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# ROLE OF CONTRAST ENHANCED MAMMOGRAPHY IN MONITORING RESPONSE TO CHEMOTHERAPY

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Contrast-enhanced spectral mammography, Full-field digital mammography, neoadjuvant chemotherapy, Breast cancer.

**ABSTRACT**

The study's goal is to highlight the importance of contrast enhanced spectral mammography (CESM) in assessing response of breast cancer to neoadjuvant chemotherapy (NAC) in terms of residual tumor size and extent. CESM was performed on thirty female patients with ages between 30 and 57 years old, diagnosed as malignant breast cancer and planned to receive NAC. To ensure the final diagnosis of residual masses and to determine the specificity and sensitivity of CESM, the final histopathology and/or at least 6 months of clinical and radiological follow-up were employed as reference standards. In current study, the enrolled subjects underwent both contrast enhanced spectral mammography (CESM) and conventional full field digital mammography (FFDM) before and after neoadjuvant chemotherapy (NAC) and prior to surgery and results were compared to final pathological response. CESM was shown to be better than FFDM in terms of sensitivity, specificity, and accuracy, measuring 71.4 %, 100% and 90% for (CESM), compared to 56%, 75% and 75% for (FFDM). Contrast-enhanced spectral mammography is a growing technique showing high accuracy in monitoring response of breast cancer to NAC regarding tumor residual size and extent so that the physician can make the optimal therapy decision.



## 1. INTRODUCTION

Neoadjuvant chemotherapy (NAC) aim at reducing the proportion of non-surgically treatable breast cancers and decreasing the need for mastectomy and/or axillary lymph node dissection [1]. After neoadjuvant chemotherapy, the imaging evaluation of treatment response and residual disease helps guide surgical management. Current practice involves clinical examination and multiple imaging modalities, with MRI as the most accurate modality [2]. Contrast enhanced spectral mammography (CESM) is an emerging modality that combines digital mammography with the administration of intravenous contrast material. Breast cancers can be identified at CEM by density and morphologic characteristics as well as by the neovascularity associated with malignancy [3]. CESM has been proven to be a viable alternative imaging tool in the detection of breast cancer, as compared with full field digital mammography (FFDM), application of CESM significantly increased positive rate, accuracy, and sensitivity for breast cancer detection and reduced the mortality of breast cancer because this recombined image could overcome the overlapping of normal breast tissues and eliminate the fibrous glands of breasts [4].

CESM has the diagnostic efficacy comparable to MRI and possesses the merits of convenient operation and low costs. Therefore, future studies are needed to investigate whether CESM can be used to evaluate the response of breast cancer to NAC [5]. Since CEM performs similarly to MRI to help evaluate disease extent. It may also be useful in evaluating treatment response. Multiple studies have investigated this use of CEM [6].

The study's goal is to highlight the importance of contrast enhanced spectral mammography (CESM) in assessing response of breast cancer to neoadjuvant chemotherapy (NAC) in terms of residual tumor size and extent.

## 2. Methods

Patients: From March 2019 to March 2021, 30 breast cancer patients scheduled for neoadjuvant chemotherapy were enrolled in this prospective study. Age range of patients was between 30 and 57 years. The study was approved by the review board and all patients gave their consent. All patients initially had undergone a core needle biopsy for diagnosis.

All patients had an initial mammography and ultrasound examination followed by a core needle biopsy from suspicious lesions. Patients were evaluated by a Multidisciplinary team and scheduled for neoadjuvant chemotherapy. All patients had two separate breast CESM examinations 6 to 12 weeks apart; one examination was done prior to neoadjuvant chemotherapy, and the other examination was performed after completion of chemotherapy and prior to final surgery. The maximum interval between the second CESM examination and surgery was 3 weeks.

### *2.1 Inclusion Criteria*

1. Patients known to have breast cancer.
2. Patient with indication for NAC.

### *2.2 Exclusion Criteria*

- Pregnancy or possible pregnancy
- History of allergy to an iodinated contrast agent
- Renal impairment

Reference standard: The final histopathological response.

### *2.3 Imaging protocol*

Peripheral IV access was obtained in the antecubital fossa contralateral to the breast of concern with intravenous injection of a non-ionic contrast agent (Ultravist 300 or Omnipaque 300) at a dose of 1.5 ml/kg.

### *2.4 Image acquisition*

All data were acquired using GE Senographe 2000D full-field digital mammography system from GE Healthcare. A pair of high-energy and low-energy images were acquired in rapid succession and used to make the final image, via a weighted logarithmic subtraction. Both images were acquired after the contrast injection by about 2 min after the end of the injection to allow the contrast to be taken up in the tissue. The standard positions CC and MLO were obtained, with low- and high-energy images acquired in each view, with compression. Image acquisition was done in the following sequence; CC of the normal breast, CC of the

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affected breast, MLO of the affected breast, and finally MLO of the normal breast.

The duration of the procedure was approximately 10 min. The final dual-energy subtraction image equalizes the density of fibroglandular tissue and fat, thereby minimizing the visibility of the breast tissue and increasing the conspicuity of the iodinated contrast agent.

The high- and low-energy beams are created by adjusting the peak kilovoltage (kVp) of the X-ray tube and changing the filtration. KVp values between 28 and 32 are typically used for the low-energy beam, and those between 45 and 49 are typically used for the high-energy beam. In addition, extra filtration, typically copper, is added to the high-energy beam to further harden it.

#### *2.4.1 Image interpretation*

Image analysis and interpretation were done by an experienced breast radiologist.

A-Regarding mammographic examination, the lesions were evaluated according to:

*1-The enhancement pattern:*

The initial pattern divided as solitary, grouped, separated and replaced. Post NAC pattern divided into Type 1-4 shrinkage pattern, no residual and no change pattern.

*2- The response evaluation criteria in solid tumors (RECIST) regarding the size:*

1-Stable response (SD).

2-Partial response (PR).

3-Complete response (CR).

*3- The combined response:*

1- Stable disease.
2- Poor response.
3- Moderate response.
4- Marked response.
5- Complete response.

### *2.5 B-Regarding the pathological response (gold standard)*

Histopathologic tumor regression was semi-quantitatively graded by one pathologist based on the Miller-Payne grading system. Patients were divided into two groups: pathologic responders and non-responders. Patients showing Miller-Payne grades 3, 4, and 5 were categorized as responders, and patients showing grades 1 and 2 were non-responders.

## 3. Results

This study included 30 female patients with known malignant breast cancer in which 25 patients were invasive duct carcinoma (IDC), 3 patients were invasive lobular carcinoma (ILC), 1 was mixed invasive duct and lobular carcinoma and one patient was mucinous carcinoma (IMC). The initial patterns of contrast enhancement were 10 patients having solitary lesions, 5 patients were grouped lesions, 12 were separated lesions and 3 were replaced lesions. The post NAC enhancement pattern indicated that 9 patients show type 1 shrinkage pattern, 5 patients show type 2 shrinkage pattern, 4 patients show type 3 shrinkage pattern, 3 patients show type 4 shrinkage pattern, 8 patients show no residual and one patient shows no change. The response evaluation criteria in solid tumors (RECIST) showed that 11(36.7%) were stable disease (SD), 12(40%) were partial response (PR) and 7(23.3%) were complete response (CR), while the combined response evaluation approach showed, 2(6.7%) were stable disease, 4(13.3%) were poor response, 8(26.7%) were moderate response, 9(30%) were marked response (21 partial response) and 7(23.3%) were complete response.

Combined response showed highly significant results (P value <0.001) compared to (RECIST) alone.

The gold standard in these study was the pathological response evaluation using Miller-Payne Grade system showing 2(6.7%) were Miller-Payne Grade 1, 5(16.7%) were Miller-Payne Grade 2, 7(23.3%) were Miller-Payne Grade 3, 8(26.7%) were Miller-Payne Grade 4 and 8(26.7%) were Miller-Payne Grade 5. It showed highly significant results (P value <0.001) in comparison with CESM response.

Compared to FFDM, CESM was shown to be better in terms of sensitivity, specificity and accuracy measuring 71.4 %, 100% and 90%, compared to 56%, 75%, 75% respectively.

## 4. Discussion

CEM is an emerging modality that provide critical information in a number of clinical scenarios, it is most commonly used to evaluate disease extent in patients with contraindications to MRI. It is also increasingly being used in the diagnostic setting for patients recalled from screening [7]. This was a prospective study conducted on 30 women with breast cancer and indicated for NAC study over a period of two years. These current study reported using the area under the ROC curve that the calculated sensitivity, specificity and accuracy for CESM to discriminate response patients from non-response were 71.43%. 100.0%, 90%. In agreement with our results the study done by [8] that showed sensitivity and specificity 83.33% and 100%. While the results of the study by [9] showed that the calculated sensitivity, specificity and accuracy for CESM to discriminate response patients from non-response were 95.2%. 98.3%, 95.2% respectively. As well the study by [10] reported that the sensitivity and specificity were 100% and 84%, respectively, for CESM. The study by [11] reported that the sensitivity, specificity and accuracy of CESM for prediction of all the tumor responses are 40%, 91% and 66% respectively.

Regarding the distribution of histologic tumor type, 25(83.3%) were invasive ductal carcinomas (IDC), 3(10%) were invasive lobular carcinomas (ILC), 1(3.3%) were mixed invasive ductal and lobular carcinomas and one (3.3%) was mucinous carcinoma (IMC). The study done by [11] shows 18 (85.7 %) were IDC, 1 (4.8 %) was mixed IDC and ILC and 2 (9.5 %) were ILC. While the study by [10] reported that in their studied patients there are 94% of the cases were invasive ductal carcinomas (IDC), 3% of the cases were invasive lobular carcinomas (ILC), and 3% were mucinous carcinoma.

Regarding Post NAC shrinkage pattern on CEM, the current study showed that 9(30%) were type 1 shrinkage pattern, 5(16.7%) were type 2 shrinkage pattern, 4(13.3%) were type 3 shrinkage pattern, 3(10%) were type 4 shrinkage pattern, 8(26.7%) no residual and one (3.3%) no change was noted. In agreement with the study by [9] showed that (29.6%) were type 1 shrinkage pattern, (18.5%) were type 2 shrinkage pattern, (11.1%) were type 3 shrinkage pattern, (11.1%) were type 4 shrinkage pattern, (24.75%) no residual and (4.95%) no change was noted. While study done by [12] showed that pattern 1 was seen in 29 (51.7%) lesions, pattern 2 in 13(23.2 %) lesions, pattern 3 in 5 (8.9%) lesions, and pattern 4 in 4 (7.1%) lesions, no residual 3 (5.3%).

According to radiological response the present results revealed that based on RECIST 11(36.7%) were stable disease, 12(40%) were partial response and 7(23.3%) were complete response. While study done by [13] showed that 4 (12.9%) were stable disease, 14(45.1%) were partial response and 13(41.9%) were complete response. While the study by [9] reported that according to RECIST criteria, non-responders constituted 28/81(34.6%) lesions and responders constituted 53/81 (65.4%) lesions; out of which 20/81 (24.7%) showed complete radiological response. While the study by [10] revealed that histopathological response to NAC in surgical specimen according to RECIST revealed that there were 17% complete response, 70% partial response, 11% stable disease and 2% progressive disease.

Based on the combined response evaluation approach current study showed 2(6.7%) were stable disease, 4(13.3%) were poor response, 8(26.7%) were moderate response, 9(30%) were marked response and 7(23.3%) were complete response with highly significant P value < 0.001 compared to the RECIST response. [9] also reported that according to the combined response, non-responders constituted 16/81 (19.7%) of lesions and responders constituted 65/81 (80.3%) lesions; out of which 20/81 (24.7%) showed complete radiological response. Combined response results were highly significant in comparison to RECIST alone.

In the current work, regarding pathological response evaluation 2(6.7%) were Miller-Payne Grade 1, 5(16.7%) were Miller-Payne Grade 2, 7(23.3%) were Miller-Payne Grade 3, 8(26.7%) were Miller-Payne Grade 4 and 8(26.7%) were Miller-Payne Grade 5. The study done by [14] showed that one (3.8%) was Miller-Payne Grade 1, 5(11.5%) were Miller-Payne Grade 2, 6(23.1%) were Miller-Payne Grade 3, 2(7.7%) were Miller-Payne Grade 4 and 3(11.5 %) were Miller-Payne Grade 5. While the study by [9] reported that according to histopathology results, 60/81 patients (74%) were responders (Miller-Payne grades III, IV, and IV) and 21/80 patients (26%) were non-responders (Miller Payne grades I and II).

In agreement with our results the study by [9] reported that the P value for the overall correlation between size measurements assessed by CESM compared to pathological tumor size was P < 0.001 (highly significant correlation with CEM).

There is good evidence that no additional information is provided by the conventional mammogram that cannot be obtained from a CESM study and so when CESM is planned the conventional mammogram can safely be omitted. The additional staging information and more accurate tumor sizing is available immediately and any further biopsies to confirm disease extent or multifocality can be performed at the first clinic visit. This approach to CESM use also has the advantage of reducing the radiation burden with only one mammographic study required [15].

CESM has other advantages, it is one of several techniques under consideration as a potential screening tool for these women, leading to a more personalized approach to screening [15]. CESM has added value in dense breast as it is not affected by the breast density as only the enhancing masses will stand out while the rest of the glandular element is represented by background parenchymal enhancement [16]. One main advantage of CESM is that it allows the assessment of functional changes in residual tumor cells in addition to size discrepancy [9].

**5. Recommendations**

- More number of patients, longer follow-up, and multicenter experience are all necessary to accurately figure out the accuracy of CESM technique in predicting the residual tumor size and extent post NAC to be accurately matching with the final pathological response.
- Further studies should be implemented to investigate its accuracy compared to the MRI with contrast in predicting pathological response to NAC.

**6. Conclusions**

CESM is a superior diagnostic performance in detecting residual tumor size and extent post NAC with levels of sensitivity, specificity and accuracy better than FFDM and with highly significant results matching with the final pathological results.

**7. List of abbreviations**

CESM: Contrast enhanced spectral Mammography; NAC: Neoadjvuant chemotherapy; FFDM: full field digital mammography; MRI: magnetic resonance imaging; SD: stable disease; PR: Partial response; CR: complete response.

**8. References**

[1] Cardoso, F.; Senkus, E.; Costa, A.; Papadopoulos, E.; Aapro, M.; André, F.; Harbeck, N.; Aguilar Lopez, B.; Barrios, C.H.; Bergh, J.; et al. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4). Annu. Oncol. 2018, 29, 1634–1657.

[2] Perez, J. V. D., Jacobsen, M. C., Damasco, J. A., Melancon, A., Huang, S. Y., Layman, R. R., & Melancon, M. P. (2021). Optimization of the differentiation and quantification of high-Z nanoparticles incorporated in medical devices for CT-guided interventions. Medical physics, 48(1), 300-312.

[3] Kacen, M. G., Sangle, N., & Kornecki, A. (2021). Contrast-Enhanced Mammography in the Diagnosis of Breast Angiosarcoma. Case reports in radiology, 2021 Aug 12; 2021:5542786.

[4] Jochelson, M. S., & Lobbes, M. B. (2021). Contrast-enhanced Mammography: State of the Art. Radiology, 299(1), 36-48.

[5] Eliwa, G. S., El Sheikh, H. E. S. E. S., Habbaa, G. E., & Salah El Din, L. A. (2021). Role of contrast enhanced spectral mammography in assessment of focal breast asymmetry. Benha Medical Journal. Vol. 38:( 640-656).

[6] Neeter, L. M., Raat, H. P. J., Alcantara, R., Robbe, Q., Smidt, M. L., Wildberger, J. E., & Lobbes, M. B. (2021). Contrast-enhanced mammography: what the radiologist needs to know BIR. Vol. 299, No. 1.

[7] Lobbes, M. B. I., Heuts, E. M., Moossdorff, M., & van Nijnatten, T. J. A. (2021). Contrast enhanced mammography (CEM) versus magnetic resonance imaging (MRI) for staging of breast cancer: The pro CEM perspective. European Journal of Radiology, 2021 Apr; 299(1):36-48.

[8] Barra FR, Souza FF, Camelo REFA, Ribeiro ACO, Farage L. Accuracy of contrast-enhanced spectral mammography for estimating residual tumor size, Radiol Bras. Jul-Aug 2017;50(4):224-230.

[9] Kamal, R. M., Saad, S. M., Moustafa, A. F. I., Gomaa, M. M., Mokhtar, O., Gouda, I., & ElZayat, A. (2020). Predicting response to neo-adjuvant chemotherapy and assessment of residual disease in breast cancer using contrast-enhanced spectral mammography: a combined qualitative and quantitative approach. Egyptian Journal of Radiology and Nuclear Medicine, 51(1), 1-14.

[10] Lotti V., Ravaioloi S., Vacondio R. (2017). Contrast-enhanced spectral mammography in neoadjuvant chemotherapy monitoring: a comparison with breast magnetic resonance imaging Breast Cancer Res 2017 Sep 11;19(1):106.

[11] ElSaid, N. A. E., Mahmoud, H. G., Salama, A., Nabil, M., & ElDesouky, E. D. (2017). Role of contrast enhanced spectral mammography in predicting pathological response of locally advanced breast cancer post neo-adjuvant chemotherapy. The Egyptian Journal of Radiology and Nuclear Medicine, 48(2), 519-527.

[12] Kim TH, Kang DK, Yim H, Jung YS, Kim KS, Kang SY (2012) MRI patterns of tumor regression after neoadjuvant chemotherapy in breast cancer patients: correlation with pathologic response grading system

based on tumor cellularity. J Comput Assisst Tomogr 36(2):200–206.

[13] Xing D.,Mao N., Dong J.,Quantitative analysis of contrast enhanced spectral mammography grey value for early prediction of pathological response of breast cancer to neoadjuvant chemotherapy,Scientific Reports volume 11, Article number: 5892 (2021.

[14] O'Toole SA, Spillane C., Huang Circulating tumor cell enumeration does not correlate with Miller–Payne grade in a cohort of breast cancer patient undergoing neoadjuvant chemotherapy Breast Cancer Research and Treatment (2020) 181:571–580.

[15] Sorin V., Yagil Y., Yosepovich A., Contrast-Enhanced Spectral Mammography in Women With Intermediate Breast Cancer Risk and Dense Breasts AJR Am J Roentgenol 2018 Nov;211(5):W267-W274.

[16] James J.J. and Tennant S.L.,Contrast-enhanced spectral mammography (CESM),Clin Radiol.2018Aug;73(8):715-723.doi:10.1016/j.crad.2018.05.005. Epub 2018 Jun 21 after neoadjuvant chemotherapy in patients with breast cancer: a feasibility study. Radiol Bras. 2017 Jul/Ago; 50(4):224–230.

**Table 1:** Distribution of the studied cases according to patterns of contrast enhancement.

| Patterns of contrast enhancement | No. | % |
|---|---|---|
| **Initial** | | |
| Solitary lesion | 10 | 33.3 |
| Grouped lesion | 5 | 16.7 |
| Separated lesion | 12 | 40.0 |
| Replaced lesion | 3 | 10.0 |
| **Post NAC** | | |
| Type 1 shrinkage pattern | 9 | 30.0 |
| Type 2 shrinkage pattern | 5 | 16.7 |
| Type 3 shrinkage pattern | 4 | 13.3 |
| Type4 shrinkage pattern | 3 | 10.0 |
| No residual | 8 | 26.7 |
| No change was noted | 1 | 3.3 |

**Table 2:** Distribution of the studied cases according to radiological response evaluation.

| Radiological response evaluation | No. | % |
|---|---|---|
| **Based on RECIST (mass size)** | | |
| Stable disease | 11 | 36.7 |
| Partial response | 12 | 40.0 |
| Complete response | 7 | 23.3 |

| | | |
|---|---|---|
| **Based on the combined response evaluation approach (mass size and enhancement)** | | |
| Stable disease | 2 | 6.7 |
| Partial responses: | | |
| • Poor response | 4 | 13.3 |
| • Moderate response | 8 | 26.7 |
| • Marked response | 9 | 30.0 |
| Complete response | 7 | 23.3 |
| Stable disease | 2 | 6.7 |
| Partial response | 21 | 70 |
| Complete response | 7 | 23.3 |

**Table 3:** Comparison between RECIST and Combined according to response evaluation.

| | **RECIST Response evaluation** | | | | | | $\chi^2$ | $^{MC}p$ |
|---|---|---|---|---|---|---|---|---|
| | **Stable disease** | | **Partial response** | | **Complete response** | | | |
| | **No.** | **%** | **No.** | **%** | **No.** | **%** | | |
| **Combined response evaluation** | | | | | | | | |
| Stable disease | 2 | 6.7 | 0 | 0.0 | 0 | 0.0 | | |
| Partial response | 9 | 30.0 | 12 | 40.0 | 0 | 0.0 | 26.938* | <0.001* |
| Complete response | 0 | 0.0 | 0 | 0.0 | 7 | 23.3 | | |
| **κ (Level of agreement)** | **0.532 (Moderate)** | | | | | | | |

**Table 4:** Comparison between CESM and Pathological according to mass size.

| | **CESM** | **Pathological** | **Z** | **p** |
|---|---|---|---|---|
| **Mass Size** | | | | |
| Min. – Max. | 0.0 –9.30 | 0.0 – 11.20 | | |
| Mean ± SD. | 2.36 ±2.16 | 3.35 ±2.71 | 4.110* | <0.001* |
| Median (IQR) | 2.65 (0.0 –3.30) | 3.95 (0.0 –4.90) | | |
| **Mean diff. ±SD.** | **1.0 ±1.11** | | | |

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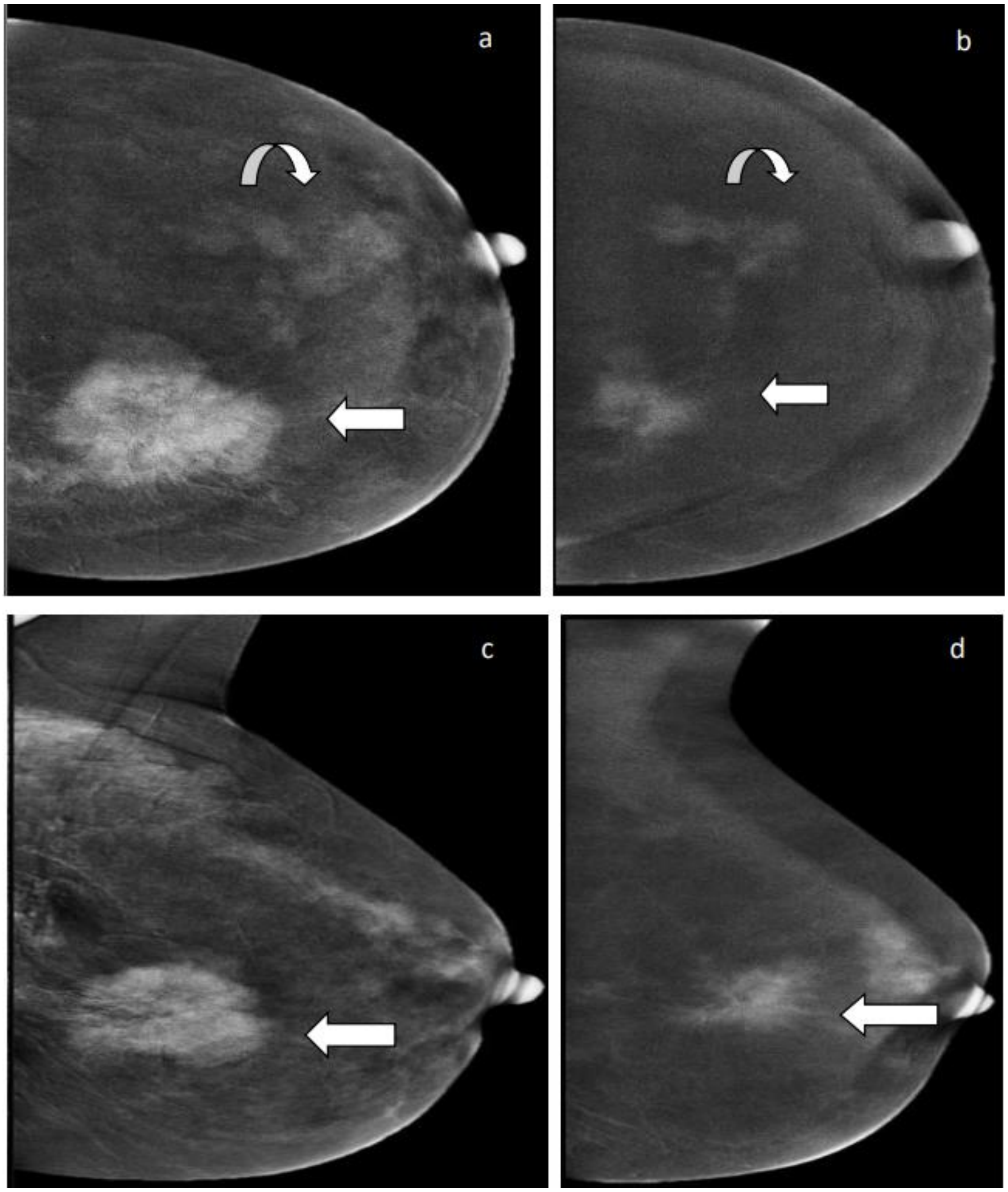


**Figure (1):** A 55 years female patient. A and c: Pre-NAC, left breast CESM medio-lateral and cranio-caudal views showed separated lesions; lower inner heterogeneously enhancing speculated mass (straight arrow) measuring 3.3 cm with UOQ clumped nodular enhancement (curved arrow). b and d: Post-NAC, CESM the mass measures 1.3 cm showed type II shrinkage pattern with 40% reduction in target lesion size and moderate reduction in the intensity of enhancement. Both radiological evaluations classified this patient as a partial responder. Pathological evaluation of the residual lesions confirmed this patient as a partial responder (Miller-Payne grade 3).

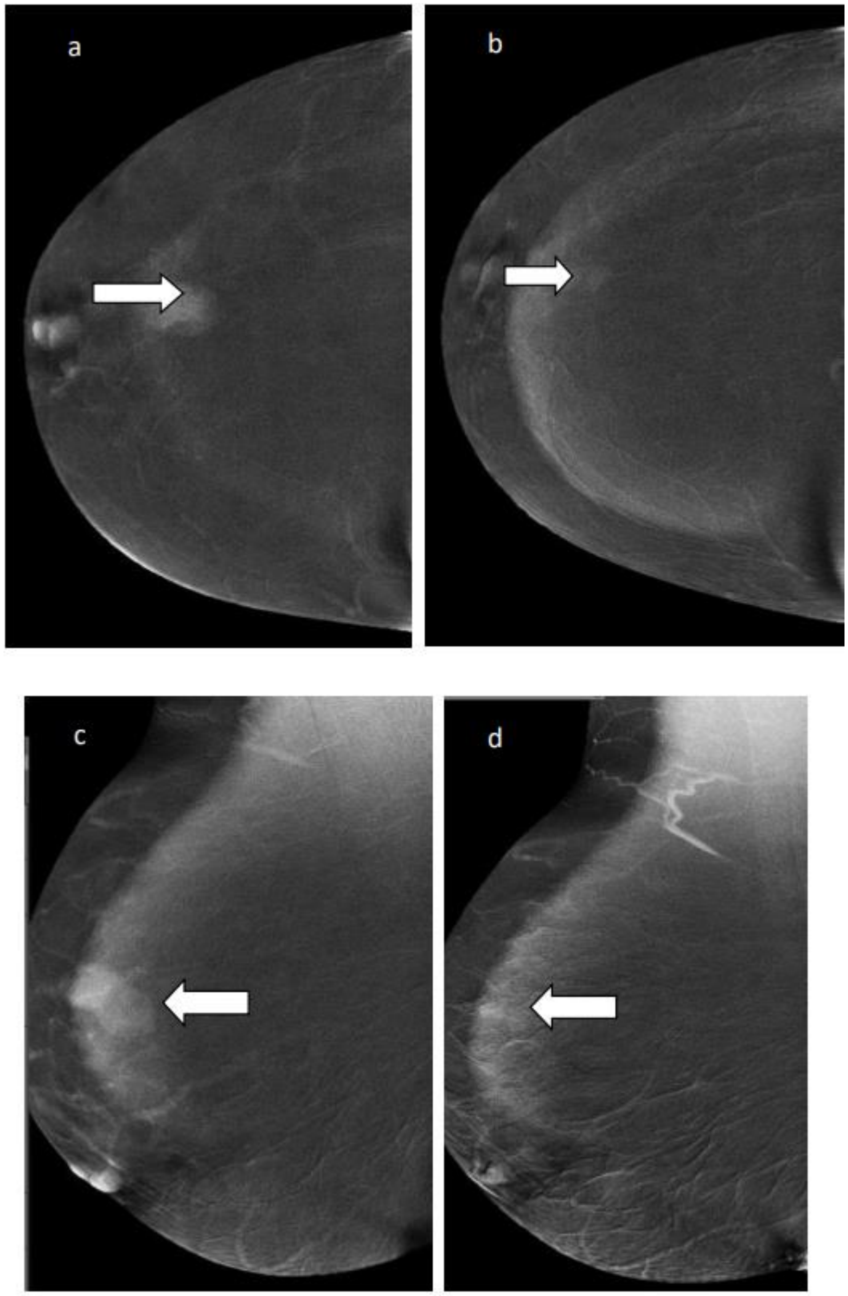


**Figure (2):** A 61 years old female patient heterogeneously enhancing circumscribed mass 2 cm. a and c: Pre-NAC, right breast CESM medio-lateral and cranio-caudal views showed solitary lesion; upper outer quadrant (UOQ) heterogeneously enhancing circumscribed mass. b and d: Post-NAC mass size was 0.8 cm on CESM showing type I shrinkage pattern with more than 40% reduction in lesion size and marked reduction in the intensity of enhancement. Both radiological evaluations classified this patient as a partial responder. Pathological evaluation classified this patient as a complete responder (Miller-Payne grade 5), making this a false positive case by CESM. Pathologic finding in this case was hyalinosis entangling some ectatic breast ducts.

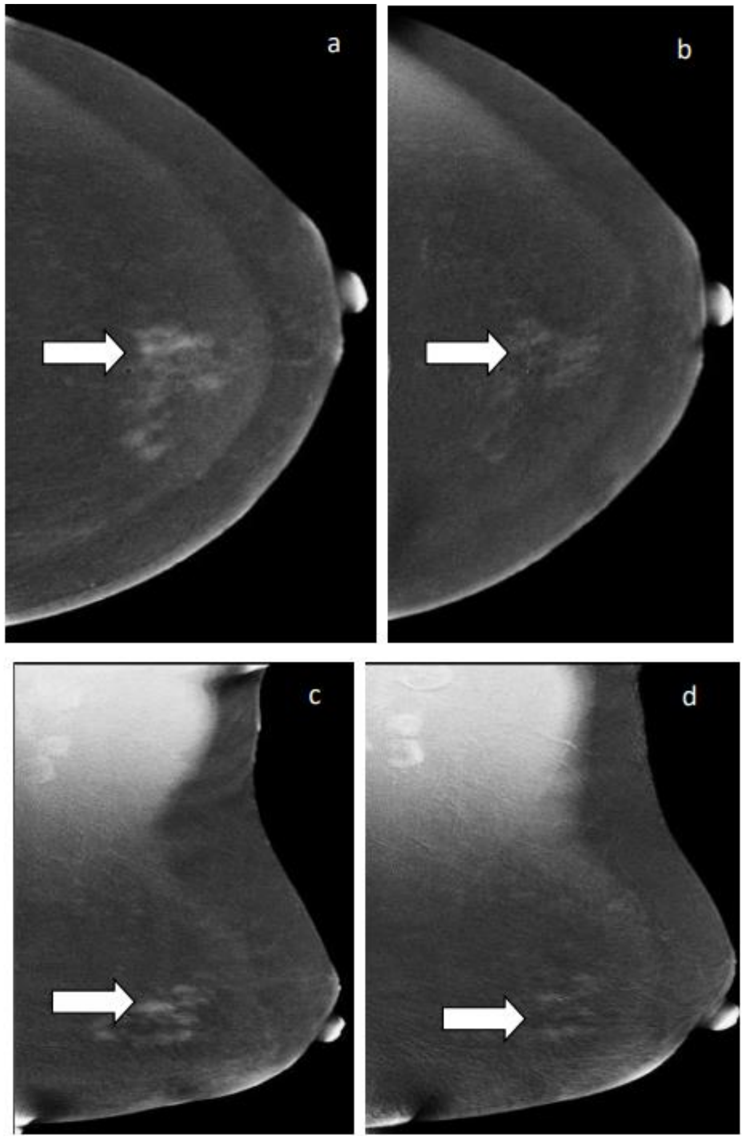


**Figure (3):** A 57 years old female patient a and c: Pre-NAC, left breast CESM medio-lateral and cranio-caudal views showed grouped lesions 2.6 cm; lower inner quadrant (LIQ) focal heterogeneous nodular non-mass enhancement and d: Post-NAC, CESM showed no significant reduction in the lesion size, however with moderate reduction in the intensity of enhancement. Both radiological evaluations classified this patient as a non-responder as the reduction in intensity of enhancement wasn't accompanied by any reduction in tumor size. Pathological evaluation confirmed this patient as a non-responder (Miller-Payne grade 1).

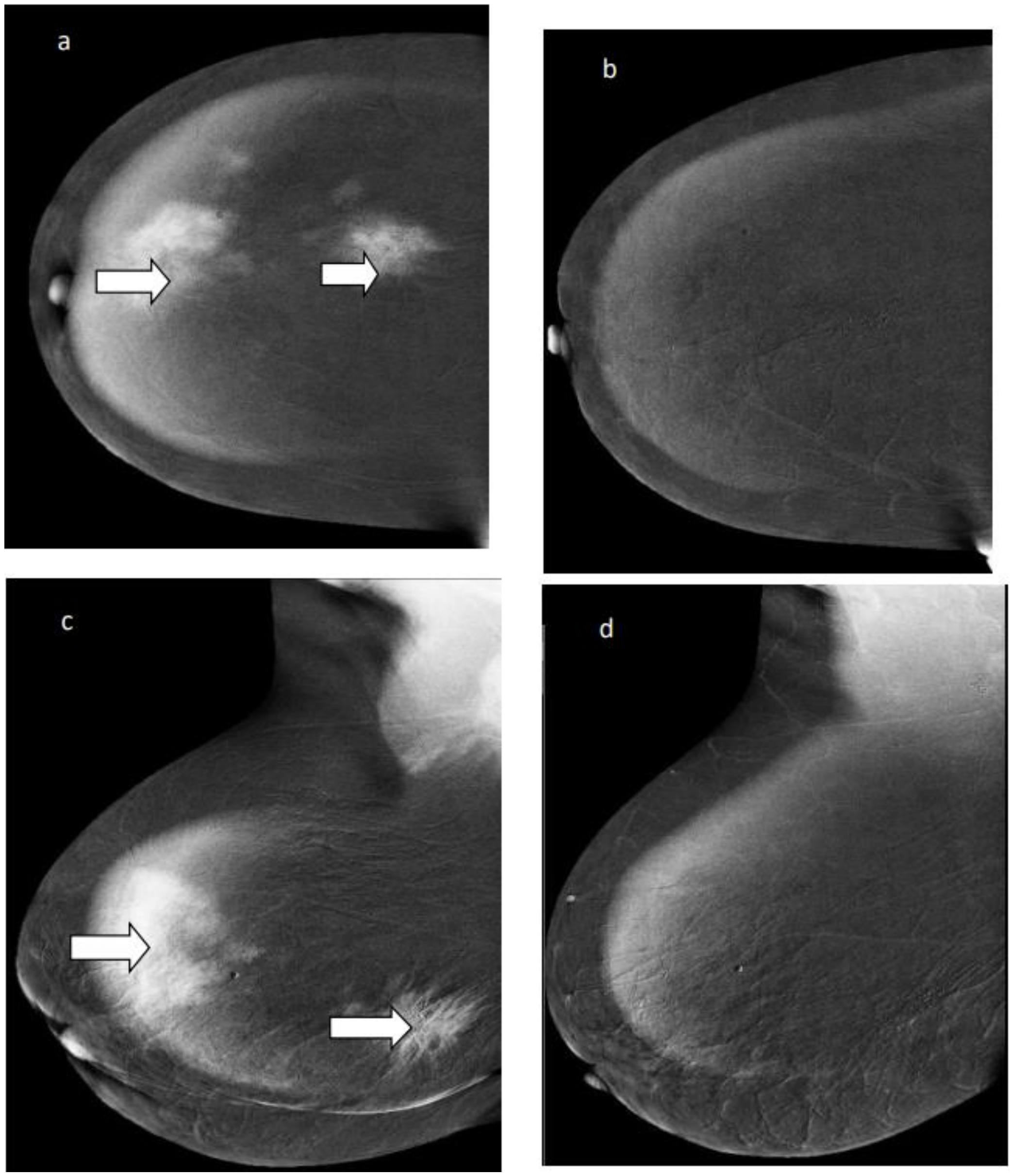


**Figure (4):** A 59 years old patient with IDC of the right breast. a and c: Pre-NAC, right breast CESM medio-lateral and cranio-caudal views showed separated lesions; UOQ and LOQ heterogeneously enhancing masses with smaller surrounding nodules b and d: Post-NAC, CESM showed no residual enhancing lesions (Non-visualization). CESM classified this patient as a complete responder. Pathological evaluation confirmed this patient as a complete responder (Miller-Payne grade 5).

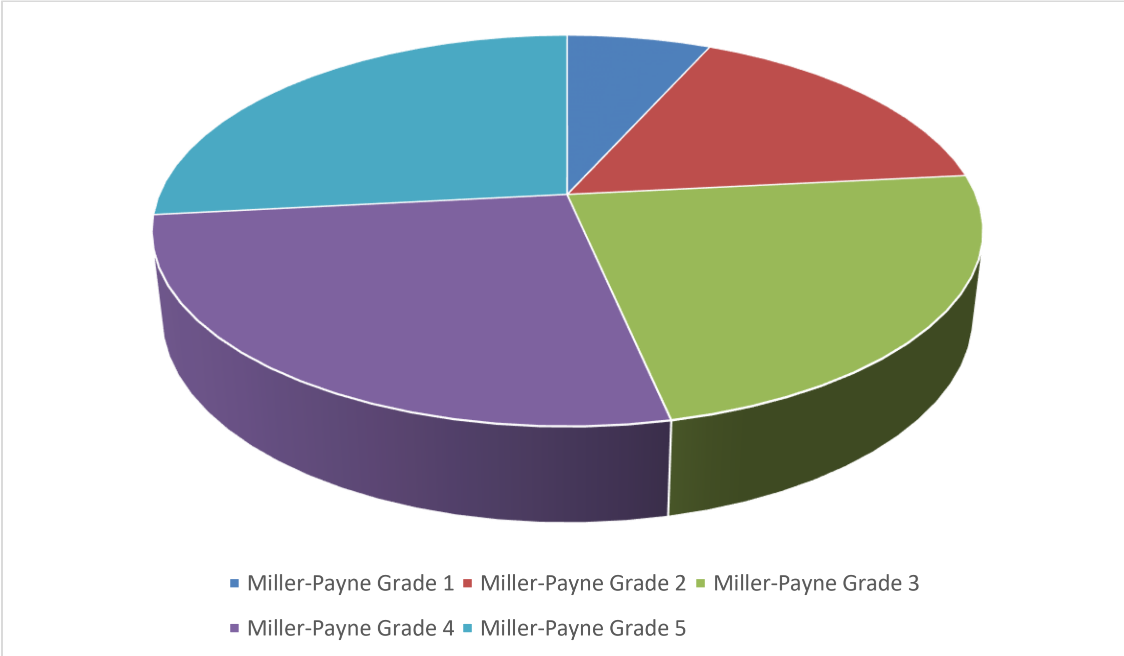


**Figure (5):** This figure shows pathological response evaluation 2(6.7%) were Miller-Payne Grade 1, 5(16.7%) were Miller-Payne Grade 2, 7(23.3%) were Miller-Payne Grade 3, 8(26.7%) were Miller-Payne Grade 4 and 8(26.7%) were Miller-Payne Grade 5.

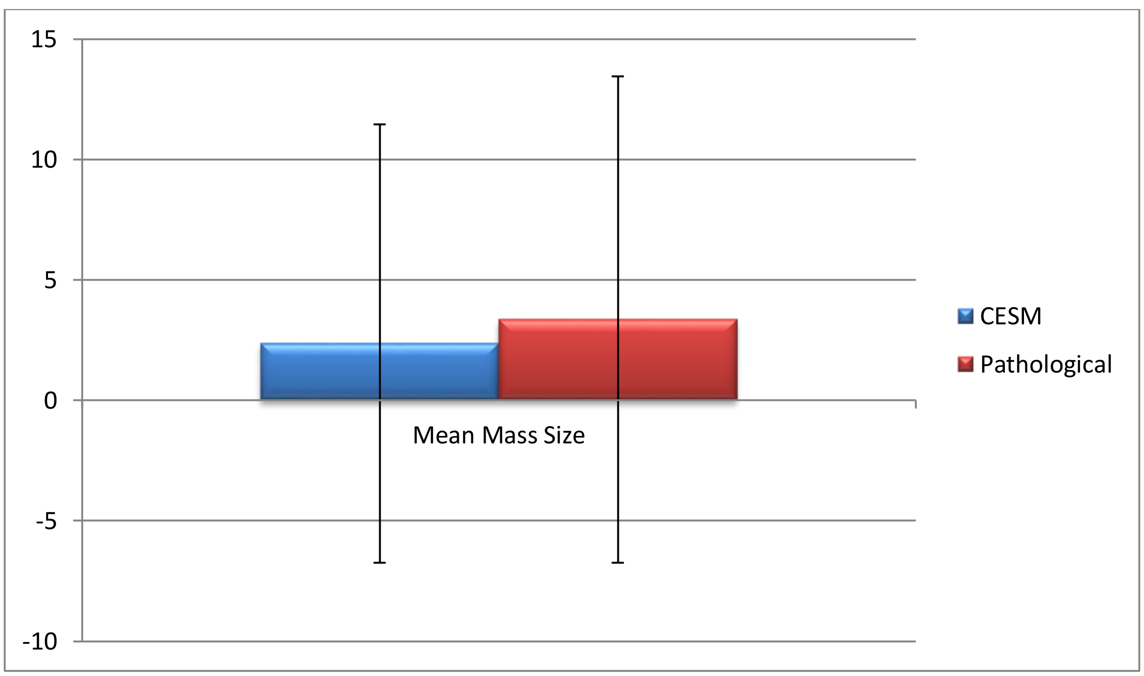


**Figure (6):** Graph showing difference between CESM and Pathological according to mass size.