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RESEARCH

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The added role of contrast-enhanced spectral mammography in the evaluation of pathological nipple discharge

Sherihan Fakhry[1,2*], Rasha Wessam Abdel Rahman[1,2], Hanan Shawky Shaalan[2], Maher Hassan Ibraheem Hassan[1,3], Safy Hosny Tealab[3] and Safia Badr Sayed[2]

Abstract

Background: Nipple discharge is one of the commonest encountered complaints in the field of breast imaging. Excluding malignancy as a cause of pathological nipple discharge is of utmost importance. Our aim in this study was to assess the role of contrast-enhanced spectral mammography (CESM) in the diagnostic workup of patients with pathological nipple discharge (PND).

Results: In the current prospective study, 59/140 lesions were benign and 81/140 lesions were malignant. Analysis of CESM had achieved a higher sensitivity of 97.5% and a similar specificity of 54.2% as compared to sono-mammography, which achieved a sensitivity of 92.6% and specificity of 54.2%. The diagnostic accuracy of CESM was higher (79.3%) than sono-mammography (76.3%). CESM performed better than sono-mammography in the assessment of disease extent, as it was able to detect multifocality, multicentricity, and diffuse abnormalities, which were found in 24.1%, 43.0% and 8.9% of cases, respectively, as compared to 20.5%, 37.2%, and 3.8% of cases by sono-mammography.

Conclusion: CESM can be a valuable diagnostic imaging tool in the detection of malignancy associated with PND if sono-mammographic findings are equivocal. Its greater impact is on the delineation of disease extent, which will alter the treatment strategy.

Keywords: Contrast-enhanced spectral mammography, Pathological nipple discharge, Ductal carcinoma in situ, Papilloma

Background

Nipple discharge is one of the commonest complaints encountered in breast clinics and has been seen with increased prevalence recently. Nipple discharge can be broadly categorized into physiological and pathological. Physiological nipple discharge occurs in pregnancy, during lactation, and secondary to other diseases as hypothyroidism and hypothalamic disorders, or even secondary to the use of medications like antipsychotics [1]. Conversely, pathological nipple discharge (PND) most commonly occurs secondary to a benign pathology, such as duct ectasia and papilloma, yet the risk of malignancy cannot be neglected [2].

Excluding malignancy as a cause of PND is of utmost importance. Diagnostic workups begin with a clinical examination that considers the onset, frequency, quantity, and color of the nipple discharge, and it is then necessary to determine if there is history to suggest physiological causes [2]. Physiological nipple discharge is characterized by its bilateral, multi-orificial, and non-spontaneous nature, and it is white or yellow in color. Worrisome nipple discharge is unilateral, uniorifical, and spontaneous, and can be serous or blood-stained [3].

*Correspondence: shery4@yahoo.com
[1] Baheya Center for Early Detection and Treatment of Breast Cancer, Giza, Egypt
Full list of author information is available at the end of the article

It is worth mentioning that 20% of breast cancers are not palpable, and analysis by cytology is necessary when evaluating PND [4]. Though cytology is an easy and painless procedure, it has variable sensitivity and features a high false-negative rate for malignancy [5].

Diagnostic imaging is essential for assessment, and it begins with mammography complemented by an ultrasound; a malignant pathology may be mammographically occult, and further intervention may be warranted, if indicated [6]. Further, mammography may detect suspicious microcalcifications in cases of ductal carcinoma in situ (DCIS) presenting with PND [7].

Contrast-enhanced magnetic resonance imaging (MRI) is a valuable clinical examination tool when initial standard imaging is inconclusive or negative despite high clinical suspicion [8]. MRI has a high sensitivity when detecting benign and malignant causes of PND, with rates as high as 88%–95% in invasive cancer diagnosis; however, its main limitation is that it features lower specificity [9].

Contrast-enhanced spectral mammography (CESM) is advantageous insofar as it is readily available, tolerated by patients, has contrast doses similar to those of digital mammography, and it may be associated with lower costs when compared with MRI [10]. CESM increases the sensitivity of mammography when detecting breast lesions, especially malignant breast lesions; it is also able to assess the local extent of the disease and can determine if there is multifocal/multicentric involvement. However, it has limited value when assessing certain benign lesions and small lesions [11]. To our knowledge, there are few studies that have discussed the role of CESM in the evaluation of PND; the goal of our study was to address this gap.

Methods

Patient population

This study was a prospective analysis that was approved by the ethics committee at our institute. This study was conducted from April 2018 to April 2021. It included 140 patients who complained of PND (83 cases of bloody discharge and 57 cases of non-bloody discharge) referred from the breast clinic of our institution. Informed consent was obtained from all patients included in this study. Diagnosis was established by means of open surgery or a core needle biopsy (considered to be the gold standard), or via ultrasound or routine follow-up in typically benign lesions. Pregnant patients, those with physiological nipple discharge, or those who are contraindicated for contrast medium administration, were excluded from our study.

Contrast-enhanced spectral mammography

All patients underwent triple assessment (clinical examination, sono-mammography, and cytology), followed by CESM. During CESM, an intravenous injection of an iodinated contrast agent (Iohexol; 300 mg/mL) at a dose of 1.5 mL/kg was administered followed by a 2-min wait before breast compression. Then, dual-energy CESM image acquisition in the two standard positions (craniocaudal and mediolateral oblique views) was performed (GE senographe DS Digital Mammography, USA). Low- and high-energy images were consecutively acquired in each view. Low-energy images were compared to the standard mammography images, which yielded morphological information; the high-energy images were acquired to allow for post-processing and to obtain recombined enhanced images. Enhanced images were calculated by weighted logarithmic subtraction of the two images.

Image analysis

Image analysis of the recombined CESM images was done by two breast imaging consultants with at least 10 years of experience in the field of breast imaging; the final diagnosis was reached by their agreement (upon achieving consensus). Image interpretation was based on the MRI Breast Imaging-Reporting and Data System (BI-RADS) lexicon 2013, considering lesion morphology, degree of enhancement, and distribution. The assessment began by detecting enhancing lesions and classifying them as mass or non-mass enhancements. In enhancing mass lesions, further assessment of the lesion's margins (circumscribed, not circumscribed), shape (oval, round, or irregular), and internal enhancement characteristics (homogeneous, heterogeneous, septations, or ring enhancement) was performed.

In cases of non-mass enhancement, further assessment of distribution (focal, linear, segmental, regional, multiregional, or diffuse) and the pattern of internal enhancement (homogeneous, heterogeneous, clustered, and clumped) was done. Lesion distribution (single, multifocal, multicentric) and the presence of bilaterality were also assessed.

Final categorization of breast lesions was made based on BI-RADS; the results were then compared to the pathology results (obtained by cytology, core biopsy, and/or following a surgical procedure), which were used as the gold standard. Typical benign findings with negative cytological results were attributed in 14 (10.0%) of our cases and showed stability on follow-up, eliminating the need for core biopsy or surgical intervention.

Statistical analysis

Data were coded and entered into the statistical package SPSS (Statistical Package for the Social Sciences) version 26 (IBM Corporation, Armonk, NY, USA). Quantitative data were summarized using means, standard deviations, and the minimum and maximum; categorical data were expressed as the frequency (count) and relative frequency (percentage). Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic efficacy were calculated as described by Galen (1980). To compare categorical data, the chi-squared (χ^2) test was performed. Fisher's exact test was used when the expected frequency was <5 [12]. A P value <0.05 was considered to be statistically significant.

Results

This study included 140 patients who presented clinically with PND. Their ages ranged from 30 to 70 years (mean age: 51 years). In 83 cases (59.3%), the patients presented with bloody nipple discharge, while 57 (40.7%) presented with non-bloody nipple discharge.

A final histopathological diagnosis was not obtained in 14 of our cases, as they showed typical benign imaging findings, the absence of malignant cells on cytology, and stability on follow-up. When examining the final diagnosis achieved during histopathology (126/140) or on follow-up after 6 months for 2 consecutive times (14/140), it was determined that 59/140 (42.1%) of cases were benign, while 81/140 (57.9%) were malignant. The different pathologies encountered in our study are illustrated in Table 1. Papilloma was the commonest pathology, found in 30/140 cases (21.4%) while DCIS was the most frequently represented malignant pathology, found in 24 cases (17.1%).

When examining the cytology findings, 103/140 (73.6%) cases showed no malignant cells, out of which 55 cases (53.4%) were pathologically benign, while 48/103 cases (46.6%) turned out to be pathologically malignant, as verified by core biopsy or final specimen pathology.

Among the studied population, 63 cases (75.9%) that presented with bloody nipple discharge were malignant, while 20 (24.1%) were benign. Conversely, 39 cases (68.4%) that presented with non-bloody discharge were benign, while 18 (31.6%) were malignant.

Sono-mammographic findings

Based on the sono-mammographic imaging findings, 38/140 cases were determined to be probably benign and were assigned a BI-RADS 3 category, while 102/140 cases were assigned as suspicious and were given a BI-RADS 4 category. Their association to the final pathology is illustrated in Table 2.

Table 1 Final diagnosis of the studied cases (proven by histopathology or by cytology and routine follow-up in 14 cases with typically benign features)

Final diagnosis	No. of patients ($n=140$)	%
Benign	59	42.1
Papilloma	30	21.42
Duct ectasia	14	10
Mastitis	4	2.8
Fibroadenosis	5	3.57
Fibrocystic changes	6	4.28
Malignant	81	57.9
DCIS	24	17.2
IDC	22	15.7
ILC	9	6.4
Tubular and mucinous carcinoma	9	6.4
Invasive cribriform and tubular carcinoma	6	4.3
Mixed IDC and ILC	6	4.3
Invasive cribriform carcinoma	5	3.6

DCIS ductal carcinoma in situ, *IDC* invasive duct carcinoma, *ILC* invasive lobular carcinoma

Table 2 Correlation between sono-mammographic findings and final pathology

	Pathology				*P* value
	Malignant		Benign		
	Count	%	Count	%	
BIRADS (sono-mammography)					
Suspicious	75	92.6	27	45.8	<0.001
Probably benign	6	7.4	32	54.2	

There were 6/38 false-negative cases that were pathologically proven to be DCIS; 3 of these cases presented with dense breasts (either American College of Radiology [ACR] C or D) featuring bilateral diffuse punctate microcalcifications; there were no suspicious abnormalities identified on ultrasound (Fig. 1). The other 3 presented with focal or regional asymmetry, as determined by mammography and on ultrasound; these cases corresponded with dilated ducts featuring echogenic contents, yet no intra-ductal vascularity was found. Conversely, there were 27/102 false-positive cases that included intra-ductal papillomata, peri-ductal mastitis, fibroadenosis, and fibrocystic mammary changes.

Regarding the lesion distribution in malignant cases (81/140), sono-mammography was able to detect single abnormalities in 30 cases, multifocal abnormalities

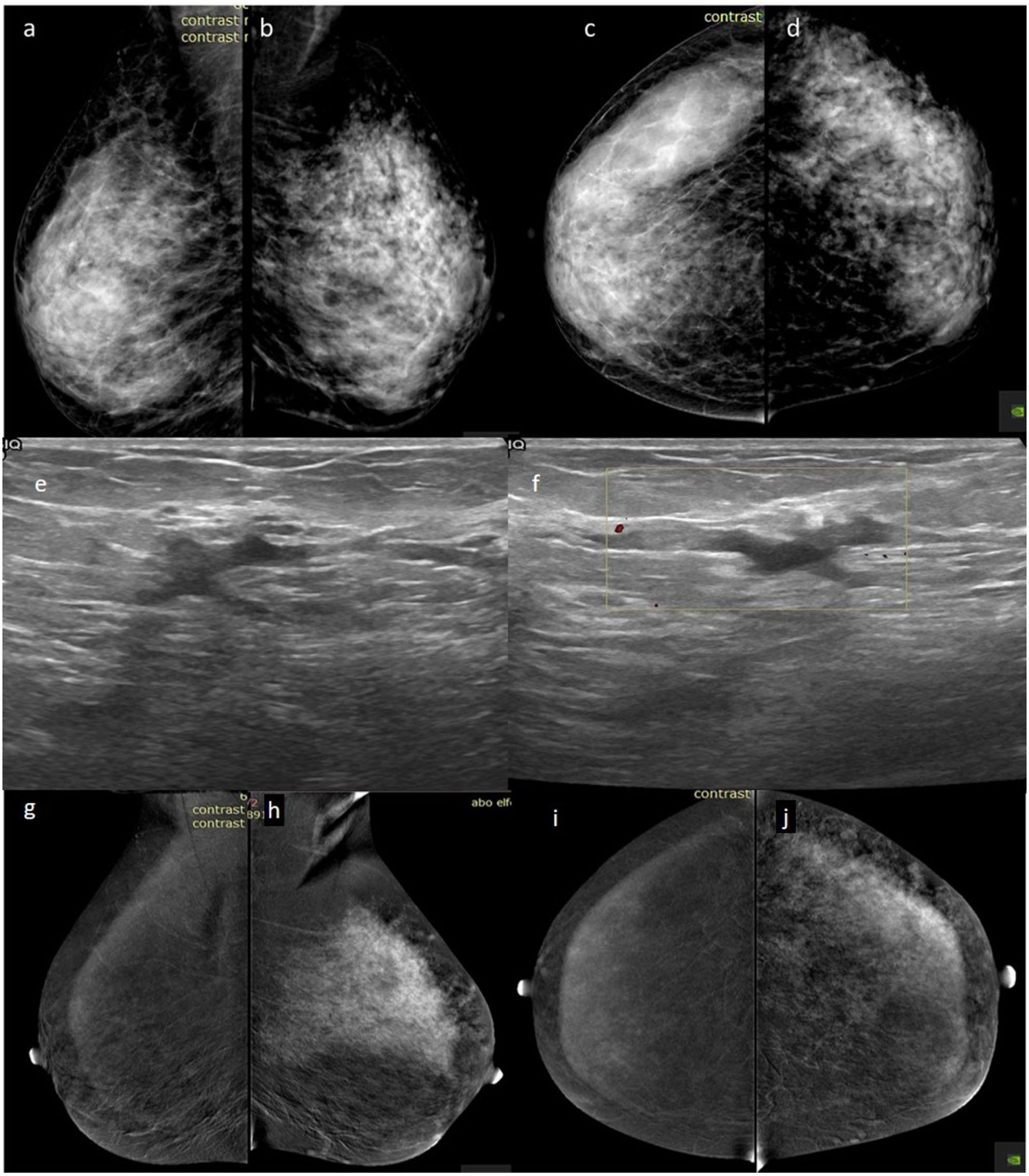

Fig. 1 A 56-year-old female patient complaining of continuous bloody nipple discharge from the left breast. Mammography MLO (**a**, **b**) and CC views (**c**, **d**) showed extremely dense breast parenchyma (ACR D). An ultrasound (**e**, **f**) was performed and dilated ducts with non-vascular echogenic contents were identified. Cytology was performed and revealed atypical epithelial cells, suspicious but inconclusive for malignancy. CESM in MLO (**g**, **h**) and CC views (**i**, **j**) showed intense, heterogeneous, regional, non-mass enhancement and was categorized as BI-RADS 4. Pathology revealed DCIS. MLO, mediolateral oblique; CC, craniocaudal, CESM, contrast-enhanced spectral mammography; DCIS, ductal carcinoma in situ

in 16 cases, multicentric abnormalities in 29 cases, and diffuse abnormalities in 3 cases. Bilateral abnormalities were detected in 14 cases. Sono-mammography was not able to delineate the abnormalities in 3 cases featuring dense breasts; these were considered to be false-negative cases.

Table 3 Relationship between clinical condition and contrast mammography according to BI-RADS category

	Discharge				*P* value
	Bloody		Non-bloody		
	Count	%	Count	%	
BIRADS (contrast)					
Probably benign	16	19.3	18	31.6	0.095
Suspicious	67	80.7	39	68.4	

Contrast-enhanced spectral mammography

Based on the CESM findings, a 'probably benign' category was assigned in 16 (19.3%) cases that presented with bloody nipple discharge, and in 18 (31.6%) cases with non-bloody nipple discharge. The 'suspicious' category was assigned in 67 (80.7%) cases presenting with bloody nipple discharge and 39 (68.4%) cases with non-bloody nipple discharge, as shown in Table 3.

Analysis of the CESM findings was based on morphology and enhancement patterns in the 140 cases (Fig. 2), as shown in Tables 4 and 5. A BI-RADS score was given according to the most suspicious criteria, and correlations were performed with the final pathology or on follow-up (in 14 cases), as illustrated in Table 6.

Based on the CESM findings, the 'suspicious findings' category was assigned in 106/140 cases (75.5%), while 34/140 cases (24.3%) were classified as probably benign. Twenty-seven (19.3%) cases were false-positive, either presenting as a non-circumscribed mass or a suspicious,

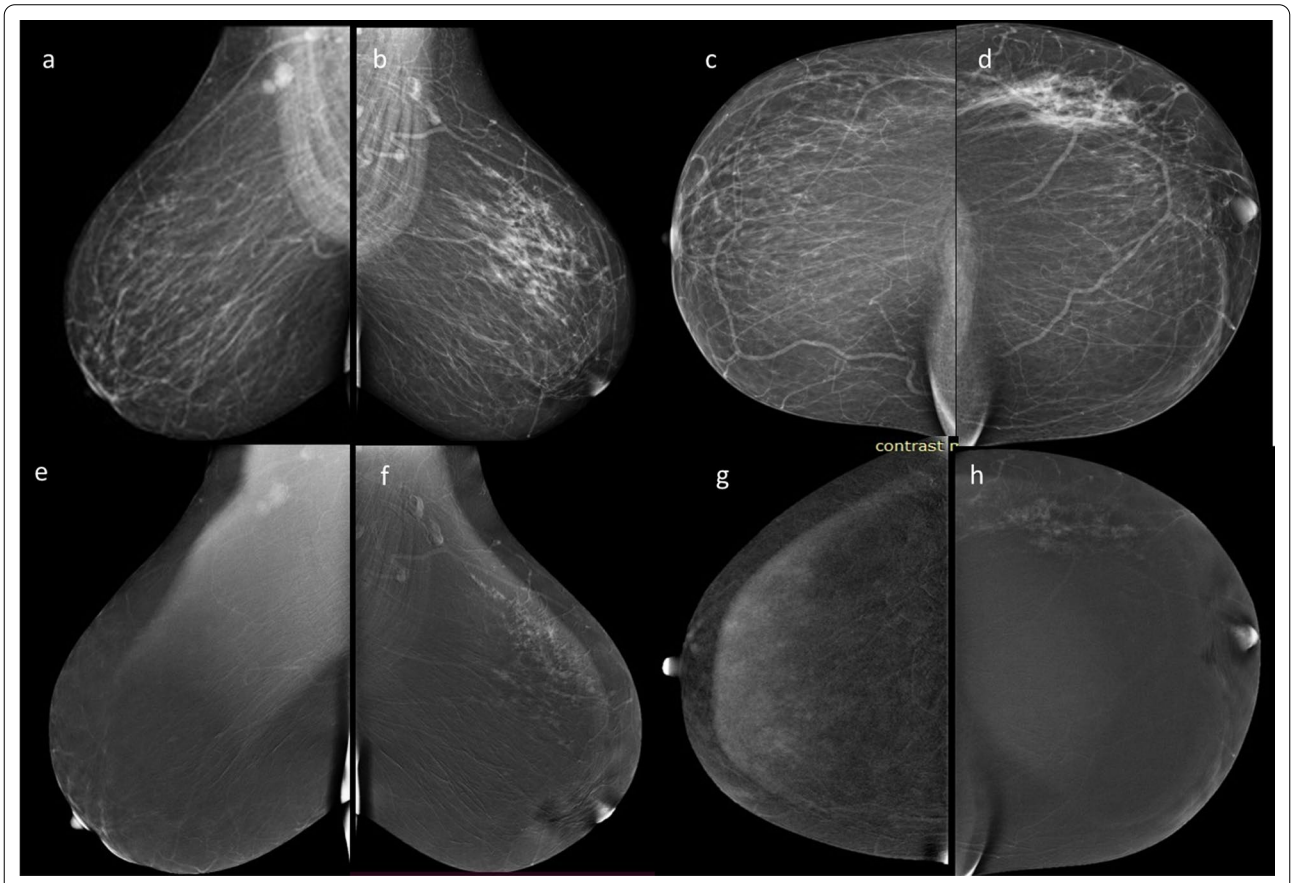

Fig. 2 A 56-year-old female patient complaining of bloody nipple discharge from the left breast. Mammography MLO (**a**, **b**) and CC views (**c**, **d**) showed left upper outer focal asymmetry. An ultrasound was performed, which revealed left-sided prominent ducts. Cytology was suggestive of intra-ductal papilloma and excision was recommended. CESM in MLO (**e**, **f**) and CC views (**g**, **h**) showed a suspicious, left, clumped, non-mass enhancement of segmental distribution (BI-RADS 4). Pathology revealed DCIS. MLO, mediolateral oblique; CC, craniocaudal, CESM, contrast-enhanced spectral mammography; DCIS, ductal carcinoma in situ

Table 4 Correlation between mass morphology descriptors and enhancement characteristics with their histopathological results

	Benign		Malignant	
Shape				
Round	13	48.1%	14	35.0%
Oval	10	37.0%	6	15.0%
Irregular	4	14.8%	20	50.0%
Margin				
Circumscribed	19	70.4%	9	22.5%
Non-circumscribed	8	29.6%	31	77.5%
Internal enhancement characteristics				
Homogeneous	13	48.1%	7	17.5%
Heterogeneous	12	44.4%	31	77.5%
Rim enhancement	2	7.4%	2	5.0%

Table 5 Correlation of non-mass morphology descriptors and enhancement characteristics with their histopathological results

	Benign		Malignant	
	Count	%	Count	%
Distribution				
Focal	9	36.0	2	3.3
Linear	6	24.0	21	34.4
Regional	2	8.0	16	26.2
Multiple regions	2	8.0	2	3.3
Diffuse	0	0.0	7	11.5
Segmental	6	24.0	8	13.1
Linear and regional	0	0.0	2	3.3
Linear and seg	0	0.0	3	4.9
Internal enhancement characteristics				
Homogeneous	11	44.0	0	0.0
Heterogeneous	10	40.0	47	77.0
Clumped	4	16.0	14	23.0
Clustered	0	0.0	0	0.0

Table 6 Correlation between CESM and final pathology

	Pathology				*P* value
	Malignant		Benign		
	Count	%	Count	%	
BIRADS					
Suspicious	79	97.5	27	45.8	< 0.001
Probably benign	2	2.5	32	54.2	

non-mass enhancement (mostly linear or segmental) (Fig. 3); the pathology in these cases was papillomata (22 cases), peri-ductal mastitis (3 cases), and fibroadenosis (2 cases).

Two false-negative cases (1.4%) were diagnosed as benign; however, the pathology identified malignancy. One DCIS case showed bilateral multiple regional enhancement with diffuse, scattered, punctate calcification on mammography; another DCIS case presented on the left side, yet showed bilateral nodular enhancement (Fig. 4).

When analyzing the malignant cases (excluding the two false-negative cases), CESM detected a single abnormality in 18 cases, multifocal abnormality in 20 cases, multicentric abnormality in 34 cases, and diffuse abnormality in 7 cases. Bilateral abnormalities were detected in 16 cases.

The accuracy measures and diagnostic indices of sono-mammography and CESM were calculated individually and showed that CESM had better sensitivity (97.5%) and NPV (94.1%) when compared to sono-mammography, which had a sensitivity of 92.6% and an NPV of 84.2%. The overall accuracy of CESM was 79.3%, as compared to sono-mammography (76.4%). This is illustrated in Table 7.

Discussion

Though PND is most commonly caused by benign breast disorders, its association with malignancy risk is a serious issue that may necessitate major duct excision for exclusion [12]. The urge to achieve a systematic approach in the workup and management of PND is increasing, especially given the high prevalence of PND-related complaints.

In general, CESM has been used a problem-solving tool to detect breast lesions given its ability to assess the morphological criteria and enhancement patterns of different lesions, similar to MRI. Our study attempted to evaluate the added value of incorporating CESM in the diagnostic workup of PND, especially if the sono-mammographic findings were inconclusive and could alter the treatment strategy (or not).

It was noted that most of the malignant lesions we encountered in our study presented with bloody nipple discharge (77.8%). This finding was in accordance with those of Chen et al. [1], who stated that there is an association between the color of nipple discharge and breast cancer risk. Yet, based on our study, discharge color does not exclude malignancy, as noted in 18 malignant cases (22.2%) that presented with non-bloody discharge. Similarly, Abdalla et al. [13] noted that non-bloody discharge does not exclude breast cancer; as such, both bloody and non-bloody (serous and serosanguinous) PND should still be fully investigated.

PND is caused by a wide range of benign and malignant breast disorders. Despite the fact that PND is most commonly caused by benign breast disorders, we

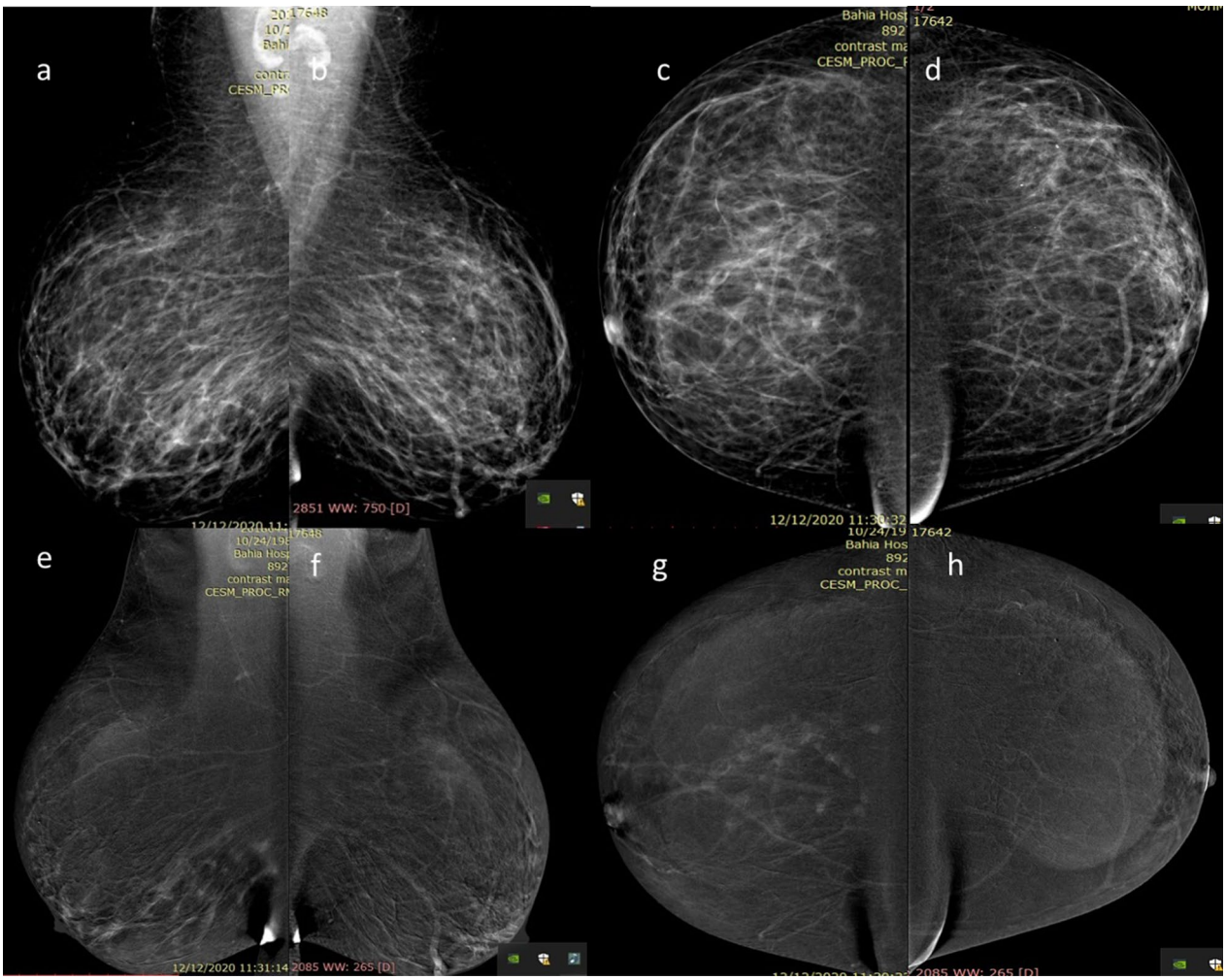

Fig. 3 A 37-year-old female patient complained of bloody nipple discharge from the right breast. Mammography MLO (**a**, **b**) and CC views (**c**, **d**) showed right lower central focal asymmetry. Ultrasound showed right dilated ducts with echogenic content, and inspissated secretion with peri-ductal increased vascularity in color Doppler. Cytology was negative for malignant cells. CESM in MLO (**e**, **f**) and CC views (**g**, **h**) showed a clumped, non-mass enhancement of segmental distribution and was categorized as BI-RADS 4. Pathology revealed peri-ductal mastitis. MLO, mediolateral oblique; CC, craniocaudal, CESM, contrast-enhanced spectral mammography

encountered 81 malignant cases, representing 57.9% of all cases identified in our study. This may be related to patients' decreased awareness of PND, and they may have also presented with a more advanced clinical condition. Benign causes were encountered in 59 cases (42.1%), with the most commonly identified benign cause being intra-ductal papilloma (21.4%). The most common malignant cause was DCIS (17.2%).

Based on the findings from our study, the sensitivity of cytology when detecting malignancies was 40.7%, while its specificity was 93.3%. These rates are in accordance with the findings of Leong et al. [14], who stated that negative cytology findings should not exclude malignancy and that the results should be correlated with clinical and radiological findings.

The sensitivity and specificity of sono-mammography in our study were 92.6% and 54.2%, respectively. False-negative cases typically featured dense breasts that showed bilateral diffuse calcification or asymmetries that did not show suspicious ultrasound abnormalities. Yet, this finding does not influence the fact that the use of ultrasound as a complementary method to mammography has increased the diagnostic sensitivity when assessing PND. Paula and Campos [15] stated that mammography alone had a low sensitivity (20–25%) given its challenges assessing the retroareolar area. Similarly,

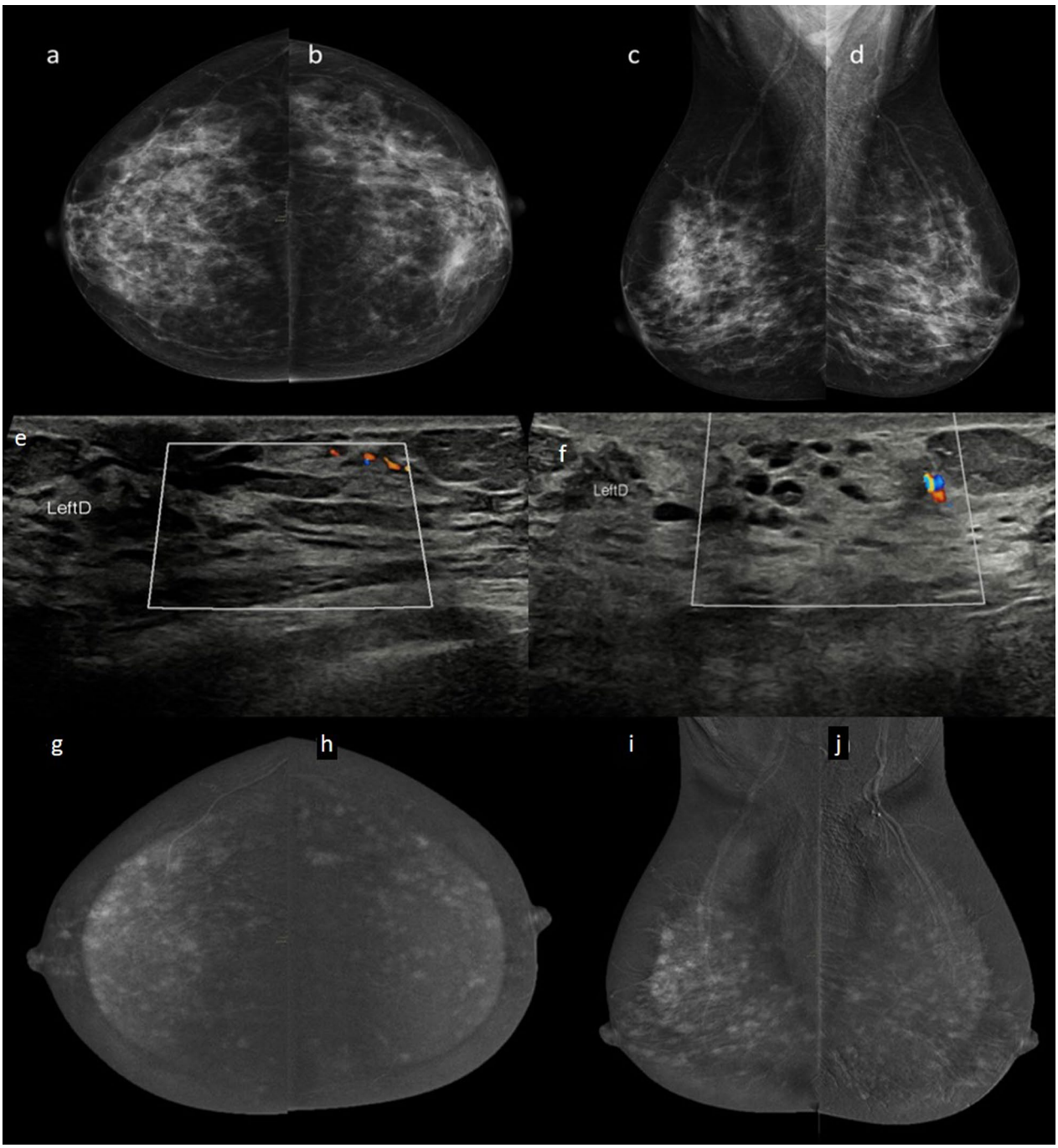

Fig. 4 A 49-year-old female patient complained of continuous bloody nipple discharge from the left breast. Mammography CC (**a**, **b**) and MLO views (**c**, **d**) showed a heterogeneous, dense, breast parenchyma (ACR C) with left retroareolar asymmetry. An ultrasound (**e**, **f**) was performed, which identified dilated ducts with non-vascular echogenic contents. Cytology was performed and revealed atypical epithelial cells, suspicious but inconclusive for malignancy. CESM in MLO (**g**, **h**) and CC views (**i**, **j**) showed marked bilateral nodular enhancement and was categorized as BI-RADS 3. Pathology revealed DCIS. MLO, mediolateral oblique; CC, craniocaudal, CESM, contrast-enhanced spectral mammography; DCIS, ductal carcinoma in situ

Table 7 Diagnostic indices of CESM in the detection of malignancy

	Value (%)
Sensitivity	97.53
Specificity	54.24
Positive predictive value	74.53
Negative predictive value	94.12
Accuracy	79.29

Abdallah et al. [13] assessed the combined use of mammography and ultrasound in their study and found that when combined, their sensitivity was 80%.

Many studies, like those carried out by Paula and Campos [15], Zaky et al. [16], and Panzironi et al. [17], have studied the role of MRI as a problem-solver in cases of PND. They concluded that a higher sensitivity was achieved using contrast-enhanced MRI. Based on its ability to assess the neoangiogenesis of lesions (similar to MRI), we thought to study CESM as an alternative method to MRI given its wider availability, lower cost, and higher tolerance among patients. To our knowledge, this is the first study to have evaluated the role of CESM in detecting malignancies among cases presenting with PND.

The interpretation of CESM findings depends on the analysis of morphological criteria and enhancement patterns, as based on the MRI BI-RADS lexicon. In the current study, a non-circumscribed margin (77.5%) was most commonly encountered with malignant masses, while a circumscribed margin (70.4%) was most commonly encountered with benign masses. Regarding non-mass enhancements, linear distribution was most commonly seen with malignant lesions (34.4%), followed by regional non-mass enhancements (26.2%) and segmental non-mass enhancements (13.1%), yet this distribution is also most commonly found in benign lesions (24.0%), which can explain the increased number of false-positive cases (27 cases). These are similar to the worrisome criteria detected by MRI in patients with PND, which included the "non-mass enhancement" of segmental and linear distribution [17]. Based on the findings from our study, the false-negative cases were mainly attributed to bilateral symmetrical diffuse or nodular enhancement, which was falsely estimated to be background parenchymal enhancement with fibroadenosis.

In our study, the sensitivity and specificity of CESM were 97.5% and 54.2%, respectively, with an overall accuracy of 79.3%. The lower specificity of CESM may be related to non-circumscribed margins, which may be encountered with enhancing intra-ductal papillomas; it might also be associated with the distribution of non-mass enhancements associated with some benign processes, which were comparable with malignant ones. To date, we found that CESM, unlike MRI, has not been widely studied in patients presenting with PND. In 2020, Hegazy et al. [18] performed a study comparing MRI and CESM in the evaluation of intra-ductal papilloma; the authors concluded that MRI had a higher sensitivity and lower specificity when compared to CESM.

In their 2019 study, Xing et al. [19] concluded that CESM led to altering treatment plans to include more extensive surgery +/− neoadjuvant chemotherapy in 57.0% of cases diagnosed with breast cancer. In our study, CESM was able to detect multifocality in 24.1%, multicentricity in 43.0%, diffuse abnormalities in 8.9%, and bilaterality in 20.2%, while sono-mammography detected multifocality in 20.5%, multicentricity in 37.2%, diffuse abnormalities in 3.8%, and bilaterality in 17.9%. These findings emphasize the role of CESM in the delineation of disease extent, allowing for proper planning and tailoring of treatment strategies that can suit each patient.

This study has two main limitations. The first limitation is the sample size which is considered small to drive a conclusion of incorporating CESM in the diagnostic workup of PND cases. The second limitation is our inability to compare the diagnostic performance of CESM with contrast-enhanced MRI examination due to the limited number of cases performing both modalities. We believe that more work still needs to be done to determine if CESM can be an alternative to contrast-enhanced MRI examination as a problem-solving tool.

Conclusion

Although sono-mammography is still a cornerstone modality in the diagnostic workup of PND, CESM can also be a valuable diagnostic imaging tool in the detection of associated malignancies, especially if sono-mammographic findings are equivocal. Its high NPV can limit the use of surgical intervention for exclusion of malignancy. Moreover, it can lead to better preoperative delineation of disease extent and ultimately alter the treatment strategy.

Abbreviations

CESM: Contrast-Enhanced Spectral Mammography; PND: Pathological Nipple Discharge; BIRADS: Breast Imaging, Reporting, and Data systems; MRI: Magnetic Resonance Imaging; DCIS: Ductal Carcinoma In situ.

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Author contributions

SF wrote the manuscript and was responsible for correspondence to journal. RW and HS collected patient data and were responsible for processing and collection of patients images. MH was responsible for surgical data collection. SH was responsible for pathological data collection. SB participated in the

design of the study and performed the statistical analysis. All authors have read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
The protocol was reviewed and approved by the Ethics Committee of Baheya center for Early detection and Treatment of Breast Cancer.

Consent for publication
A written consent for publication was obtained for these cases.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Baheya Center for Early Detection and Treatment of Breast Cancer, Giza, Egypt. [2]Radiology Department, Cairo University, Cairo, Egypt. [3]National Cancer Institute, Cairo University, Cairo, Egypt.

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