Comparison of the Mammography, Contrast-Enhanced Spectral Mammography and Ultrasonography in a Group of 116 patients

ELZBIETA LUCZYŃSKA[1], SYLWIA HEINZE[1], AGNIESZKA ADAMCZYK[2], JANUSZ RYS[3], JERZY W. MITUS[4] and EDWARD HENDRICK[5]

Departments of [1]Radiology, [2]Radiobiology, [3]Patomorphology and [4]Surgical Oncology, Center of Oncology, Cracow Branch, Cracow, Poland; [5]Radiology Dept., University of Colorado-Denver, School of Medicine, Aurora, CO, U.S.A.

Abstract. *Mammography (MG) is the gold-standard in breast cancer detection – the only method documented to reduce breast cancer mortality. Breast ultrasound (US) has been shown to increase sensitivity to breast cancers in screening women with dense breasts. Contrast-enhanced spectral mammography (CESM) is a novel technique intensively developed in the last few years. The goal of this study was to compare the sensitivity, specificity and accuracy of MG, US and CESM in detecting malignant breast lesions. The study included 116 patients. All patients were symptomatic and underwent MG, US and CESM. A radiologist with 20 years of experience in US and MG breast imaging and 1 year of experience in CESM reviewed images acquired in each of the three modalities separately, within an interval of 14-30 days. All identified lesions were confirmed at core biopsy. BI-RADS classifications on US, MG and CESM were compared to histopathology. MG, CESM and US were compared among 116 patients with 137 lesions encountered. Sensitivity of CESM was 100%, significantly higher than that of MG (90%, p<0.004) or US (92%, p<0.01). CESM accuracy was 78%, also higher than MG (69%, p<0.004) and US (70%, p=0.03). There was no statistically significant difference between AUCs for CESM and US (both 0.83). The AUCs of both US and CESM, however, were significantly larger than that of MG (p<0.0004 for each). CESM permitted better detection of malignant lesions than both MG and US, read individually. CESM found lesion enhancement in some benign lesions, as well, yielding a rate of false-positive diagnoses similar to that of MG and US.*

Correspondence to: Sylwia Heinze, Department of Radiology, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Krakow Branch, Poland. Tel: +48 124231055, e-mail: sylwia.heinze-paluchowska@ifj.edu.pl

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Mammography (MG) is called the „gold standard" in breast cancer detection; the only method documented to reduce breast cancer mortality (1). MG has been established as the primary method of screening for breast cancer. 35-45% of non-palpable invasive breast cancers are detected based only on microcalcifications visualized by MG (2). Sensitivity and specificity of MG depend on breast density: the more fibroglandular the breast is, the more difficult cancers are to detect. According to data from the Breast Cancer Surveillance Consortium (BCSC), the sensitivity of screening mammography in women with extremely dense breasts is only 63%, compared to 87% in women with fatty breast tissue (3). Specificity in women with dense breasts is 89%, compared to 96.9% in women with fatty breasts (4, 5).

Breast ultrasound (US) has been shown to increase sensitivity to breast cancer in screening women with dense breasts (6). The development of high-resolution ultrasound probes and harmonic imaging has improved image quality, increasing the diagnostic utility of breast US compared to conventional ultrasound techniques. Currently, US is useful not only in distinguishing between solid lesions and cysts, but also in enabling proper diagnosis of breast cancer (7-9).

US is also useful in younger women with dense breast tissue, high-risk women, and even in patients without symptoms. Indications for ultrasonography include examination of palpable masses incompletely evaluated with MG, masses with associated mammographic asymmetries, and in cases with a lack of findings in MG.

Contrast-enhanced spectral mammography (CESM) is a novel technique intensively developed in the last few years and accepted by the FDA for clinical use in the U.S. in 2011. This method, like MRI, is based on imaging of tumor neoangiogenesis by use of a contrast agent (10-13). CESM uses a chelated iodine-base x-ray contrast agent, while MRI uses a chelated gadolinium-based paramagnetic agent (14, 15). Because of high sensitivity of CESM (similar to sensitivity of MRI) this technique may be comparable with

MRI in some cases. The advantage of this method is possibility CESM enables accurate preoperative cancer staging (it shows more lesions than MG and US and enables visualization of intraductal component) (16).

CESM, like other diagnostic methods, has its limitations. Benign lesions enhance on CESM, just as they do on MRI. Limitation of CESM is lack of ability to generate a time-enhancement curve. In contrast-enhanced breast MRI, the shape of the time-enhancement curve is correlated with degree of cancer suspicion, which can reduce the number of unnecessary surgical procedures in some patients. Another limitation of this imaging technique is the lack of possibility to perform the CESM-guided biopsy, although it is being developed.

CESM has a 20% higher radiation dose than screening MG, what is important especially in patients with BRCA 1 and 2 mutations, where radiation exposure must be limited (17). Nevertheless, CESM is well tolerated by patients, because of faster procedure time, higher comfort and lower noise levels compared with MRI. The goal of this study was to compare the sensitivity, specificity and accuracy of MG, US and CESM in detecting malignant breast lesions.

Patients and Methods

This prospective study was accepted by an Ethics Committee and all enrolled patients provided written informed consent. The 116 subjects included in this study were diagnosed and treated between September 2011 and November 2012. The average age of subjects was 55±12 years. All subjects were symptomatic and underwent MG, US and CESM. Eight subjects 35 years of age and younger underwent US as their first examination; the remaining 108 subjects had MG as their first examination. Because of the suspicion of breast cancer, all subjects were referred for additional diagnostic examinations. Exclusion criteria were history of renal insufficiency or allergic reaction to iodinated contrast agents, pregnancy or possible pregnancy.

Mammography. The first examination performed in all subjects over 35 years of age was screening MG. MG was performed with the use of a GE Senographe Essential, (GE Healthcare, Buc, France) or a Siemens Mammomat 3000 (Siemens; Erlangen, Germany) MG unit. Every MG examination was performed with craniocaudal (CC) and medioloateral oblique (MLO) projections of each breast. If suspicious areas appeared, examinations in additional projections were performed: lateral projection views and targeted spot compressed views with magnification. Images were available on hard and soft copy.

Ultrasound examination. US was performed by radiologists with a Hitachi EUB 8500//HI VISION Preirus (Hitachi Medical, Tokyo, Japan) ultrasound system with a 12 -14 MHz linear transducer.

Contrast-enhanced spectral mammography. All CESM examinations were carried-out with a digital mammography device dedicated to perform dual-energy CESM acquisitions (SenoBright, GE Healthcare, Chalfont St-Giles, UK). Detailed techniques for performing the CESM examination were presented in previous publications (12, 18).

Prior to CESM, creatinine (estimated glomerular filtration rate - eGFR) and thyroid-stimulating hormone (TSH) blood levels were determined. Patients with a known iodine contrast allergy were excluded from the study.

An intravenous injection of 1.5 ml/kg of body mass of non-ionic contrast agent (iopromide, Ultravist 370; Bayer Healthcare) was performed using a power injector (Optistar™ Elite Injector, Covidien) at a rate of 3 ml/s with a bolus chaser of 30 ml of saline. In CESM mode, the device automatically performed a pair of exposures (low- and high-energy) in each view. Specific image processing of low-energy and high-energy images was done to obtain subtraction images to highlight contrast enhancement and suppress structured noise due to fibroglandular breast tissue (19). Each lesion visible either in US or in CESM were verified at wire localization or core needle biopsy.

Image analysis. A dedicated workstation (IDI Mammography Diagnostic Workstation, GE Healthcare) was used for image analysis. For study purposes, a radiologist with 20 years of experience in US and MG breast imaging and 1 year of experience in CESM reviewed the images separately, with a time gap no longer than 30 days between each of the three examination modalities. Type of breast anatomy and presence or absence of focal lesions was determined in each patient. The first step of evaluation comprised determining which breasts included lesions and second, localising the lesion within quadrants. In the MG examination, the size, shape and margins of lesions were assessed, as well as the presence or lack of microcalcifications. The US examination additionally evaluated echogenicity of the lesion, lesion orientation and presence or lack of enhancement behind the lesion. The next step included assessing lesion suspicion using BI-RADS. Lesions visible in MG or US examination were assigned a defined BI-RADS category: 1 (negative), 2 (benign finding), 3 (probably benign finding), 4 (suspicious abnormality), and 5 (highly suggestive of malignancy) (20, 21).

Evaluation of CESM involved the consecutive data for each identified enhanced lesion: localization (quadrant); degree of enhancement in the suspicious breast; enhancement pattern; BI-RADS category 1 to 5 (fitted to CESM) (4).

Statistical analysis. Visualized lesions (US, MG or CESM) were categorized into groups: true positive (BI-RADS ≥4, histologically proven cancer); false-positive (BI-RADS ≥4, histologically proven benign lesion); false negative (BI-RADS ≤3, histologically proven cancer); true negative (BI-RADS ≤3, histologically proven benign lesion). In each modality (US, MG and CESM), size of the observed lesion was measured and compared to lesion size determined by histopathology. To determine diagnostic test parameters, BI-RADS 4 or higher was deemed positive. Diagnostic parameters were compared using McNemar's test with continuity correction. Receiver operating characteristic (ROC) analysis was performed to compare US and CESM examination results. ROC curves were constructed using a trapezoid rule and areas under the plots were matched using a Z-test. Student's *t*-tests for dependent variables were used for lesion size analysis. Results were deemed significant at an alpha of 0.05. Statistical tests were achieved with the software STATISTICA 10.0, medical set.

Histological studies. Lumpectomy specimens were fixed in 10% buffered formalin and, after 24h fixation, were cut at 3-mm intervals resulting in 10-15 slices. The slices containing tumor tissue were usually divided into two pieces and then placed in cassettes and

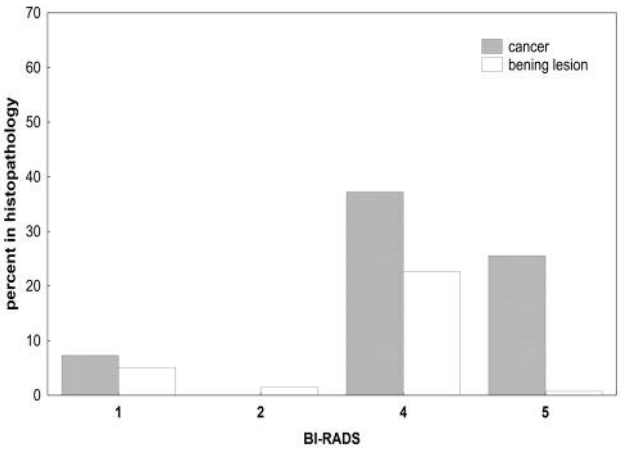


Figure 1. *Distribution of lesions according to BI-RADS on MG and their histopathology. Seventeen of the 137 identified lesions (12%) were classified as BI-RADS category 1. On histopathological examination, 10 of these lesions (7%) were cancerous. Two lesions (1%) were classified as category 2, and both were benign on histopathology. Eighty two lesions (60%) were assessed as BI-RADS category 4 on MG, of which 51 (37%) were cancers on histopathological examination. Among 36 lesions (26%) classified as category 5 on MG, 35 (26%) were cancers.*

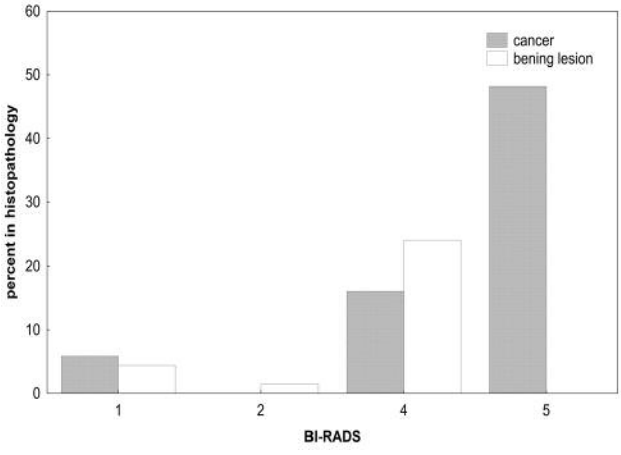


Figure 2. *Distribution of lesions according to BI-RADS on US and their histopathology. Fourteen of the 137 identified lesions (10%) were classified as BI-RADS category 1 on US; eight (6%) were cancers on histopathology. Two lesions (1%) were classified as BI-RADS category 2 on US and both were benign. Fifty-five lesions (40%) were assessed as BI-RADS category 4 on US; twenty-two (16%) were cancer. All 66 lesions classified as BI-RADS category 5 on US (48%) were confirmed as cancers by histopathology.*

embedded in paraffin. Paraffin blocks were cut at sections 4-5 microns thick and examined microscopically after HE-staining. Tumors were diagnosed histologically according to the most recent 4th edition World Health Organization classification.

Results

In this study 116 patients were diagnosed with 137 breast lesions. The average age of patients was 55±12 years. In 97 patients (83%), one lesion was diagnosed, in 17 patients (15%), two lesions, and in 2 patients (2%), three lesions were found. Histopathological examination confirmed breast cancer in 96 cases (70% of all lesions), including 89 invasive carcinomas (65% of all lesions) and 7 *in situ* carcinomas (5%). The remaining 41 lesions (30%) were benign. A detailed distribution of detected lesions in the study group is shown in Table I.

MG detected 121 lesions (88%) in 114 patients (98%). Histologically, 86 lesions (71%) were malignant and 35 (29%) were benign. Among all lesions found on MG, a single unilateral lesion was found in 10 patients (94%) and bilateral lesions were found in 7 patients (6%).

US examination identified 123 lesions (90%) in 107 patients (92%). Eighty-eight lesions (71%) were malignant, including 83 (67%) invasive carcinomas and 5 (4%) *in situ* carcinomas; the remaining 35 lesions (28%) were benign. There were 14 patients who had no lesions diagnosed by US – among them 8 (57%) were cancers (including 6 invasive and 2 non-invasive carcinomas) and 6 (43%) were benign. Unilateral lesions were identified in 92 patients (86%), bilateral lesions in 14 patients (13%) by US examination. A single patient (1%) was identified as having three lesions on US.

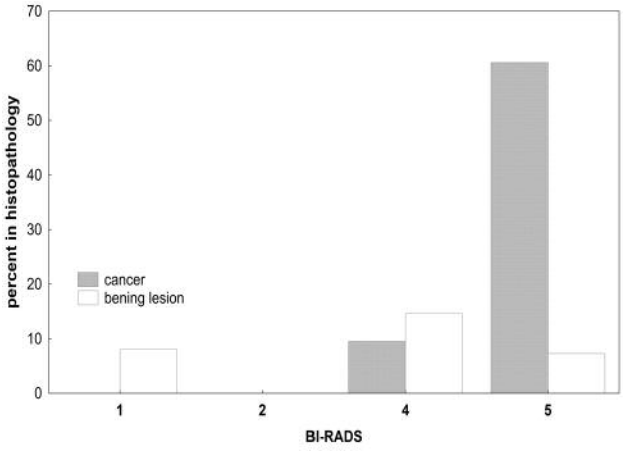


Figure 3. *Distribution of lesions according to an adapted BI-RADS scale on CESM and their histopathology. Eleven of 137 identified lesions (8%) were classified as category 1 on CESM; all of them were benign on histopathology. No lesions were assessed as category 2 on CESM. Thirty-three lesions (24%) were classified as category 4 on CESM, and among them Thirty-three (9%) were cancers and 20 (15%) were benign. Of 93 (68%) lesions assessed as category 5 on CESM, 83 (61%) were cancers on histopathology and 10 (7%) were benign.*

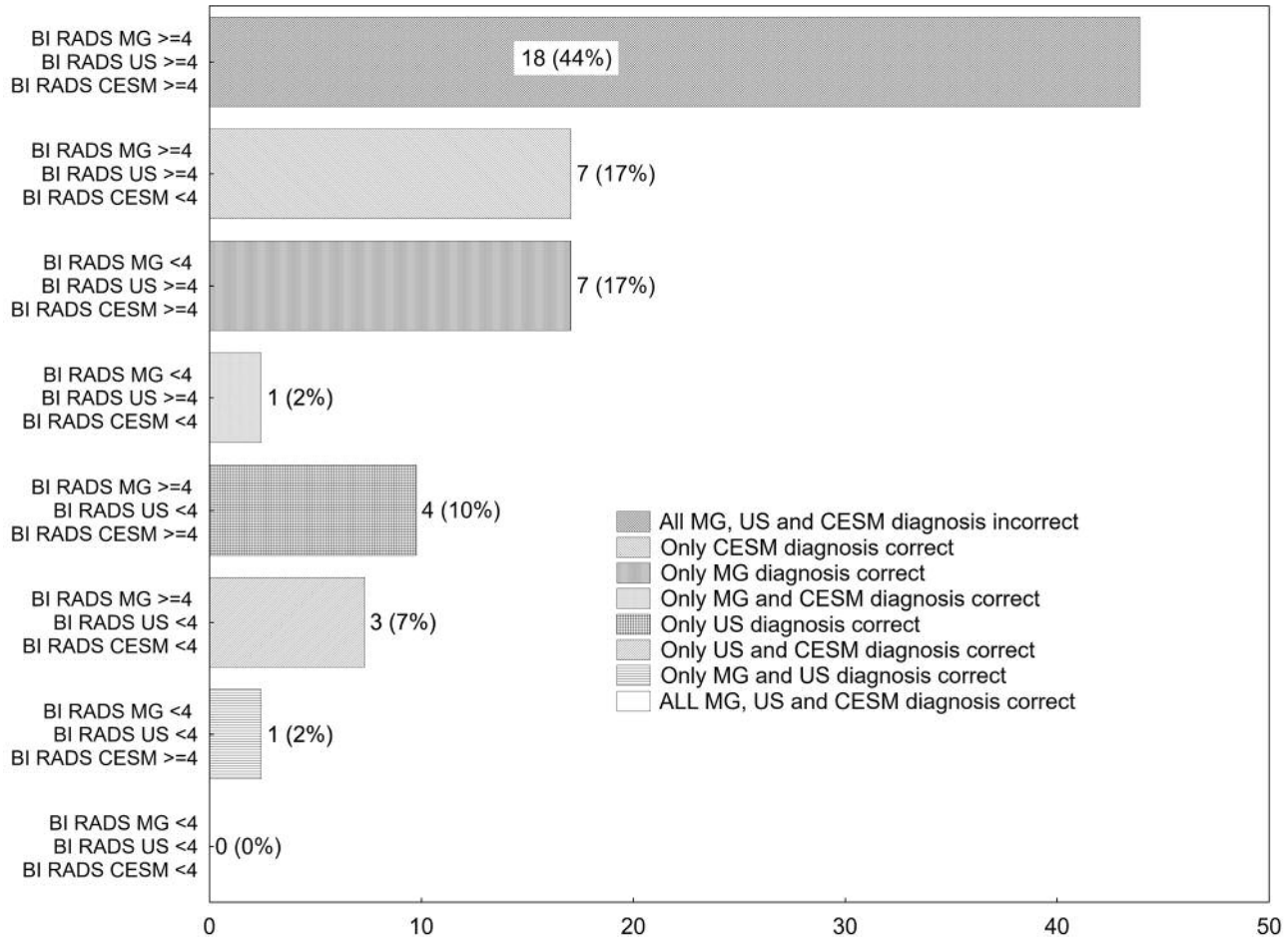


Figure 4. *Comparison of benign lesions based on BI-RADS in MG, US and CESM.*

Table I. *Detailed distribution of lesions diagnosed in histopathological examination.*

Lesion type	Cancer type	N	%
Invasive carcinoma	Invasive ductal carcinoma	69	50
	Invasive lobular carcinoma	9	7
	Apocrine carcinoma	2	1
	Papillary and micropapillary carcinoma	2	1
	Tubular carcinoma	2	1
	Mixed cases	5	4
Non-invasive carcinoma	Ductal carcinoma *in situ*	6	4
	Lobular carcinoma *in situ*	1	1
Benign lesions	Fibroadenoma	25	18
	Others	16	12

In CESM, contrast enhancement was observed in 126 lesions (92%) in 105 patients (91%). Eighty-nine lesions (71%) identified by CESM were invasive carcinomas and 7 (6%) were non-invasive carcinomas. Eleven lesions (8%) showed no enhancement, and in histopathological examination all were confirmed to be benign. Contrast enhancement in one breast appeared in 86 patients (82%), in two breasts in 17 patients (16%), and 2 patients (2%) had three enhancing lesions.

Among the 16 lesions (12%) (10 cancers and 6 benign lesions) not visible on MG, 12 (9%) were diagnosed on both

Table II. *Accuracy results for MG, US and CESM based on diagnostic test assessment.*

	TP (True-positive)	FP (False-positive)	FN (False-negative)	TN (True-negative)
MG	86 (63%)	32 (23%)	10 (7%)	9 (7%)
US	88 (64%)	33 (24%)	8 (6%)	8 (6%)
CESM	96 (70%)	30 (22%)	0 (0%)	11 (8%)

US and CESM (7 cancers and 5 benign lesions), while 4 (3%) of them were seen only on CESM (3 cancers and one benign lesion).

The detailed distribution of lesions on MG, US, and CESM according to BI-RADS classification and histopathology results is shown in the Figures 1-3.

Specificity based on BI-RADS classification on MG, US and CESM is presented in Figure 4. Figure 5 presents differences between digital mammography, US and CESM images. Comparing BI-RADS assessments of all 3 modalities (Table II), the largest number of false-negative diagnoses was made by MG (7%), followed by US (6%); no false-negative assessments were made with CESM. Table III shows sensitivity, specificity and accuracy of MG, US and CESM.

Analysing ROC curves based on BI-RADS assessments (Figure 6), US and CESM have similar accuracies in differentiating benign and malignant cases; the area under ROC curve (AUC) for each was 0.83. The smaller AUC for MG (0.69) suggests that, on the basis of BI-RADS, differentiation of benign and malignant lesions is less accurate with MG than with US or CESM.

Table III. *Sensitivity, specificity, and accuracy of MG, US and CESM.*

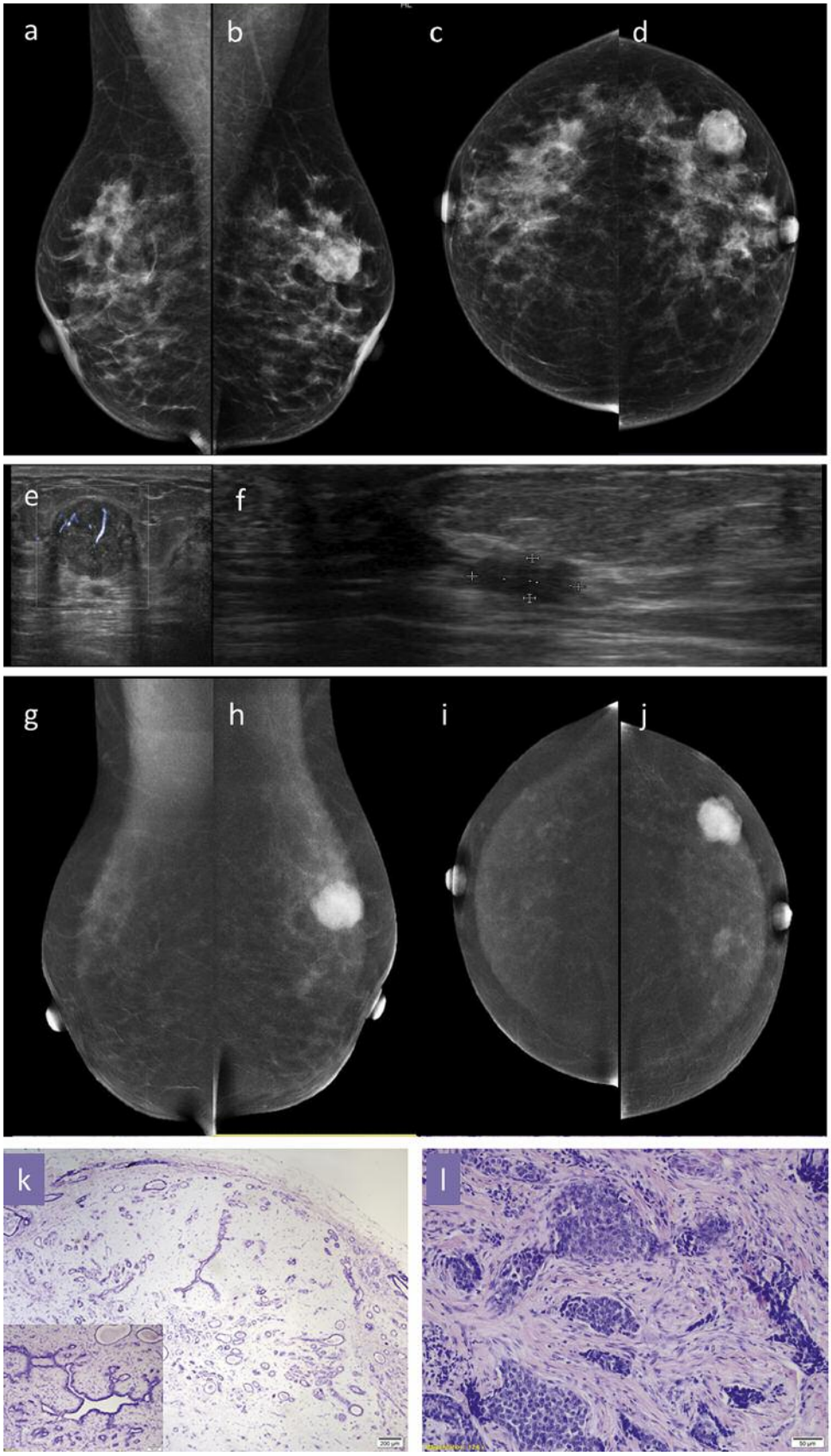
Examination	Sensitivity	Specificity	Accuracy
MG	90% [82%; 95%]	22% [11%; 38%]	69% [61%; 77%]
US	92% [84%; 96%]	20% [9%; 35%]	70% [62%; 78%]
CESM	100% [96%; 100%]	27% [14%; 43%]	78% [70%; 85%]
p-value: MG *vs*. US	0.77	0.99	0.99
p-value: MG *vs*. CESM	0.004	0.81	0.04
p-value: US *vs*. CESM	0.01	0.57	0.03

Discussion

CESM is a new diagnostic method based on angiogenesis assessment, accepted by FDA in 2011. Before that date only clinical studies were conducted. In our study three diagnostic methods: MG, US and CESM were compared among 116 patients with 137 lesions. Sensitivity of CESM was 100%, significantly higher than that of MG (90%, $p<0.004$) or US (92%, $p<0.01$). CESM accuracy was 78%, also higher than MG (69%, $p<0.004$) and US (70%, $p=0.03$). There was no statistically significant difference between AUCs for CESM and US (both 0.83). The AUC of US, however, was significantly larger than that of MG ($p<0.0004$); likewise, the AUC of CESM was significantly higher than that of MG ($p<0.0004$). Since our study focused on subjects with suspicious lesions and there was a limited number of benign lesions among examined subjects, presented values are not necessarily representative of the general population.

The sensitivity of CESM in our study is comparable to results presented in other publications, where CESM sensitivity ranged from 63.5 to 100% (22, 23). The first study where all three modalities were compared was that of Lewin *et al*. There were only 26 subjects examined, 13 with invasive cancers and one with DCIS. Of the 13 invasive cancers, 11 enhanced strongly, 1 moderately, and 1 weakly; the duct in the one subject with DCIS enhanced weakly. No quantification of the performance of the method was performed in this study, however, because of the small number of subjects.

The second study that compared contrast-enhanced spectral mammography with MG and US was Dromain *et al*. (24). That study included 120 subjects with 142 lesions found. Sensitivity of CESM plus MG was 93%, significantly higher than the 78% sensitivity of MG alone ($p<0.001$). In a subsequent study, Dromain *et al*. described 110 consenting women with 148 breast lesions (84 malignant, 64 benign) who underwent two-view dual-energy CESM in addition to MG and US. The reference standard was histology for 138 lesions and follow-up for 12 lesions. Six radiologists from 4 institutions interpreted the images. Sensitivity, specificity and ROC curve areas were estimated for each reader and overall. Analysis using BIRADS revealed that the average per-lesion sensitivity across all readers was significantly higher for MG+US+CESM than for MG+US (0.78 *vs*. 0.71, $p=0.006$). All readers improved their clinical performance with the addition of CESM and the average area under the ROC curve was significantly higher for MG+US+CESM than for MX+US (0.87 *vs*. 0.83, $p=0.045$). Lesion visibility was similar or better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on MG+CESM than MG+US in 80% of cases. It is worth noting that both the number of subjects included in the Dromain *et al*. studies and their results are comparable to our study. Our study, however, found higher specificity. Both studies indicate that the diagnostic accuracy of CESM for detection of breast carcinoma is superior not only to that of mammography alone, but also to mammography interpreted in association with ultrasound. Additionally, compared to mammography alone, CESM increased the sensitivity without decreasing specificity. In comparison to the combined diagnostic examinations (MG and US), CESM had a better diagnostic accuracy mainly due to improved specificity, and had better positive and negative predictive values.

In summary, these findings in a symptomatic cohort suggest that CESM is an accurate technique for breast cancer diagnosis. CESM allows for detection of a greater number of malignant lesions than either MG or breast US. It remains to verify that this advantage persists in a lower risk or asymptomatic population of women.

Conclusion

CESM permitted better detection of malignant lesions than both MG and US, read individually. CESM found lesion enhancement in some benign lesions, as well, yielding a rate of false-positive diagnoses similar to that of MG and US. This method has the potential to play an important role in assessing multicentricity or multifocality in breast cancer and gives easily available and clinically useful information. CESM can be performed in routine practice changing the diagnostic, and further, the treatment strategy.

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Figure 5. *A 44-year-old patient. Mammography (a-d): the breasts are heterogeneously dense, which may obscure small mases. In the upper-outer quadrant of the left breast (shown on the right), 6 cm from the nipple, a well-circumscribed 25 mm diameter lesion is seen: BI-RADS 4 on MG. US (e-f): At the 2 o'clock position in the left breast, 5 cm from the nipple, a polycystic, sharply defined hypo-echogenic lesion of dimensions 22 mm x 15 mm is observed: BI-RADS 4 on US. The same breast, centrally, 1 cm from the nipple shows a poorly differentiated hypoechogenic area (dimensions: 8 mm x 4 mm), BI-RADS 5 on US (g-j). On CESM, the right breast (displayed on the left) shows no significant enhancement. In the left breast, a strongly enhancing, well-circumscribed lesion is visible in the upper outer quadrant, 6 cm from the nipple. In the same breast, a poorly circumscribed, weakly enhancing lesion is seen on the border of the inner quadrant, 5 cm from the nipple. Histopathology (k-l): Outer quadrant - large lesion is diagnosed as pericanalicular fibroadenoma. Additionally, in the parenchyma surrounding that lesion the different proliferative epithelial changes are noticed including atypical ductal hyperplasia and a single focus 1.2 mm in diameter of ductal carcinoma in situ, cribriform type. Centrally and in the inner quadrant, the smaller lesion is diagnosed as intraductal carcinoma in situ and invasive carcinoma NST grade 2.*

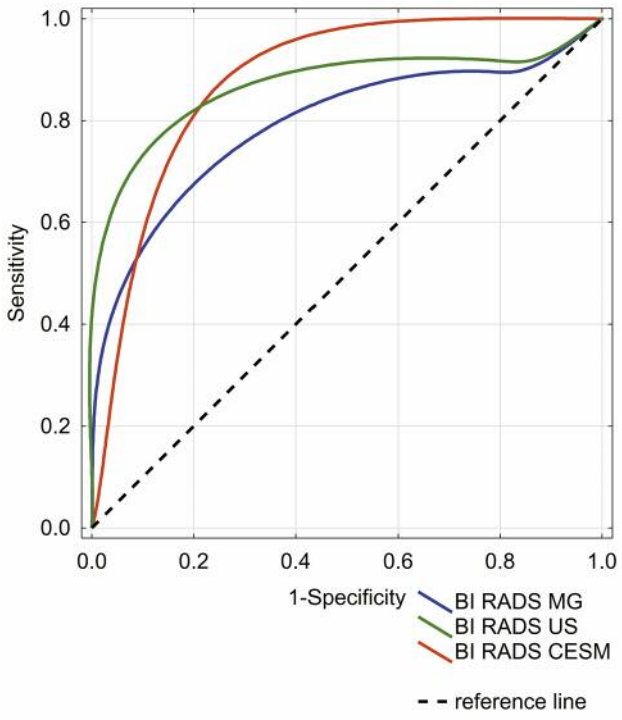

Figure 6. *Receiver operating characteristic curves (ROC) based on BI-RADS for conventional mammography (MG), ultrasonography (US) and contrast enhancement spectral mammography (CESM). Dashed line shows the ROC curve for a random test result.*

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