Contrast-Enhanced Spectral Mammography in Women With Intermediate Breast Cancer Risk and Dense Breasts

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OBJECTIVE. The purpose of this study was to compare the diagnostic performance of contrast-enhanced spectral mammography (CESM) and ultrasound with that of standard digital mammography for breast cancer screening of women at intermediate risk who have dense breasts.

MATERIALS AND METHODS. In a retrospective cohort of 611 consecutively registered women who underwent screening CESM from 2012 to 2017, BI-RADS scores of the screening modalities were compared with actual disease status, assessed by histopathologic analysis or imaging follow-up. Sensitivity, specificity, and positive and negative predictive values were calculated.

RESULTS. Among the 611 women included, 48.3% (295/611) had family or personal history of breast cancer, the BI-RADS breast density score was C or D in 93.1% (569/611). The mean follow-up period was 20 months. Mammography depicted 11 of 21 malignancies, sensitivity of 52.4%, specificity of 90.5% (534/590), positive predictive value of 16.4% (11/67), and negative predictive value of 98.2% (534/544). CESM depicted 19 of 21 malignancies, sensitivity of 90.5%, specificity of 76.1% (449/590), positive predictive value of 11.9% (19/160), and negative predictive value of 99.6% (449/451). Differences in sensitivity ($p = 0.008$) and specificity ($p < 0.001$) were statistically significant. Adjunct ultrasound revealed 73 additional suspicious findings; all were false-positive. In 39 women MRI was needed to assess screening abnormalities; two MRI-guided biopsies were performed and yielded one cancer. The incremental cancer detection rate of CESM was 13.1/1000 women (95% CI, 6.1–20.1). Of eight cancers seen only with CESM, seven were invasive (mean size, 9 mm; two of four cancers lymph-node positive).

CONCLUSION. CESM was significantly more sensitive than standard digital mammography for detecting breast cancer in this screening population. No added benefit was found in the performance of ultrasound as an adjunct to CESM screens with negative results. CESM may be a valuable supplemental screening modality for women at intermediate risk who have dense breasts.

Keywords: breast, breast cancer, contrast media, mammography, screening

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Mammography is currently the only imaging modality approved for breast cancer screening [1, 2]. However, standard 2D digital mammography has limitations, particularly for women with dense breast tissue, among whom the sensitivity can be as low as 50–60% [3–7]. Supplemental breast cancer screening with additional imaging modalities has been proposed for improving breast cancer detection. The most widely offered supplemental modality is whole-breast ultrasound (US), whereas MRI is recommended for women at high risk. Breast imaging technologies for supplemental screening have been developed and implemented for everyday use; among those is contrast-enhanced spectral mammography (CESM) [8].

CESM provides anatomic and functional imaging of breast tissue by combining standard 2D digital mammography with IV injection of an iodine-based contrast agent [9–11]. Several studies have shown that CESM has diagnostic accuracy superior to that of standard 2D digital mammography [11–16]. However, all of these studies were performed with small patient groups and with high prevalence of breast cancer (28–100%) [14]. There are limited data on the role of CESM as a screening examination.

Our hypothesis was that CESM is an efficient imaging tool for breast cancer screening of women at intermediate risk. The purpose of this retrospective study was to evaluate the performance of CESM as a supplemental

screening imaging method, compare it with standard 2D digital mammography, and assess the added value of US as an adjunct to CESM.

Materials and Methods

Study Design and Participant Population

This retrospective cohort study was approved by the hospital institutional review board with a waiver of the requirement for informed consent. Women with dense breasts or at intermediate risk of breast cancer who are referred to our institution (Chaim Sheba Medical Center) for breast cancer screening are routinely offered CESM after a thorough explanation of its benefits and risks. Contraindications are known allergy to iodine, abnormal renal function, pregnancy, and lactation. Each woman completes a questionnaire regarding breast cancer risk factors, known allergy to contrast material, and impaired renal function. The questionnaire also includes an area for signing agreement to contrast agent injection. Breast cancer risk was based on data obtained from these questionnaires, each woman's medical records, and prior breast imaging reports. According to the American College of Radiology, intermediate breast cancer risk was defined as 15–20% lifetime risk and included women with a personal history of breast cancer, those with a previous biopsy showing lobular carcinoma in situ or atypical ductal or lobular hyperplasia, women with dense breasts, and those with a family history of breast cancer [17–19]. All CESM examinations were performed free of additional charge to the patients.

Study participants included asymptomatic women presenting at our institution for routine screening mammography during the study period who underwent screening CESM. We excluded women younger than 40 years and women who underwent CESM for indications other than screening. We also excluded all patients with negative CESM screens who participated in less than 12 months of follow-up.

Among 1406 consecutively registered women who underwent screening CESM at our institution between May 2012 and January 2017, 611 individuals had either undergone biopsy or had sufficient imaging follow-up to substantiate a reference benchmark for the CESM interpretation (Fig. 1).

Reference Standard

For suspicious CESM screens (BI-RADS category 4 or 5), we defined the reference standard as the results from the histopathologic analysis. For benign CESM screens (BI-RADS 1–3) the reference standard was defined as at least 12 months of imaging follow-up or earlier detection of cancer. At our institution we recommend annual breast cancer screening. Most women enrolled in our screening program undergo routine annual or biennial mammographic screening.

According to the 5th edition of the BI-RADS atlas, the accepted definition of true disease status is the presence or absence of a breast cancer diagnosis within the time period recommended for routine screening. We used that definition in our study and defined cancers detected during the first year (365 days) of follow-up of each patient as cancers missed (false-negative) at the initial screening.

Most (520/611 [85.1%]) of the women in the study had prior 2D mammograms or US images available. All women were included in the cohort at their first CESM examination, and therefore, none had prior CESM images. Each woman in the analysis was represented once regardless of the number of subsequent CESM examinations she underwent. Although some women had undergone CESM during their follow-up, these examinations were used merely as a reference benchmark for negative screening results. No analysis was performed for subsequent second or third rounds of CESM screening. The imaging follow-up in this study constituted subsequent imaging screens the participants underwent as part of their routine screening program, comprised at least one examination: standard 2D digital mammography, CESM, breast US, or breast MRI. None of the women included in the study underwent tomosynthesis imaging during the study period.

Imaging Technique

All CESM studies were performed with a digital mammography system (Senographe Essential, GE Healthcare) upgraded to enable acquisition of dual-energy exposures. A nonionic contrast agent (iopamidol, Iopamiro 370, Bracco) was injected IV (1.5 mL/kg bodyweight; flow rate, 3 mL/s, followed by a saline flush) through an automated power injector (Medrad Mark V ProVis, Bayer HealthCare). Image acquisition began with a 2-minute delay after contrast injection and was completed within 7–8 minutes after initiation of contrast administration. Standard craniocaudal and mediolateral oblique projections of each breast were acquired. The sequence for screening CESM image acquisition was as follows: right craniocaudal, left craniocaudal, right mediolateral oblique, left mediolateral oblique. The low-energy exposures were acquired at 26–31 kVp. High-energy images were acquired at 33.2 kV, just above the peak kilovoltage threshold of iodine. An image-processing software algorithm was used to subtract the two exposures to generate two images. The first was a low-energy image with maximum soft-tissue contrast that was analogous to a standard 2D digital mammogram [20]. The second image was a subtracted image displaying areas of contrast enhancement. This technology is described in further detail elsewhere [9, 11].

US was performed with an Acuson S2000 system with a linear transducer 14–5 MHz or 18–6 MHz (Siemens Healthcare). All examinations were hand held US performed by a physician and reported according to BI-RADS category assessment criteria [21].

Imaging Interpretation and Reports

Patient information, including demographic and clinical data, was obtained from our institution's electronic medical records. We retrospectively re-

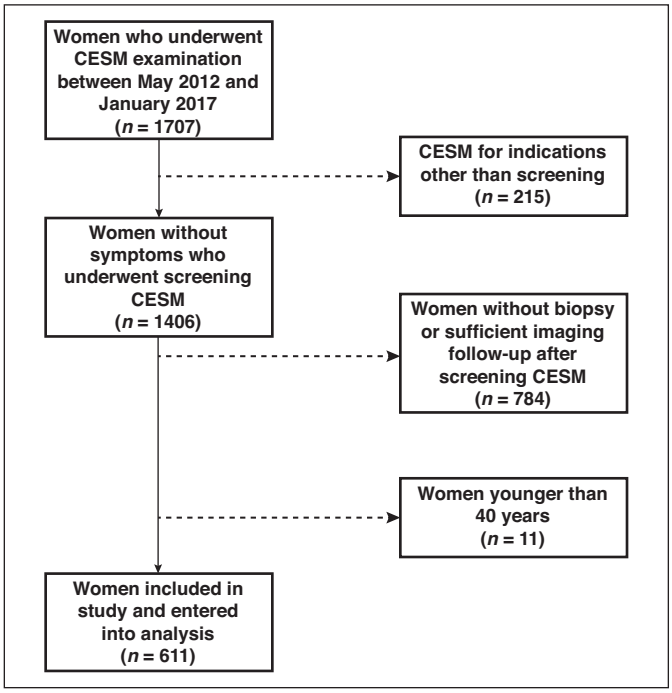

Fig. 1—Patient flow diagram. CESM = contrast-enhanced spectral mammography.

viewed the reports of CESM, US, and MRI. All examinations were reported in a standard manner according to BI-RADS [21]. We considered low-energy images to be analogous to standard 2D digital mammograms on the basis of 2014 findings by Francescone et al. [20]. None of the women in the current study underwent standard mammography in addition to CESM at the time of screening. In all cases, the low-energy images were regarded as the standard 2D mammography [20].

At our institution, CESM images are interpreted by five dedicated breast imaging radiologists with 2–4 years of experience in reading CESM. A CESM report includes an initial BI-RADS score for the low-energy images alone and another final BI-RADS score that includes the findings on both the low-energy and the subtracted images. Women with dense breasts are routinely screened with whole-breast US as an adjunct to standard 2D mammography [22, 23] performed by the same radiologist who interpreted the mammograms. In addition, regardless of breast density, whenever a suspicious focal finding is detected at mammography, targeted US is performed for further evaluation. MRI examinations are performed for inconclusive findings of the screening examinations and are interpreted by the same radiologist for comprehensive correlation with the other modalities.

Management of Suspicious Lesions

Whenever a suspicious lesion (BI-RADS 4 or 5) was detected on low-energy images, either mammographically guided stereotactic vacuum-assisted biopsy or US-guided biopsy was performed. In cases in which the low-energy images showed no correlate with the enhancement on CESM but a lesion was detected in correlation at adjunct US, US-guided biopsy was performed. When no correlate was found with either 2D mammography or US, MRI was performed, MRI-guided biopsy was performed when a lesion was detected. The size of invasive cancers was obtained from the pathologic specimen when surgery was performed and from imaging of individuals who did not undergo surgery or who did not have pathologic results available.

Statistical Analysis

We considered BI-RADS categories 1 and 2 to be negative screening results and BI-RADS categories 3, 4, 5, and 0 to be positive screening results [24]. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were calculated for standard 2D mammography (low-energy images), CESM (both low-energy and subtracted images), and CESM combined with US.

Differences in diagnostic parameters between the modalities were tested for statistical significance by McNemar test for paired proportions. ROC curves were constructed for the imaging modalities with the following ordering of the BI-RADS categories, as proposed by Barlow et al. [25] to obtain an ordinal scale: 1, 2, 3, 0, 4, and 5. AUCs with corresponding 95% CIs were calculated [26]. Association between background parenchymal enhancement (BPE) and false-positive CESM examination findings was tested by chi-square test. All statistical analysis was performed with SPSS Statistics software (version 22, IBM). A value of $p \leq 0.05$ in a two-sided test was considered statistically significant. Results were reported according to Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines [27, 28].

Results

Demographic Information

A total of 611 women (mean age, 54 years; median, 52 years; range, 40–84 years) were included in the analysis. Among the 611, 295 (48.3%) had a family or personal history of breast cancer, 569 (93.1%) had breast density BI-RADS classification C or D, and 274 (44.8%) had both (Table 1). Three patients had mild nonspecific pruritus and rash that were treated with oral antihistamines and resolved immediately. Otherwise, no clinically significant adverse reactions to the contrast agent were noted.

Screening Results

Most of the CESM screens (454/611 [74.3%]) were graded BI-RADS 1 or 2, followed by 48/611 screens (7.8%) graded BI-RADS 3 and 64/611 (10.5%) screens graded BI-RADS 4 or 5. There were 45 (7.4%) CESM screens graded BI-RADS 0, and of those, 16 were upgraded to BI-RADS 4 at US and were biopsied. The other 29 were downgraded to BI-RADS 3, and the patients underwent MRI and imaging follow-up. Among the BI-RADS 0 screens, no cancers were detected at either biopsy or follow-up. Fourteen of 48 BI-RADS 3 CESM screens were upgraded to BI-RADS 4 at US; all lesions were biopsied and confirmed benign. All other patients had undergone 6-month follow-up imaging before returning to routine annual or biennial screening. At follow-up, eight of them underwent biopsy, and all biopsy results were benign.

Most (575/611 [94.1%]) of the women in the study underwent breast US examinations as an adjunct to CESM. Among them 157 underwent targeted US to assess abnormalities found at CESM, and 418 underwent whole-breast US. Adjunct US increased the number of positive screens from 160 to 233 and the number of women needing biopsy from 80 to 134. All 54 additional biopsies were confirmed benign at histopathologic analysis.

MRI was performed for 53 of 611 women (8.7%). Six of these women underwent MRI after a malignant finding at breast biopsy for evaluation of disease extent. Eight underwent MRI after normal CESM findings but negative biopsy results (to definitively rule out a malignant lesion). Eleven women had enhancing lesions on CESM with no sonographic correlate and were referred to MRI. Two of the 11 underwent MRI-guided biopsy

TABLE 1: Patient Characteristics (*n* = 611)

Characteristic	Value	%
Age (y)		
Mean	54	
Median	52	
Range	40–84	
Cancer history		
Personal history of breast cancer	95	15.5
Family history of breast cancer	160	26.2
Family and personal history of breast cancer	40	6.5
Neither personal nor family history of breast cancer	316	51.7
BI-RADS breast density		
A	3	0.5
B	39	6.4
C	543	88.9
D	26	4.2

Note—Except for age, values are numbers of patients.

(one lesion was malignant ductal carcinoma in situ [DCIS]). The other nine underwent imaging follow-up. One of the nine had DCIS detected after 8 months at standard follow-up mammography and was considered false-negative; the others had benign follow-up imaging for at least 12 months. Twenty-eight women had inconclusive screening interpretations because BPE showed nonspecific enhancing foci or because of nonspecific postoperative changes. All inconclusive CESM lesions evaluated with MRI were ultimately benign at follow-up.

One hundred thirty-four biopsies in 132 women were performed and 19 malignant lesions were detected.

The histopathologic results are detailed in Table 2.

TABLE 2: Biopsies Performed After Initial Screening Examinations (*n* = 134)

Final Diagnosis	No.[a]	%
Benign		
Fibrocystic changes	43 (9)	32.1
Fibroadenoma	33 (18)	24.6
Adenosis	12 (4)	9.0
Ductal hyperplasia	10 (3)	7.5
Inflammatory changes	6 (1)	4.5
Papilloma	3 (1)	2.2
Scar	2 (2)	1.5
Lymph node	2	1.5
Fibrosis	1	0.7
Apocrine metaplasia	1	0.7
Postradiation changes	1	0.7
Breast tissue	1 (1)	0.7
Malignant		0
Invasive ductal carcinoma	14 (7)	10.4
Ductal carcinoma in situ[b]	4 (1)	3.0
Invasive lobular carcinoma	1	0.7

Note—Histopathologic diagnosis from biopsies performed because of abnormalities seen at one or more of the initial screening examinations. Data do not include biopsies performed during the follow-up period. Percentages do not total 100 owing to rounding.

[a]Values in parentheses are numbers of biopsies prompted by contrast-enhanced spectral mammography findings of suspicious lesions (i.e., enhancements) not appearing as suspicious on 2D mammograms.

[b]Two additional cancers, both ductal carcinoma in situ, were detected within 12 months of follow-up.

Follow-Up

Most of the women (537/611 [87.9%]) underwent follow-up comprising subsequent imaging screens that were part of the routine screening program. The mean follow-up time was 20 (SD, 7) months (median, 18 months; range, 8–52 months). Details regarding the length of follow-up and imaging examinations are shown in Table S1. (Tables S1 and S2 can be viewed in the *AJR* electronic supplement to this article, available at www.ajronline.org.) During the follow-up period two DCIS cancers were detected. Both appeared as new microcalcifications at standard 2D mammography performed 8 months (follow-up mammography) and 12 months (screening mammography) after the initial screening and were considered false-negative screens.

Cancer Detection

Ultimately 21 of 611 (3.4%) breast cancers were considered present at the initial CESM screening; 19 of them were detected at screening, and two were detected during follow-up. Among the 21 cancers were 14 invasive ductal carcinomas (IDCs), six DCIS, and one invasive lobular carcinoma (Table 2). The mean size of the longest diameter of the invasive component was 11.8 mm (range, 4–25 mm). Detailed characteristics of the invasive cancers are available in Table S2.

Eleven (52.4%) of the 21 cancers were detected with 2D mammography; four of these cancers appeared as microcalcifications. Three were DCIS, and one was IDC plus DCIS. Another DCIS was detected as an area of enhancement at CESM. CESM (i.e., low-energy plus subtracted contrast images) depicted 19 of 21 (90.5%) cancers. Of the eight cancers seen with CESM but not 2D mammography, seven were invasive with a mean size of 9 mm (range, 4–25 mm). The incremental cancer detection rate for CESM was 13.1 per 1000 women (95% CI, 6.1–20.1) in a single prevalence screen. Figure 2 shows an example of a positive CESM examination of one patient.

Background Parenchymal Enhancement

Among the 611 CESM examinations, 279 (45.7%) showed BPE. We found BPE to be positively associated with false-positive CESM results: BPE positive, 100 of 279 (35.8%) false-positive CESM results; BPE negative, 41 of 332 (12.3%) false-positive CESM results ($p < 0.001$).

Sensitivity, Specificity, and AUC

The diagnostic parameters of standard 2D digital mammography, CESM, and CESM with adjunct US are shown in Table 3. Differences in sensitivity ($p = 0.008$) and specificity ($p < 0.001$) between 2D mammography and CESM were statistically significant. The difference in specificity between CESM and CESM with US was also statistically significant ($p < 0.001$). ROC curve analysis (Fig. 3) of the imaging techniques showed AUC values ranging from 0.768 and 0.924 ($p < 0.001$). CESM had a larger AUC than standard mammography alone. The addition of US after CESM had a lower AUC than did CESM (Table 3).

Discussion

CESM has the unique capability of combining anatomic and functional data, revealing underlying masses and architectural distortions that are difficult to interpret at standard 2D mammography due to overlapping breast glandular tissue [9]. Because CESM is a newer imaging technique, there are insufficient data regarding the proper indications for it. Suggested indications include those currently accepted for MRI, as both techniques are based on the same principle of vascular enhancement, providing functional information [9, 29–31]. However, the role of CESM in screening remains controversial.

In this study, CESM was found to be significantly more sensitive for detecting breast cancer than was standard 2D digital mammography (90.5% vs 52.4%, $p = 0.008$). Furthermore, the high NPV and good nega-

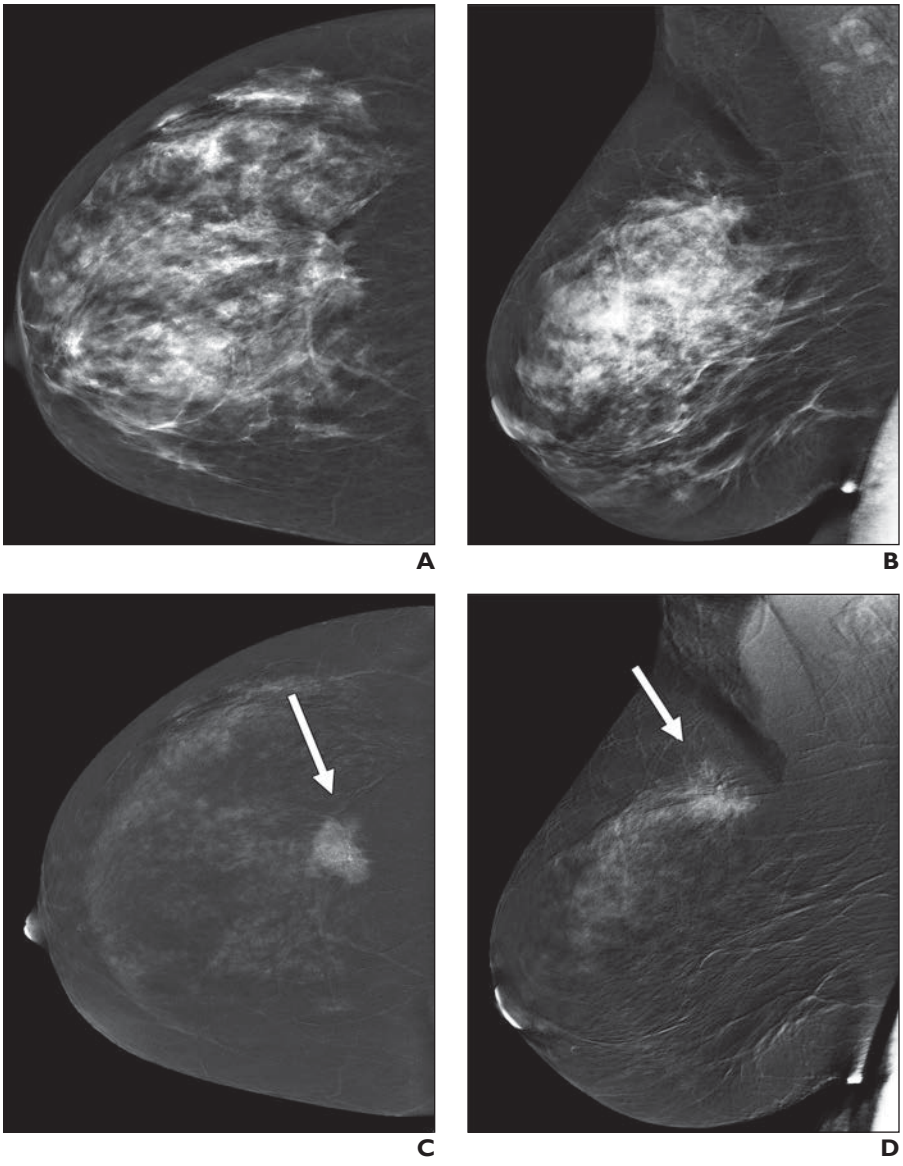

Fig. 2—51-year-old woman undergoing contrast-enhanced spectral mammography (CESM) for breast cancer screening because of dense breast tissue.
A and **B,** Right craniocaudal (**A**) and mediolateral oblique (**B**) low-energy images show no suspicious findings.
C and **D,** Right craniocaudal (**C**) and mediolateral oblique (**D**) subtracted CESM images show enhancing mass (*arrow*), which proved to be 25-mm grade 2 invasive ductal carcinoma and ductal carcinoma in situ, estrogen and progesterone receptor positive with one metastatic axillary node.

TABLE 3: Performance Characteristics of Screening Modalities

Modality	Total No. of Screens	No. of Abnormal Screens	No. of Cancers Detected	Sensitivity (%)[a]	PPV (%)[a]	Specificity (%)[a]	NPV (%)[a]	PLR	NLR	AUC[b]
Standard 2D digital mammography	611	67	11	52.4 (11/21)	16.4 (11/67)	90.5 (534/590)	98.2 (534/544)	5.53	0.52	0.768 (0.639–0.897)
Contrast-enhanced spectral mammography	611	160	19	90.5 (19/21)	11.9 (19/160)	76.1 (449/590)	99.6 (449/451)	3.79	0.12	0.924 (0.856–0.992)
Contrast-enhanced spectral mammography with adjunct ultrasound	575	233	19	90.5 (19/21)	8.1 (19/233)	61.4 (340/554)	99.4 (340/342)	2.34	0.15	0.889 (0.804–0.974)

Note—PPV = positive predictive value, NPV = negative predictive value, PLR = positive likelihood ratio, NLR = negative likelihood ratio.
[a]Values in parentheses are raw numbers used to calculate percentage.
[b]Values in parentheses are 95% CIs.

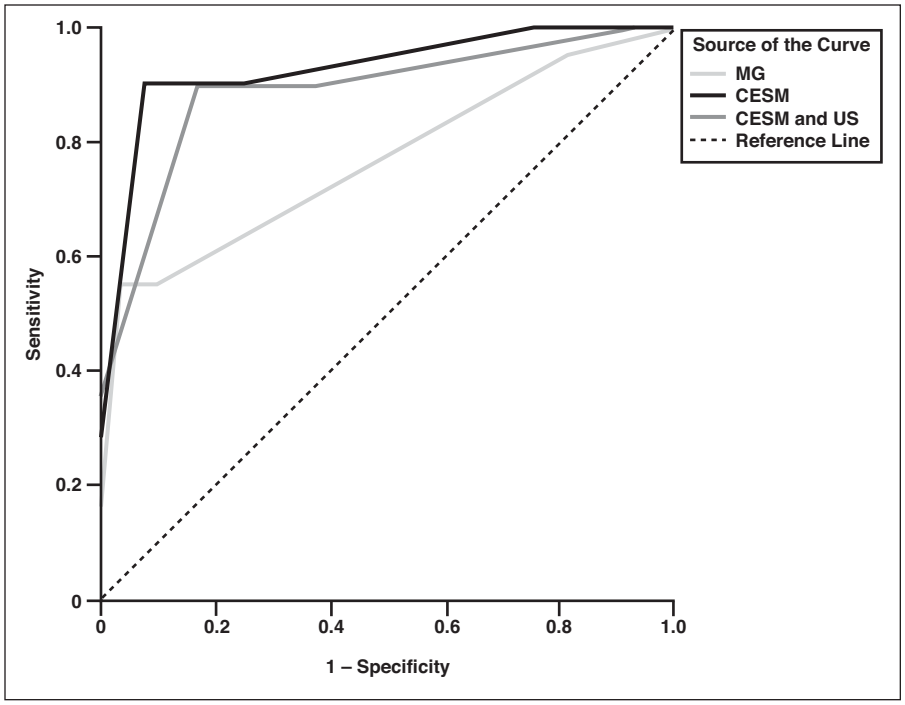

Fig. 3—ROC curve shows largest AUC for contrast-enhanced spectral mammography (CESM). MG = standard 2D digital mammography, US = ultrasound.

tive likelihood ratio of CESM indicate that it is a suitable examination for ruling out a breast cancer diagnosis. This may prove advantageous if applied to the analysis of inconclusive findings of standard 2D digital mammography [32, 33]. Our results are similar to those reported in previous studies that also showed higher diagnostic accuracy of CESM than of standard 2D mammography alone and of mammography combined with US. However, the previously published studies were conducted in populations with high prevalence of breast cancer and evaluated CESM as a diagnostic but not as a screening tool [14]. In the literature there is a consensus that breast US is a valuable adjunct to 2D mammography in the characterization of breast lesions, showing high sensitivity at a variable but generally moderate specificity [34]. We found that CESM had significantly lower specificity than standard 2D mammography (76.1% vs 90.5%, $p < 0.001$) and, consequently, increased false-positive findings and recall rate. These further increased with the addition of adjunct US, which caused even lower specificity (61.4% vs 76.1%, $p < 0.001$) without depicting additional cancers not seen with CESM. We conclude that there is no benefit in the performance of whole-breast US as an adjunct to negative CESM screens.

In this study CESM increased cancer detection rate beyond that of mammography with an incremental cancer detection rate of 13.1 per 1000 screens, higher than was reported for supplemental whole-breast US. The reported rate for supplemental US in cohorts with elevated breast cancer risk is 3.7 per 1000 screens [22], whereas in cohorts of women with dense breasts, the rate is 1.7–7.7 per 1000 screens [34–37]. Because in the current study US examinations were performed after CESM interpretation by the same radiologist, we were unable to compare the performance of US as an adjunct to standard mammography with CESM. Head-to-head evaluations of CESM with US and other supplemental screening modalities in the same population of women are essential to directly compare the strengths and weaknesses of each modality and establish the most appropriate screening workup for women with dense breasts.

Four cancers (three DCIS, one IDC plus DCIS) were detected on low-energy images as microcalcifications (DCIS), and another DCIS was detected only as an area of enhancement at CESM. The advantage of the CESM technique is that it depicts microcalcifications on low-energy images in addition to nonmass enhancement on recombined images, allowing identification of DCIS even when microcalcifications are not seen.

Compared with standard 2D digital mammography, CESM has limitations. These include a variable 20–70% increase in radiation dose depending on the mammography vendor [11, 38], limited image interpretation experience of reading radiologists, and slightly higher costs. It also requires IV administration of an iodine contrast agent. Another important disadvantage is the unavailability of CESM-guided interventions, such as biopsies. However, CESM is an overall feasible test for clinical screening and is less expensive than MRI. It also takes less time to perform and for interpretation by a radiologist (only eight images). It is generally well tolerated by patients, who have a higher overall preference for CESM over MRI [39, 40].

Limitations

A major limitation of the current study was that the same radiologist interpreted both the low-energy images and the entire CESM examination without blinding. Potentially, reinterpretation of standard mammography after evaluation of the contrast-enhanced images could occur, increasing findings on the low-energy images that would otherwise be missed. However, this could only work to the benefit of standard 2D mammography because CESM was graded on the basis of both images.

Another limitation was that only the reports were evaluated, not the images themselves. Furthermore, mammograms were single read, as opposed to the double reading used in some centers worldwide. Although several studies have shown double reading to increase cancer detection rate, others have questioned the cost-effectiveness of double reading and described a potential increase in false-positive findings [41]. At our institution, the common practice for screening mammography interpretation is single reading of mammograms. The design of the study was retrospective with the aim of evaluating the true clinical experience with contrast mammography as a screening tool for individuals at intermediate breast cancer risk at our institution. Therefore, we chose to record the results as reported by the interpreting radiologists.

The study had several other limitations. First, it was retrospective, so not all confounders could be accounted for or measured. Second, among the invasive cancers detected, there was a rather low percentage of node-negative cancers (three of nine with staging). Third, breast density was based on subjective assessment; breast density analysis with an automated system would have

been more accurate and reliable. Finally, the reference benchmark used to confirm negative CESM screening results was follow-up imaging subjective analyses as opposed to positive results in which objective histopathologic analyses were used.

Conclusion

CESM was significantly more sensitive than standard digital mammography for detection of breast cancer in the screening population of this study, composed of women with personal or family history of breast cancer and women with dense breasts. No added benefit was found in the performance of US as an adjunct to negative CESM screens. Our findings suggest the potential of CESM as a supplemental screening imaging modality for women at intermediate breast cancer risk and women with dense breasts.

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