SL-ultrasound + SL-DBT) detected 97/128 CESM Als: 52/57 (91.2%) malignant lesions, 35/61 (57.4%) benign lesions, and 10/10 (100%) B3 lesions.

Table 2. Histology of B5 and B3 lesions detected with SL-ultrasound, SL-DBT individually or combined, or with negative SL, in 121 women with 128 ALs found with presurgical CESM

B5 and B3 additional lesions	Detected at SL-ultrasound	Detected at SL-DBT	Detected at both SL-ultrasound and SL-DBT	Not detected at SL-DBT neither SL-ultrasound
B5 lesions (n = 57)	**39 (68.4%)**	**41 (71.9%)**	**28 (49.1%)**	**5 (8.8%)**
Invasive ductal carcinoma	31	27	22	4
Microinvasive ductal carcinoma	1	0	0	0
DCIS	3	10	3	1
Invasive lobular carcinoma	4	4	3	0
B3 lesions (n = 10)	**5 (50.0%)**	**8 (80.0%)**	**4 (40.0%)**	**0**
Atypical ductal hyperplasia	1	1	1	0
Lobular neoplasia	0	2	0	0
Flat epithelial atypia	0	2	0	0
Radial Scar	1	1	1	0
Papilloma	2	2	1	0
Atypical apocrine adenosis	1	1	1	0

CESM, contrast enhanced spectral mammography; DBT, digital breast tomosynthesis; DCIS, Ductal carcinoma in situ; SL, second-look.
Note: the three DCIS with an imaging correlate detected by SL-ultrasound, also had a correlate with SL-DBT; no DCIS positive with SL-ultrasound and negative with SL-DBT were observed.

In our study, 31/128 CESM ALs negative in both SL-ultrasound and SL-DBT underwent CE-MRI and 28/31 showed an imaging correlate. Of the 5/31 malignant ALs, 4 (all BI-RADS 4 in CESM and CE-MRI) underwent MR-guided biopsy and 1, negative with CE-MRI, was confirmed after surgical excision with wider margins, as it was <10 mm from the index lesion; the undetected malignant ALs were one DCIS, two G1 IDC, one G2 IDC and one G3 IDC. Of the 26/31 benign ALs, 24/31 were confirmed as benign after at least a 2-year negative follow-up with CESM, and 2/31 by histology after MR-guided biopsy.

The subcategories identified in our sample, in particular histology (malignant, B3, benign lesion), and when malignant, the cancer histological type (IDC, ILC, DCIS), type of enhancement in CESM (focus, mass, NME), maximum diameter (≤10 mm; >10 mm), level of suspicion (BI-RADS 2 or 3, BI-RADS 4, BI-RADS 5) are reported in Table 3.

SL-ultrasound alone *vs* SL-DBT alone showed no significant performance difference in terms of detectability of CESM ALs in the overall sample (SL-DBT 61.7% *vs* 55.5% SL-ultrasound), while the combination of DBT and ultrasound (SL-DBT + SL-ultrasound) showed a significantly higher performance *vs* SL-ultrasound alone (75.8% *vs* 55.5%; *p*: <0.001) and *vs* SL-DBT alone (75.8% *vs* 61.7% *p*: <0.001).

SL-DBT alone proved significantly better in terms of detectability *vs* SL-ultrasound alone in DCIS histological type (90.9% *vs* 27.3%; *p*: 0.008) and in the NME category (64.7% *vs* 41.2%; *p*: 0.032). In the remaining subcategories identified, no significant difference was found in the performance of SL-DBT alone *vs* SL-ultrasound alone.

When considering histology, the combination of both techniques (SL-DBT + SL-ultrasound), showed a significantly improved performance *vs* SL-ultrasound alone and SL-DBT alone in malignant lesions (91.2% *vs* 71.9% SL-DBT. $p < 0.001$; *vs* 68.4% SL-ultrasound. $p < 0.001$), especially in IDC histological type (90.2% *vs* 65.8% SL-DBT. *p*: 0.002; *vs* 78.0% SL-ultrasound. 0.025), and benign lesions (57.4% *vs* 47.5% SL-DBT. *p*: 0.014; *vs* 44.3% SL-ultrasound. *p*: 0.005); SL-DBT + SL-ultrasound also showed better performance *vs* SL-ultrasound alone in DCIS histological type (90.9% *vs* 27.3%; *p*: 0.008) and in B3 lesions (100.0% *vs* 50.0%; *p*: 0.025).

When considering the type of enhancement of CESM ALs, SL-DBT + SL-ultrasound improved the detectability *vs* both SL-ultrasound and SL-DBT alone in the mass category (81.2% *vs* 63.8% SL-DBT. *p*: 0.008; *vs* 71.0% SL-ultrasound. *p*: 0.001), and it also proved better *vs* SL-ultrasound alone in the NME (73.5% *vs* 41.2%; *p*: 0.001) and focus (64.0% *vs* 32.0%; *p*: 0.005) categories.

In relation to the AL size, the combination of SL-DBT + SL-ultrasound improved the performance *vs* SL-ultrasound alone and SL-DBT alone in both the ≤10 mm (75.6% *vs* 59.8% SL-DBT, $p < 0.001$; *vs* 57.3% SL-ultrasound. $p < 0.001$) and >10 mm categories (76.1% *vs* 65.2% SL-DBT, *p*: 0.025; 52.2% SL-ultrasound. $p < 0.001$).

As regards the level of suspicion. combined SL-DBT + SL-ultrasound improved the detectability of ALs *vs* both SL-ultrasound and SL-DBT alone in the BI-RADS 3 (65.7% *vs* 50.7% SL-DBT. $p < 0.001$; 45.2%. SL-ultrasound. $p < 0.001$) and BI-RADS 4 categories (88.7% *vs* 75.5% SL-DBT. *p*: 0.008; *vs* 67.9% SL-ultrasound. $p < 0.001$).

The other evaluations were not statistically significant.

Examples of malignant CESM ALs with only a correlate detected by SL-ultrasound and only a correlate by SL-DBT, are shown in Figures 2 and 3.

DISCUSSION

To our knowledge, this is the first study to report the role of SL-DBT and combined SL-DBT and/or SL-ultrasound in detecting ALs observed in CESM exams performed for pre-surgical staging.

In our study, we found 128 ALs in 304 presurgical CESMs, with a rate of 39.80%, higher than the few studies published in literature on this topic,[6,7] namely, 23.6% in the study of Bicchierai et al, and 16% in Ali-Mucheru et al, but similar to some studies of presurgical MRI,[17,19,20] such as that of Clauser et al which reports 39% of additional findings.

The overall malignancy rate for ALs was 44.5%, in agreement with several studies in literature,[6,21] including 54.3% that of Houben et al, and with other studies on MRI[17,22,23] ; similar values were also found in the study of Åhsberg et al. (48%).[24] This result confirms the already demonstrated accuracy of CESM in assessing multifocal, multicentric and bilateral lesions.[25,26]

Out of the 128 ALs, 68 were ipsilateral while 60 contralateral, with a significantly higher malignancy rate for the ipsilateral group, similar to previous studies in literature.[27] In our study, we included females with histologically proven breast cancer which underwent pre-surgical CESM with at least one additional lesion reported on recombined images, including females with high-risk females and those who had undergone previous surgery, as in clinical practice. This sample bias may have affected the high rate of contralateral synchronous lesions.

Our SL-ultrasound performance (55.5%) was in line with literature data,[13,17] while for SL-DBT it was 61.7%, higher than that of MRI,[17] 52 and 50% respectively in the study of Clauser et al. In our opinion, this may be due to the similar spatial representation of the recombined CESM image and of the DBT image, performed both in the same CC and MLO projections, allowing for easy detection of AL correlates; previous studies have already confirmed the equivalence between imaged LE and 2DFFDM.[28,29]

SL-DBT alone showed a higher detection rate *vs* SL-ultrasound in the NME pattern on CESM (p:0.0325) and in the DCIS histologic subtype (*p*: 0.0081). These results could be explained by the fact that microcalcifications are often the imaging correlate of NME and DCIS, and subtle microcalcifications can be exceedingly difficult to detect with ultrasound.[30] The 22 ALs corresponding to microcalcifications detected on SL-DBT in our study were visible also on the previously performed FFDM and on the LE CESM images; they

Table 3. Detectability of 128 CESM additional lesions at SL-DBT and SL-ultrasound overall and according to CESM characteristics and malignant, high-risk, or benign outcome

	n	Ultrasound	DBT	Ultrasound and DBT	Ultrasound and/or DBT
Overall	128	71 (55.5%)	79 (61.7%)	53 (41.4%)	97 (75.8%)
p-value Ultrasound *vs* DBT		0.227800			*vs* Ultrasound **0.000001**
					vs DBT **0.000022**
MALIGNANT	57	39 (68.4%)	41 (71.9%)	28 (49.1%)	52 (91.2%)
p-value Ultrasound *vs* DBT		0.683091			*vs* Ultrasound **0.000311**
					vs DBT **0.000911**
Invasive ductal carcinoma	41	32 (78.0%)	27 (65.8%)	22 (53.7%)	37 (90.2%)
p-value Ultrasound *vs* DBT		0.196706			*vs* Ultrasound **0.025347**
					vs DBT **0.001565**
Invasive lobular carcinoma	5	4 (80.0%)	4 (80.0%)	3 (60.0%)	5 (100.0%)
p-value Ultrasound *vs* DBT		1.000.000			*vs* Ultrasound 0.317311
					vs DBT 0.317311
Ductal carcinoma *in situ*	11	3 (27.3%)	10 (90.9%)	3 (27.3%)	10 (90.9%)
p-value Ultrasound *vs* DBT		**0.008151**			*vs* Ultrasound **0.008151**
					vs DBT N/A
High-risk lesions (B3)	10	5 (50.0%)	9 (90.0%)	4 (40.0%)	10 (100.0%)
p-value Ultrasound *vs* DBT		0.102470			*vs* Ultrasound **0.025347**
					vs DBT 0.317311
BENIGN	61	27 (44.3%)	29 (47.5%)	21 (34.4%)	35 (57.4%)
p-value Ultrasound *vs* DBT		0.592980			*vs* Ultrasound **0.004678**
					vs DBT **0.014306**
FOCUS	25	8 (32.0%)	13 (52.0%)	5 (20.0%)	16 (64.0%)
p-value Ultrasound *vs* DBT		0.131668			*vs* Ultrasound **0.004678**
					vs DBT 0.083265
MASSES	69	49 (71.0%)	44 (63.8%)	37 (53.6%)	56 (81.2%)
p-value Ultrasound *vs* DBT		0.251349			*vs* Ultrasound **0.008151**
					vs DBT **0.000532**
Non-mass enhancement	34	14 (41.2%)	22 (64.7%)	11 (32.3%)	25 (73.5%)
p-value Ultrasound *vs* DBT		**0.032509**			*vs* Ultrasound **0.000911**
					vs DBT 0.083265
≤10 mm	82	47 (57.3%)	49 (59.8%)	34 (41.5%)	62 (75.6%)
p-value Ultrasound *vs* DBT		0.705457			*vs* Ultrasound **0.000108**
					vs DBT **0.000311**
>10 mm	46	24 (52.2%)	30 (65.2%)	19 (41.3%)	35 (76.1%)
p-value Ultrasound *vs* DBT		0.133614			*vs* Ultrasound **0.000911**
					vs DBT **0.025347**
BI-RADS 3	73	33 (45.2%)	37 (50.7%)	22 (30.1%)	48 (65.7%)
p-value Ultrasound *vs* DBT		0.432768			*vs* Ultrasound **0.000108**
					vs DBT **0.000911**

(Continued)

Table 3. (Continued)

	n	Ultrasound	DBT	Ultrasound and DBT	Ultrasound and/or DBT
BI-RADS 4	53	36 (67.9%)	40 (75.5%)	29 (54.7%)	47 (88.7%)
p-value Ultrasound *vs* DBT		0.345779			*vs* Ultrasound **0.000911**
					vs DBT **0.008151**
BI-RADS 5	2	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)
p-value Ultrasound *vs* DBT		N/A			*vs* Ultrasound N/A
					vs DBT N/A

CESM, contrast-enhanced spectral mammography; DBT, digital breast tomosynthesis; SL, second-look.

were classified as low-risk findings but since the corresponding contrast enhancement on the recombined images upgraded their level of suspicion, we decided to perform tomo-VAB.

We think that in comparison to FFDM or LE image, DBT could have played a role in more effectively assessing the spatial distribution and morphology of microcalcifications, thus increasing specificity, in a pre-surgical setting, as stated by Kuwabara et al in their study,[31] even though further studies will be necessary to confirm this hypothesis.

In terms of detectability, the addition of SL-DBT to SL-ultrasound improved the performance of SL-ultrasound alone, 75.8% *vs* 55.5% (*p*: 0.000001) in every subcategory identified, except for ILC (*p*: 0.317311); said improvement can be attributed to the presence of microcalcifications, architectural distortions and focal asymmetries in AL correlates, which can be more easily identified with DBT than with ultrasound.

The addition of SL-ultrasound to SL-DBT improved the detectability of ALs in the overall sample and in every category except for NME (*p*: 0.0833), foci (*p*: 0.0833) and B3 lesions (*p*: 0.3173). We have explained above what we believe to be the reasons for this result for NME. As regards B3 lesions, in our study, we had a histologic sample with uncertain malignant potential lesions, except for papilloma, which often manifests as microcalcifications (ADH, FEA) or architectural distortions (RS),[32] more easily detected with DBT.

Foci have always been a challenge for MRI, due to their difficult detectability with SL-ultrasound and the lack of data for their management [33]; we believe this improved performance of SL-DBT in foci management is due to the spatial overlap of CESM recombined image projection with DBT images, allowing for easier detection of imaging correlates. Moreover, the CE-MRI prone position for image acquisition is completely different from the position of the SL imaging methods, while CESM recombined images, paired with the low-energy image, are acquired in the same projections of FFDM and DBT. Furthermore, FFDM, DBT and CESM recombined images share a better spatial resolution than CE-MRI images. In the study of Clauser et al.,[17] SL-DBT performance is inferior to SL-ultrasound in the foci category in pre-surgical MRI, thus corroborating our opinion.

According to our results, combined second-look imaging (SL-DBT + SL-ultrasound) for CESM ALs in comparison to SL-DBT alone and SL-ultrasound alone allowed us to identify 91.2% of ALs that resulted malignant at final histology (+22.8% vs. SL-ultrasound alone); for the remaining 8.8% it was still necessary to perform MRI and MRI-guided biopsy.

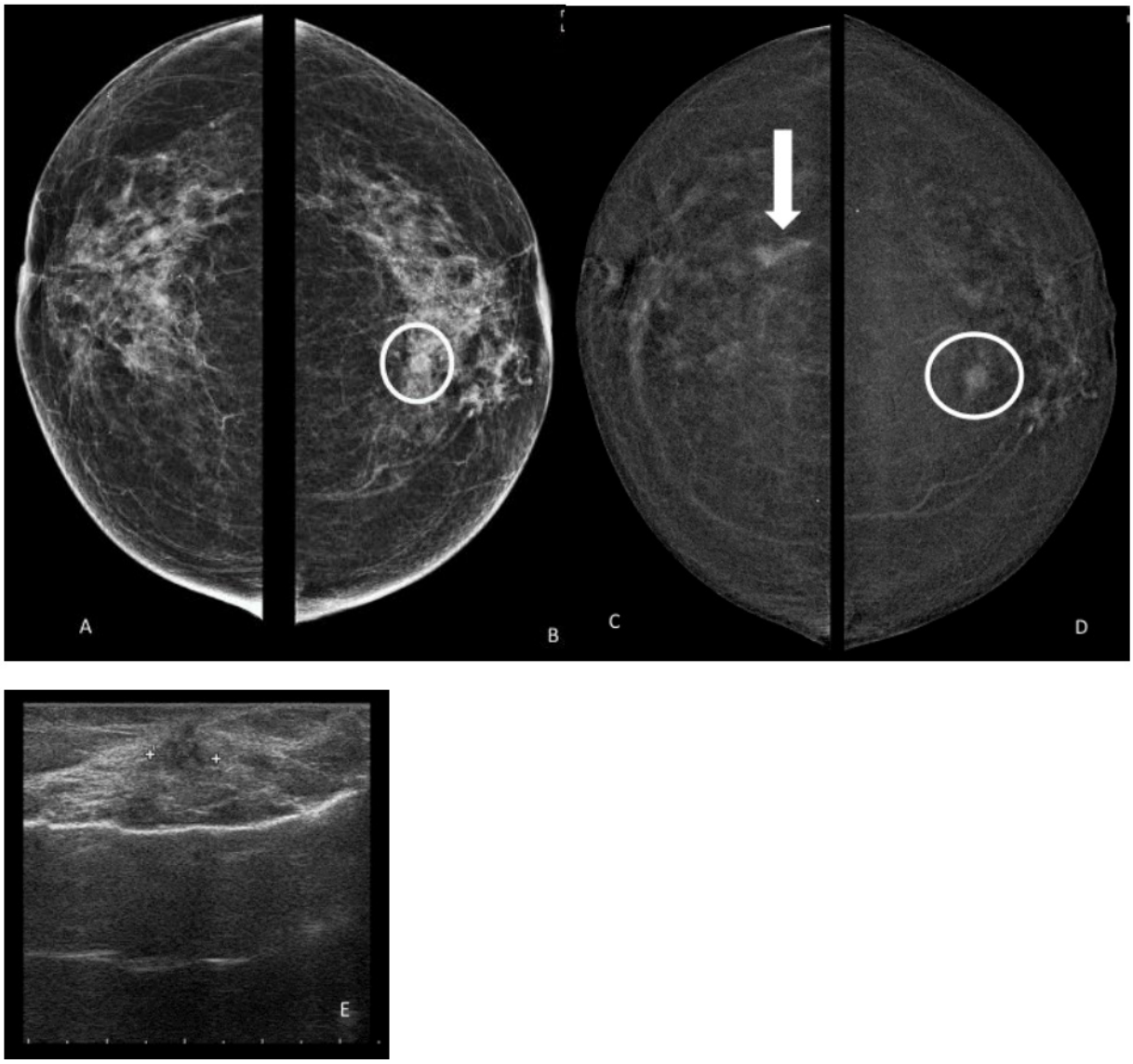
In our study, 31 (24.2%) of the 128 ALs did not have an imaging correlate with SL-ultrasound or SL-DBT. In these cases, we chose to perform CE-MRI to look for a corresponding MRI AL and when present, we performed MRI-guided biopsy. Our results showed that 57 (44.5%) ALs detected in presurgical CESM were malignant: 52 were visible with SL-ultrasound and/or SL-DBT and 5 (8.8%) not visible. The undetected malignant ALs were one DCIS, two G1 IDC, one G2 IDC, and one G3 IDC.

In 4 out of these 5 cases we performed MRI-guided biopsy and in the other case, CESM AL was ipsilateral to the index lesion with an intralesional distance of <10 mm, which was subjected to surgical excision with histologic confirmation of malignancy. As confirmed for these five ALs, it seems evident that a CESM-guided biopsy approach could be extremely helpful in cases of ALs with negative SL. CESM-guided biopsies, still awaiting FDA approval, share the same approach as the stereotactic/tomo-guided biopsy with the additional injection of intravenous iodinated contrast medium 2 min before starting the procedure. Compared with the MRI-guided biopsy, the CESM-guided approach could be faster and more feasible.

This study has several limitations. Firstly, the readers knew the site and the histology of the index lesion before evaluating the CESM images, but this is usual in clinical practice. Secondly, CESM image evaluation was performed in consensus, so it was not possible to evaluate inter-reader reliability with Cohen's κ test. Other limitations included the retrospective nature of the study, its limited sample and the inclusion of high-risk females and those who had undergone previous surgery.

In conclusion, our study has shown that combined second-look imaging (SL-DBT + SL-ultrasound) for CESM ALs is superior to both SL-DBT and SL-ultrasound alone, since it allowed us to identify more than 90% of additional malignant lesions. In B3 lesions, NME, and foci, the analysis of a larger sample could determine whether adding SL-ultrasound to SL-DBT is necessary

Figure 2. An irregular mass with spiculated margins in the upper-central quadrant of the left breast (A, white circle) was found in a 67-year-old female with mammography screening (A: right CC FFDM; B: left CC FFDM). An ultrasound-guided core biopsy of this lesion was performed, and the pathological diagnosis was ILC. The patient underwent both bilateral DBT and presurgical CESM (C: right RC CC image; d: left RC CC image). CESM confirmed the index lesion (D, white circle), and identified an AL in the outer quadrants of the right breast (C, arrow). On SL-DBT no correlate for the contralateral AL was found (images not shown); with SL-ultrasound (E) an irregular hypoechoic, ill-defined nodule was found and subjected to ultrasound-guided biopsy and the result was another ILC. At surgery, the diagnosis was bilateral invasive lobular carcinoma. AL, arterial lesion; CC, craniocaudal; CESM, contrast-enhanced spectral mammography; DBT, digital breast tomosynthesis; FFDM, full-field digital mammography; ILC, invasive lobular carcinoma; SL-second-look.

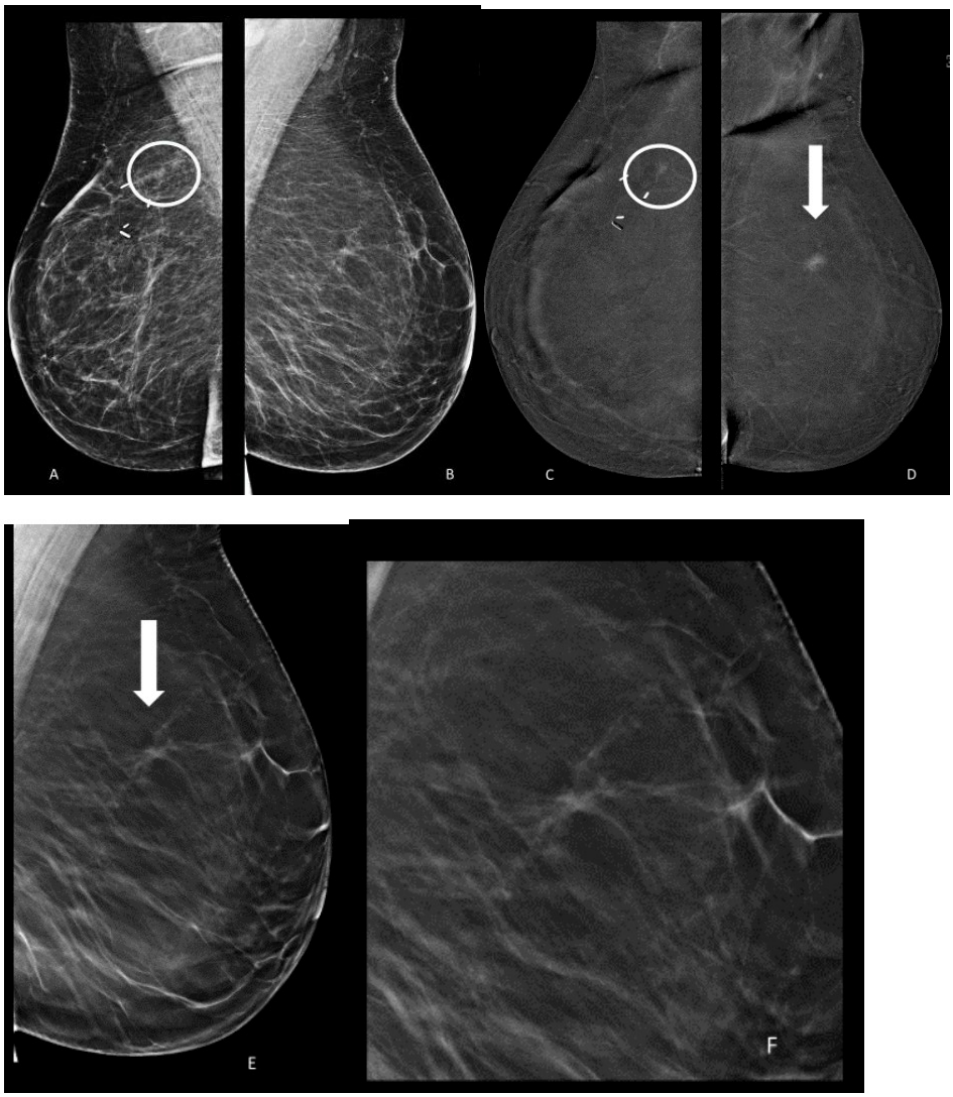


or not. CESM-guided biopsy systems might be a useful tool in cases where the second look is negative.

KEY RESULTS

(1) Combined second-look imaging (SL-DBT + SL-ultrasound) for CESM ALs is superior in terms of detectability to SL-DBT alone and SL-ultrasound alone.
(2) SL-DBT alone proved to be significantly better in terms of detectability *vs* SL-ultrasound alone in the DCIS histological type and NME category.
(3) When considering the type of enhancement of CESM ALs, SL-DBT + SL-ultrasound improved the detectability *vs* SL-ultrasound alone and SL-DBT alone in the mass category, while it also proved more effective than SL-ultrasound alone in the NME and focus categories.

Figure 3. 62-year-old female under annual surveillance (A: right MLO FFDM; B: left MLO FFDM), after a previous QUART, was diagnosed with an IDC in the upper-outer quadrant of the right breast (A, white circle) and underwent CESM as presurgical staging (C: right MLO RC image; D: left MLO RC image). The index lesion was confirmed (C, white circle), but an AL with strong enhancement was found in the upper-outer quadrant of the left breast (D, arrow). SL-ultrasound was negative (images not shown). With SL-DBT (E), an architectural distortion was found in the site of the AL (E, arrow), more visible under magnification (F), subjected to tomo-guided biopsy, the result was another IDC. At surgery, the diagnosis was bilateral IDC. AL, arterial lesion; CESM, contrast-enhanced spectral mammography; DBT, digital breast tomosynthesis; FFDM, full-field digital mammography; IDC, invasive ductal carcinoma; MLO, mediolaterial oblique; SL-second-look.IDC.



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