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Research Article

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Contrast Enhanced Mammography: A Problem-Solving Tool in Indeterminate Breast Lesions

Dr. Rafia Shahzad*[1], Dr. Farwa Malik[2], Dr. Maryam Ikram[2], Dr. Zeeshan Rashid Mirza[1], Dr. Faisal Ehsan Cheema[1], Dr. Arzoo Fatima Saleem[3]

*[1]Consultant, Department of Diagnostic Radiology, AECH INMOL, Lahore, Pakistan.
[2]Medical Officer, Department of Diagnostic Radiology, AECH INMOL, Lahore, Pakistan.
[3]Director, AECH INMOL, Lahore, Pakistan.

***Correspondence:**
Dr. Rafia Shahzad, Consultant Radiologist, Department of Diagnostic Radiology, Atomic Energy Cancer Hospital INMOL, Lahore, Pakistan.

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Abstract

Characterization of breast lesions may remain uncertain with conventional imaging techniques, especially for suspected benign and low-suspicion lesions, which affect decisions about subsequent follow-up or diagnostic biopsy. This study is a cross-sectional diagnostic accuracy study to evaluate the role of Contrast-Enhanced Mammography (CEM) in identifying malignant lesions among 60 female patients aged 20-60 years who have BI-RADS category 3 or 4A lesions on conventional mammography or sonomammography or both. Dual-energy CEM was performed, followed by biopsy or surgical excision of lesions, and the results obtained on histopathology served as the reference standard. Histopathology revealed malignancy in ten of 60 patients (16.7%). CEM classified eleven lesions as malignant and forty-nine as non-malignant, with resulting true-positive, false-positive, false-negative and true-negative results of 9, 2, 1 and 48, respectively. The diagnostic accuracy of CEM, including sensitivity, specificity, PPV, NPV and accuracy rate, was calculated as 90%, 96%, 81.8%, 98% and 95%, respectively, with 95% confidence intervals (CI) for the detection of malignant lesions. CEM also showed positive and negative likelihood ratios of 22.5 and 0.10, respectively. This study demonstrates a high level of diagnostic capability of CEM, especially with a strong predictive power in ruling out malignancy in the studied population. Hence, CEM is considered to be a useful problem-solving tool for the evaluation of BI-RADS category 3 and 4A breast lesions.

Keywords: Breast Cancer; Contrast-Enhanced Mammography; Diagnostic Accuracy; BI-RADS; Breast Lesions; Histopathology.

Introduction

Breast cancer is a global health problem that remains a major cause of mortality in women worldwide. GLOBOCAN 2022 statistics estimate nearly 2.30 million new breast cancer cases diagnosed and 666,103 deaths globally.[1] In Pakistan, breast cancer is the most frequent oncological entity seen in women, with more than 30,682 new cases to be registered and 15,552 breast cancer-related deaths predicted to occur in 2022.[2] This highlights the burden of the disease in the country, thereby making more effective diagnostic tools essential.

Conventional mammography has played a significant role in breast imaging; nevertheless, it is sometimes difficult to differentiate a malignant from a benign lesion, particularly those that are small and have low or intermediate suspicion. BI-RADS 3 defines a lesion as probably benign, in which the probability of malignancy is 2% or lower.[3] BI-RADS 4A indicates an abnormality of low suspicion that ranges from a slightly elevated probability of >2% to no more than 10%.[4] These categories are clinically significant because patient management decisions lie near thresholds for short interval follow-up or tissue biopsy.

Contrast-enhanced mammography involves the simultaneous or sequential use of contrast material (typically iodine-based) to enhance the lesion and the subsequent utilization of dual-

energy image acquisitions, with the low- and high-energy images subtracted/recombined to produce an image in which contrast uptake is visible against a suppressed background. The combined display of the conventional low-energy mammogram and the subtracted (recombined) image has been shown to demonstrate high diagnostic performance, which is superior to displays of the subtracted image alone.[5] A meta-analysis of the use of contrast-enhanced mammography to help with equivocal results in dense breasts shows pooled estimates of 95% sensitivity and 81% specificity.6 Updated guidelines and reviews have more and more emphasized the role of contrast-enhanced mammography as a useful screening, diagnostic and problem-solving technique.[7,8,9]

The aim of this study was to evaluate the effectiveness of contrast-enhanced mammography (CEM) in distinguishing malignant from benign BI-RADS category 3 or 4A breast lesions with histopathological diagnosis as the gold standard. This study assessed the sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios and overall diagnostic accuracy of CEM.

Materials and Methods

Study design and setting

This was a cross-sectional, prospective diagnostic accuracy study conducted at the Radiology Department, Atomic Energy Cancer Hospital INMOL, Lahore, Pakistan, between October 2025 and March 2026. Sixty female patients aged 20-60 years with BI-RADS 3 or 4A breast lesions on conventional mammography and/or sonomammography, requiring further problem-solving evaluation and with histopathology as the gold standard, underwent dual-energy contrast-enhanced mammography. The analysis included all participants with complete CEM and histopathology results during the study period.

Eligibility criteria

The inclusion criteria were female patients aged 20 and above, diagnosed to have a lesion of either BI-RADS category 3 or BI-RADS category 4A on conventional mammography and/or sonomammography who need further problem-solving imaging, having subsequent tissue diagnosis for proper confirmation and willing and able to undergo contrast-enhanced mammography and to give consent for the procedure. Female patients who were pregnant, those with a prior severe allergic reaction to iodinated contrast materials, those with acute renal injury or significantly impaired renal function, those who had previous surgery or treatment altering the index lesion prior to CEM, patients with technically inadequate CEM images and those without a final histopathological diagnosis were excluded.

Pre-examination assessment and contrast administration

Before CEM, all patients were assessed for pregnancy status and for contraindications to iodinated contrast, including previous history of severe contrast reactions and clinically relevant renal impairment. IV access line established by a 20-gauge cannula. All CEM examinations were performed on the Digital Mammography machine (Hologic Selenia Dimensions 6000). The examination followed a standard dual-energy CEM protocol. A low-osmolar nonionic iodinated contrast agent was administered intravenously through a power injector at a dose of 1-1.5 mL/kg (maximum 50 mL total dose) at a rate of approximately 2-3 mL/s followed by a saline flush.[7,15]

CEM image acquisition

CEM imaging started approximately 2 minutes after contrast administration and concluded within 8 minutes.[7,15] Standard bilateral craniocaudal and mediolateral oblique views were obtained with appropriate breast compression and positioning. For each projection, paired low and high-energy exposures were acquired in rapid succession during a single compression. The system-generated recombined images suppressed background breast tissue while highlighting areas of iodine uptake. Additional projections were obtained on an as-needed basis to optimize lesion localization.

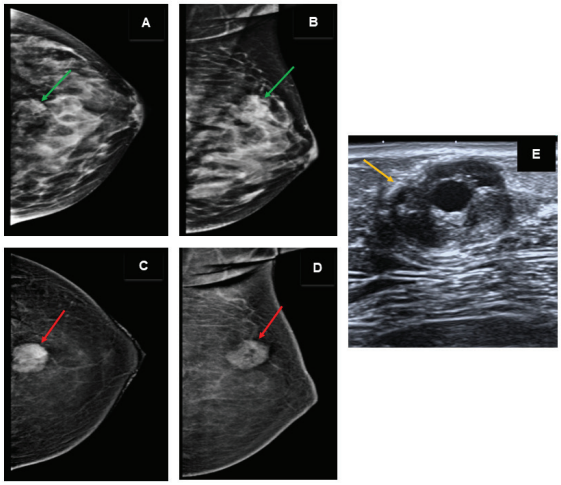

FIGURE 1: A 36-year female presented with left breast lump.
A and B: 2D Mammogram revealed a relatively circumscribed lesion in central upper part of left breast with partially obscured margins (Green Arrow).
C and D: CEM revealed the lesion margins more clearly which appear mildly lobulated with marked contrast enhancement and central non enhancing area (Red Arrow)
E: USG Left Breast also shows a hypoechoic lesion with relatively defined margins and central cystic area in it (Yellow Arrow).

The lesion was indeterminate on USG and 2D Mammogram but based on its intense enhancement pattern it was interpreted as malignant on CEM and subsequent biopsy showed it to be Intra Ductal Carcinoma (IDC).

CEM interpretation

Experienced radiologists who were blinded to the final histopathological results performed interpretation of CEM examinations. Low-energy images were evaluated for mammographic morphology using BI-RADS principles. Recombined images were assessed for the presence or absence of enhancement and for enhancement morphology and distribution. The combined findings of the low-energy and recombined images were taken into consideration during each interpreted study because it improves diagnostic performance.[5,8,9,10] In order to analyze the performance of CEM for the study cohort, the initial CEM findings were characterized either as malignant/suspicious or as non-malignant. A CEM-positive result represented a lesion considered suspicious for malignancy on the combined morphologic and enhancement assessment, whereas a CEM-negative result represented a lesion without suspicious enhancement or suspicious low-energy morphology. The combined CEM findings were subsequently compared with histopathology.

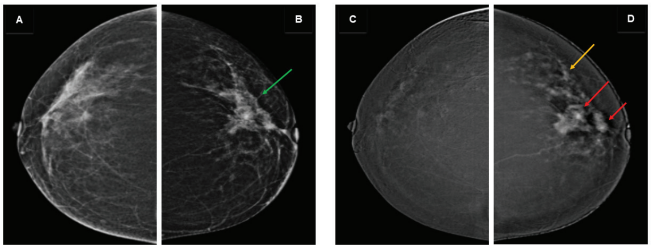

FIGURE 2: A 42-year female presented with left breast lump.
A and B: 2D Mammogram revealed an indeterminate area of asymmetric density in upper outer quadrant of left breast (Green Arrow).
C and D: CEM revealed two irregularly marginated markedly enhancing lesions (Red Arrows). In addition, an area of non-mass enhancement is also noted in its vicinity (Yellow Arrow). Biopsy revealed both lesions were malignant (IDC) with associated DCIS.

Reference standard

Final histopathological results, derived from biopsy or surgical specimens, were used as the reference standard. Diagnoses made at histopathology were coded as benign or malignant for the diagnostic accuracy analysis.

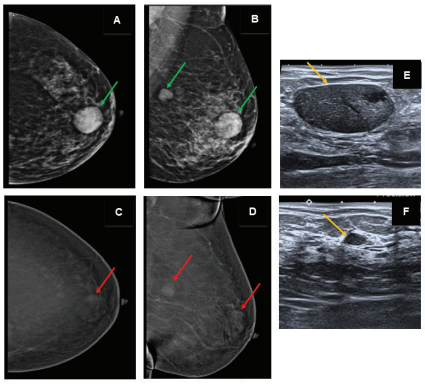

FIGURE 3: A 39-year female presented with left breast lump.
A and B: 2D Mammogram revealed two well circumscribed slightly lobulated lesions in the left breast (Green Arrows)
C and D: CEM shows minimal enhancement (Red Arrows)
E and F: USG left breast also shows two well-defined oval shaped hypoechoic lesions (Yellow arrows). Biopsy showed them to be fibroadenomas.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and categorical data were presented as frequencies and percentages. The results were organized in a 2 × 2 contingency table using histopathology results as the reference standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy were defined as: sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); PPV = TP/(TP + FP); NPV = TN/(TN + FN); and accuracy = (TP + TN)/(TP + FP + FN + TN). Exact binomial 95% confidence intervals (CI) were reported for the aforementioned metrics. Positive and negative likelihood ratios were also calculated. Stratified results for age were tabulated and analyzed descriptively.

Ethical considerations

Approval was obtained by the Institutional Review Board and consent from the participants was provided in written form prior to the study's execution. All participant data were stored and managed confidentially. No clinically identifiable information for individual patients is contained within this manuscript.

Results

The cohort consisted of sixty participants. Mean age ± standard deviation was 44.65 ± 11.64. The age distributions were 20 (33.3%) participants aged 20-40 years and 40 (66.7%) participants aged 41-60 years. CEM interpreted 11 (18.3%) as malignant and 49 (81.7%) as non-malignant cases. Histopathology confirmed malignancy in 10 cases (16.7%) and benign pathology in 50 cases (83.3%) (Table 1).

TABLE 1: Participant characteristics and diagnostic outcome (N = 60)

Characteristic	Value
Age, mean ± SD, years	44.65 ± 11.64
Age 20-40 years	20 (33.3%)
Age 41-60 years	40 (66.7%)
CEM classified as malignant	11 (18.3%)
CEM classified as non-malignant	49 (81.7%)
Malignant histopathology	10 (16.7%)
Benign histopathology	50 (83.3%)

Abbreviations: CEM: contrast-enhanced mammography; SD: standard deviation.

Using histopathology as the reference standard, CEM results demonstrated 9 true-positives, 2 false-positives, 1 false-negative and 48 true-negatives (Table 2).

TABLE 2: Contingency table for CEM using histopathology as the reference standard

CEM result	Malignant histopathology	Benign histopathology	Total
Malignant / positive	9	2	11
Non-malignant / negative	1	48	49
Total	10	50	60

Counts: True positive = 9; False positive = 2; False negative = 1; True negative = 48.

CEM resulted in 90.0% (95% CI: 55.5%-99.7%) sensitivity, 96.0% (95% CI: 86.3%-99.5%) specificity, 81.8% (95% CI: 48.2%-97.7%) PPV, 98.0% (95% CI: 89.1%-99.9%) NPV and 95.0% (95% CI: 86.1%-99.0%) overall accuracy. These findings translate into a positive likelihood ratio of 22.5 (95% CI: 5.70-88.86) and a negative likelihood ratio of 0.10 (95% CI: 0.02-0.67) (Table 3).

TABLE 3: Diagnostic performance of CEM using histopathology as the reference standard

Measure	Estimate	95% CI
Sensitivity	90.0%	55.5%-99.7%
Specificity	96.0%	86.3%-99.5%
Positive predictive value	81.8%	48.2%-97.7%
Negative predictive value	98.0%	89.1%-99.9%
Accuracy	95.0%	86.1%-99.0%
Positive likelihood ratio	22.5	5.70-88.86
Negative likelihood ratio	0.10	0.02-0.67

Confidence intervals for proportions were calculated using exact binomial methods. Likelihood-ratio, Confidence intervals were estimated on the log scale.

Descriptive age-stratified analysis showed an observed accuracy of 95.0% in both age groups. In participants aged 20-40 years, sensitivity was 100.0%, specificity 94.4%, PPV 66.7% and NPV 100.0%. In participants aged 41-60 years, sensitivity was 87.5%, specificity 96.9%, PPV 87.5% and NPV 96.9%. These subgroup estimates were descriptive.

Discussion

In this cohort of women with BI-RADS 3 and 4A lesions, CEM achieved favorable diagnostic performance in relation to histopathology. The sensitivity of 90.0%, specificity of 96.0% and overall accuracy of 95.0% are comparable with previously published literature. The NPV of 98.0% is also encouraging and suggests a low likelihood that patients categorized as CEM-negative will have underlying malignancy in this cohort. High PPV and a very favorable positive likelihood ratio (22.5) demonstrate increased likelihood of malignancy when a positive result is obtained with CEM. A substantially lower likelihood of malignancy is seen after a negative result on CEM (negative likelihood ratio 0.10).

These data are generally consistent with those reported in other studies involving CEM. Cozzi and colleagues analyzed 60 studies consisting of over 10,000 participants and found a receiver operating characteristic (ROC) curve area of 0.94 for contrast-enhanced spectral mammography. Pooled sensitivity for mammographically detected suspicious masses was 92% and pooled specificity was 84%.[5] Using the BI-RADS categorization, studies evaluating both BI-RADS 4 and 5 lesions suggest that pooling of individual study performance may demonstrate lower sensitivity and higher specificity.[6] The sensitivity observed in the present cohort falls within the desirable range reported across CEM trials while the observed specificity of 96% exceeded expectations.

Perhaps the most valuable characteristics of the current results are the high NPV and specificity. In a problem-solving setting, high specificity helps reduce false-positive escalation while a high NPV can increase confidence when CEM does not demonstrate suspicious findings. This combination is especially relevant for BI-RADS 3 and 4A lesions where the central clinical question is often whether an equivocal or low-suspicion abnormality truly requires additional invasive assessment. The very favorable likelihood ratios in this study further support the discriminatory value of the test beyond percentage accuracy alone.

Individual diagnostic studies support the performance metrics seen in the present cohort. Luczynska et al reported 100% sensitivity and significantly improved accuracy using contrast-enhanced spectral mammography compared with standard mammography in a histopathologically verified cohort.[11] In patients with indeterminate findings on ultrasound, CEM performed immediately prior to biopsy yielded 98.5% sensitivity and 95.1% NPV.[12] Similarly, CEM showed excellent agreement with dynamic contrast-enhanced MRI for suspicious masses in patients with indeterminate ultrasound findings.[13] While performance varies across the population studied and BI-RADS category being interpreted, the direction of clinical research is in favor of CEM as a useful functional adjunct to morphologic breast imaging.

The potential value of CEM near biopsy thresholds is particularly relevant to BI-RADS 4A lesions. Rong et al demonstrated that CEM improved decision-making in tomosynthesis BI-RADS 4A findings and had potential to reduce unnecessary biopsy in appropriately selected lesions.[14] The present study was not designed as a biopsy-avoidance trial, but its high specificity and NPV provide a strong rationale for further evaluation of CEM in this clinical role.

One significant technical strength of CEM is that it combines standard morphology with contrast-enhanced imaging. Meta-analytic evidence demonstrates that simultaneous interpretation of low-energy and recombined images provides a better sensitivity-specificity balance than that of recombined images alone.[5] In line with current BI-RADS guidance for CEM and systematic interpretation techniques, there is also a combined approach for the interpretation of low-energy morphology with contrast-enhancement findings.[8,9] Kim et al have also previously established that the presence of a low-energy finding on an enhancing lesion increases its probability of being malignant and that mass enhancement is highly correlated with malignancy.[10] Hence, the approach of integrating low-energy and enhanced imaging used in the current study is consistent with contemporary practices for CEM.

From a practical standpoint, CEM fits into routine mammography-based diagnostic workflow and also adds valuable functional information without prolonging procedure time or requiring dedicated resources such as can be the case with breast MRI in many settings. Various publications have previously reported CEM to be an effective adjunct or alternative to breast MRI when the latter is not available, is contraindicated or is not feasible.[15] This is particularly useful in regions of high burden where access to breast MRI is restricted and a quick mammography-based problem-solving test is required to streamline patient flow.

Stratified analysis by age showed that observed accuracy is consistent with respective age groups, with 95.0% accuracy for both younger and older groups. Because these subgroup findings were descriptive, they should be viewed as supportive rather than definitive. Nevertheless, the consistency of the observed results across younger and older participants adds to the overall robustness of the main diagnostic accuracy findings.

The following features strengthen this study: all participants had histopathological confirmation, which results in a valid equal reference standard as opposed to performing differential verification among test-positive and test-negative cases; CEM interpretations were carried out and blinded to histopathology to avoid reader bias; and the target population was characterized as having a low pretest probability where additional diagnostic information can significantly influence patient management. The analysis also presents confidence intervals and likelihood ratios in addition to the conventional figures of sensitivity, specificity and predictive values. Although external validation from larger multi-institutional prospective studies would be valuable, given that this was a single-institution cohort, a combined CEM and histopathology design lends internal validation to our assessment of CEM diagnostic performance.

Conclusion

Contrast-enhanced mammography demonstrated high diagnostic performance for differentiating malignant from benign BI-RADS 3 and 4A breast lesions, with 90.0% sensitivity, 96.0% specificity, 98.0% NPV and 95.0% overall accuracy. The combination of high specificity, high NPV and favorable likelihood ratios supports CEM as a clinically useful problem-solving modality for low-

suspicion and indeterminate breast findings. Integration of low-energy morphology with contrast-enhancement information can increase diagnostic confidence and may help refine management decisions in patients close to biopsy thresholds.

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Conflict Of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: Rafia Shahzad
Data acquisition: Rafia Shahzad, Farwa Malik, Maryam Ikram, Zeeshan Rashid Mirza, Faisal Ehsan Cheema and Arzoo Fatima Saleem.
Writing - original draft preparation: All authors.
Writing - review & editing: All authors.
All authors have reviewed and approved the final manuscript.

Ethics Approval and Informed Consent

Approval was obtained from the institutional review board and written informed consent was obtained.

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