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# 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

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## Abstract

**Background:** Magnetic resonance imaging (MRI) is the gold standard imaging modality for evaluation of response for neo-adjuvant chemotherapy (NAC) in breast cancer as it has the advantage of providing both; morphology assessment together with providing functional information which can be obtained by contrast injection. Until the recent emergence of contrast-enhanced mammography as a promising breast imaging modality, these features were considered unique for MRI. The aim of the study is to evaluate the competence of contrast-enhanced spectral mammography (CESM) in the prediction of response to NAC and the assessment of residual disease extent, as well as the assessment of a new combined (quantitative and qualitative) evaluation approach that is proposed by the authors. The study included 81 patients with pathologically proved breast cancer scheduled for receiving NAC. They underwent 2 CESM examinations; pre- and post-NAC (maximum 10 days before surgery). All patients were assessed using the RECIST 1.1 criteria and a combined approach (RECIST+ qualitative subjective assessment). Results were in correlation to postoperative pathology using the Miller-Payne grading. For statistical evaluation, patients were classified into responders and non-responders.

**Results:** Postoperative histopathology showed that 60/81 lesions were responders (Miller-Payne grades 3, 4, and 5) while the combined response evaluation approach and RECIST 1.1 alone showed 57/60 (95%) patients and 46/60 patients (76.7%) as responders respectively. The combined response evaluation approach showed higher sensitivity and positive and negative predictive values compared to the evaluation based on RECIST alone (95%, 87.6%, and 81.2% compared to 76.6%, 86.7%, and 50% respectively).

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**Conclusion:** CESM can be readily used to assess tumor response to NAC and allows the assessment of functional changes in residual tumor cells in addition to size discrepancy. Using CESM, we could accurately assess residual tumor extent and thus enable better surgical planning.

**Keywords:** Mammography, Breast Cancer, Chemotherapy

## Background

Neo-adjuvant chemotherapy (NAC) allows the physicians to monitor disease development *in vivo*, hence the need for a modality that can assess tumor response during treatment and that can accurately detect any residual disease left after therapy [1].

There is increasing evidence that magnetic resonance imaging (MRI) is an excellent imaging tool to monitor response to neo-adjuvant chemotherapy, for both early response monitoring and assessment of residual disease extent [1]. However, breast MRI is expensive and not widely available. Similar to breast MRI, contrast-enhanced spectral mammography (CESM) could be of particular interest in the assessment of the extent of disease [2].

The aim of the study is to evaluate the competence of contrast-enhanced spectral mammography (CESM) in the prediction of response to NAC and the assessment of residual disease extent as well as the assessment of a new combined (quantitative and qualitative) evaluation approach that is proposed by the authors.

## Methods

### Patients

From March 2015 to June 2016, 81 patients with an age range between 27 and 77 years were enrolled in this prospective study. The study protocol was approved by the Institutional Review Board of a “Multidisciplinary Breast Cancer Institute” and informed consent was applied for the used data of the enrolled individuals. According to the decision of the “Multidisciplinary Breast Cancer Tumor Board,” all non-metastatic patients with locally advanced or triple-negative breast cancer who were scheduled for surgery after completing the full course of neo-adjuvant chemotherapy were eligible to join the study.

Patients who were not candidates for NAC or those who have already started their NAC course, patients with distant metastases, pregnant females, those with a history of allergy, or those with renal impairment were excluded from the study (Fig. 1).

### Imaging assessment schedule

All participants were subjected to a baseline CESM (pre-NAC) at the time of diagnosis and before NAC as well as another study after completion of the full course of

NAC and before surgery (post-NAC). In the post-NAC exam, only the breast of concern was examined to minimize unnecessary exposure. The maximum interval between the post-NAC exam and surgery was 10 days.

### The technique of CESM examination

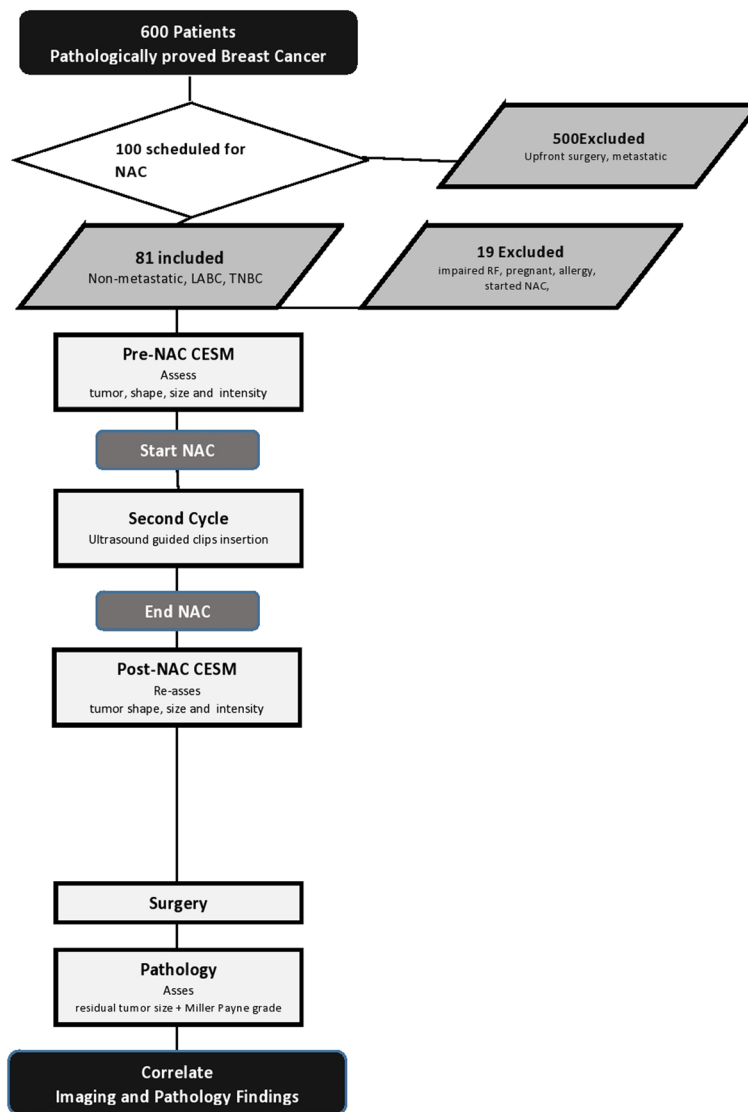
Examinations were performed on a commercial CESM device (SenoBright CESM, GE Medical Systems, Milwaukee WI).

A bolus of an iodinated contrast agent (iohexol, 300 mg I/ml) at a dose of 1.5 ml/kg is injected into the antecubital vein contralateral to the side of concern. After a 2-min wait, the 2 standard mammographic views were taken for each breast. As there was no need for a “pre-contrast” image, compression was applied after the injection to reduce the potential for movement artifacts and to retain the degree of image detail associated with standard mammography. In each mammographic position, a pair of low- and high-energy images was acquired. The low-energy images (similar to mammography) were acquired at peak kilovoltage values ranging from 26 to 31 kVp, which is below the K-edge of iodine. High-energy images (sensitive to iodine) were acquired at 45–49 kVp, which is above the K-edge of iodine.

Iodine-enhanced images are obtained by subtraction of the two images through appropriate image processing in a way to reduce the background parenchymal enhancement so that enhancing lesions are seen [3, 4].

### Interpretation of CESM findings

The analysis was performed using independent double reading by two different radiologists (10, 19 years’ experience in mammography and 4, 7 years’ experience in CESM). Readers were blinded for each other analysis, the pathology reports, and follow up the outcome. In case of disagreement between the two radiologists, the mammograms were re-evaluated by a third reader (the Chief Breast Imaging Consultant of the Department) and an agreement was achieved. The patterns of contrast uptake and lesion size were reported in both the pre- and post-NAC studies. Response to NAC was assessed in the post-NAC CESM once applying the Response evaluation Criteria in Solid Tumors (RECIST 1.1) and once using a combined quantitative and qualitative



**Fig. 1** Flow chart of included and excluded patients in the study

approach, which was proposed by the authors (see “assessment of response to NAC” detailed below).

#### Patterns of contrast enhancement pre and post-NAC

The pattern of contrast was described in both pre- and post-NAC studies as follows:

##### A. Baseline pattern of contrast enhancement (Fig. 2)

The initial contrast enhancement pattern of breast cancer was classified into four categories described by Tozaki and colleagues [5]:

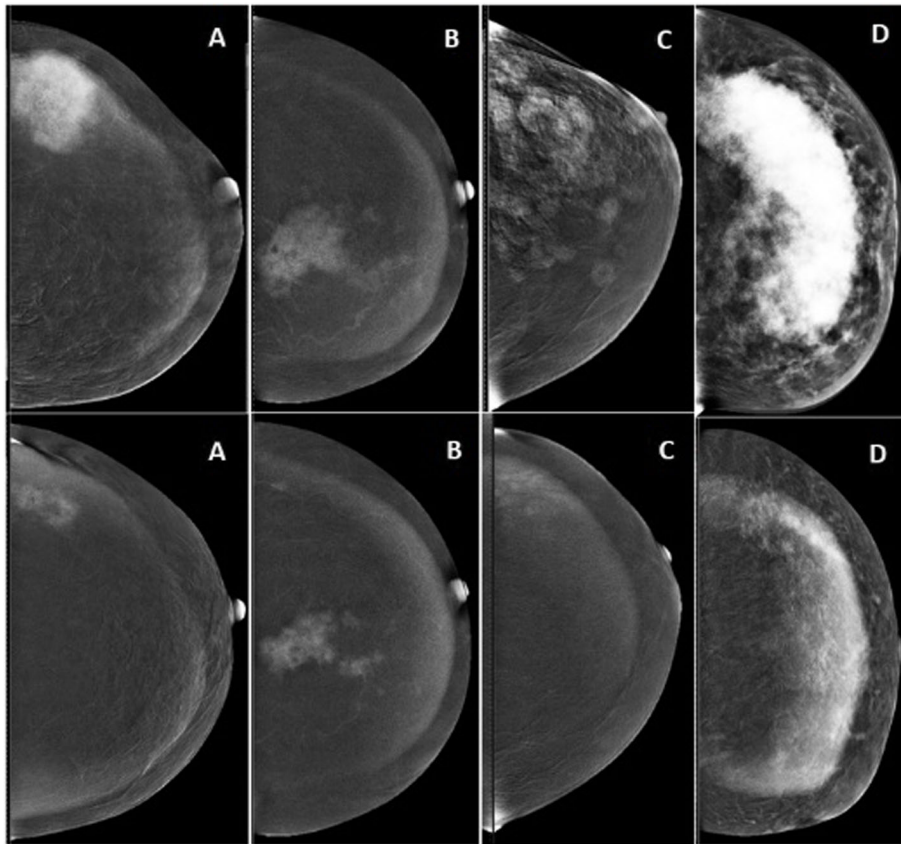
1. Solitary lesion: single rounded, oval, or irregular
2. Grouped lesion: localized mass with adjacent linear or spotty enhancement

3. Separated lesion: multifocal or multicentric masses
4. Replaced lesion: diffuse contrast enhancement in all quadrants

##### B. Post-NAC pattern of enhancement (Fig. 2)

The post-NAC shrinkage pattern was classified into four categories as described by Kim et al. [6]:

1. Type I: concentric shrinkage without surrounding lesions
2. Type II: concentric shrinkage with surrounding lesions
3. Type III: shrinkage with residual multi-nodular lesions



**Fig. 2** Different cases showing baseline enhancement patterns and post NAC shrinkage patterns. **a** Solitary lesion showing type 1 concentric shrinkage. **b** Grouped lesion showing type 2 concentric shrinkage. **c** Separated lesion showing type 3 shrinkage. **d** Replaced lesion showing type 4 shrinkage

4. Type IV: diffuse contrast enhancement in all quadrants

#### Assessment of response to neo-adjuvant chemotherapy

##### A. RECIST 1.1 evaluation

- Quantitative assessment was performed by measuring the longest dimension of the target lesion of the breast before and after NAC. After interpreting the difference in size between both measurements, response to NAC was then classified according to the response evaluation criteria in solid tumors (RECIST 1.1) [7]. According to the RECIST 1.1, lesions' response patterns were classified as complete response, partial response showing at least 30% decrease in the longest dimension of the target lesion, progressive disease showing at least 20% increase in the longest dimension of target lesion, or stable disease showing no significant change. Lesions

showing stable or progressive responses were classified as *non-responders* while lesions showing partial or complete response were classified as *responders*.

##### B. Combined quantitative and qualitative assessment (Table 1)

- The combined assessment was proposed by the involved researchers depending on a combination of assessment of change in the largest diameter of the target lesion together with the evaluation of the difference in intensity of contrast uptake between the pre- and post-NAC studies.

The largest dimension of the lesions was measured in both the pre- and post-NAC CESM studies and the percentage of change in size was calculated. According to the percent of change in lesion size, we classified the response into 6 patterns: progressive, stable, lesions

**Table 1** The proposed combined evaluation Method

Type of Response	Tumor largest diameter	Intensity of enhancement
• Progressive disease	Increase	With or without change in the intensity
• Stable disease	No change in size	No change
• Poor response	< 30% decrease	Mild decrease in intensity
• Moderate response	30–60% decrease	And/or moderate to marked decrease in intensity of enhancement
• Marked response	> 60% decrease	Residual faint enhancement
• Complete Response	No residual lesion seen	

showing < 30% decrease in size, lesions showing a 30–60% decrease in size, and lesions showing > 60% decrease and lesions showing no residual disease.

Evaluation of the change in lesion intensity was subjective. Readers had to report whether there was no change, mild to moderate decrease in intensity, marked decrease in intensity with only faint residual enhancement, and no residual enhancement.

Assessment of response patterns was based on combinations between size and intensity changes resulting in 6 response patterns:

- Progressive disease: at least a 20% increase in tumor size with/without a change in the intensity/pattern of enhancement.
- Stable disease: no change longest tumor diameter or in the intensity/pattern of enhancement or decrease in longest tumor diameter.
- Poor response: less than 30% decrease in longest tumor diameter with a mild decrease in the intensity of enhancement.
- Moderate response: 30–60% decrease in longest tumor diameter and/or moderate to marked decrease in the intensity of enhancement.
- Marked response: more than 60% decrease in tumor longest diameter with residual faint enhancement.
- Complete response: no residual enhancing lesions.

## 1. Histopathology and immuno-histochemistry

### A. Initial histopathology and immuno-histochemistry

- Initial histopathology was performed from pretreatment formalin-fixed, paraffin-embedded core biopsy samples. Immunohistochemistry (ER, PR, HER2/neu, and KI67) was performed on the same core biopsy samples. ER and PR statuses were scored from 0 to 8. Total scores of 0–2 are considered negative, a score of 3 is equivocal, and scores of 4–8 are considered positive. Testing for HER2/neu gene amplification was also performed by using the silver

enhanced in situ hybridization technique. A ratio of 2.0 or more and/or Her2 gene copy number of 6 or more is considered positive for amplification of this gene, a ratio of less than 2.0 and a gene copy number < 4 is considered negative, and a ratio of less than 2 and a gene copy number  $\geq 4$  and < 6 is scored as equivocal.

### B. Post NAC assessment

- Assessment of response was according to the percent of change of tumor size and cellularity. Negative margins of the resected specimen should be confirmed to guarantee accurate size assessment. The largest diameter of both the original tumor bed and residual area with invasive cancer were then measured in the gross specimen using a standard ruler and were confirmed microscopically by submitting the specimen to the histologic mapping of serial specimen sections under the microscope. In non-concentric shrinkage, the residual tumor size was considered as the diameter of the cross-sectional area containing residual tumor cells.
- To assess for the response, the percentage of the area with residual carcinoma within the original tumor bed is calculated and the average cellularity is estimated by calculating the average cellularity in the microscopic fields of the tumor bed.
- The abnormal (provisional tumor) area is measured in the gross specimen using a standard ruler. Consecutive blocks of the whole abnormal area (including adjacent fibrotic tissue) are submitted for microscopic examination to confirm gross tumor measurement. The total tumor size is estimated by measuring the maximum dimension of the viable invasive cancer on the examined slides fitted together. The percent of the area with residual viable invasive carcinoma within the tumor area is then calculated for assessment of therapy response.

Tumor regression was semi-quantitatively graded using surgical biopsy specimens by two pathologists



individually based on the Miller-Payne grading system which compares tumor cellularity in pre-neo-adjuvant therapy core biopsy specimens and the surgical specimens as follows [8]:

- Grade 1: No change or some alteration to individual malignant cells, but no reduction in overall cellularity.
- Grade 2: Minor loss of tumor cells, but overall cellularity still high; up to 30%.
- Grade 3: Between an estimated 30–90% reduction in tumor cells.
- Grade 4: Marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumor cells.
- Grade 5: No malignant cells identifiable in sections from the site of the tumor; only vascular fibro-elastic stroma remains often containing macrophages. However, ductal carcinoma in situ (DCIS) may be present.

Patients were divided into two groups: *pathologic responders* (lesions showing Miller-Payne grades 3, 4, and 5, and *pathologic non-responders* (lesions showing Miller-Payne grades 1 and 2).

### Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data were summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. For comparing categorical data, Chi-square ( $\chi^2$ ) test was performed. The exact test was used instead when the expected frequency is less than 5. Correlations between quantitative variables were done using Spearman correlation coefficient. A *P* value less than 0.05 was considered as statistically significant. The correlation between maximum tumor diameter based on CESM and histopathology was expressed using scatter plots. In addition, the agreement between these measurements was expressed using Bland-Altman plots.

Cohen's kappa coefficient was used to compare the inter-observer agreement. The inter-observer % of agreement was 96%.

### Results

The study included 81 patients who performed a pre- and post-NAC CESM examination.

On assessing the subjective change in intensity of contrast between the pre- and post-NAC studies, the two readers agreed in their initial independent readings on 80/81 cases (kappa 0.96).

### Baseline patterns of contrast enhancement and shrinkage patterns

The baseline patterns of contrast uptake and the corresponding shrinkage pattern of the 81 lesions are shown in Tables 2 and 3.

*Solitary lesions* constituted 26/81 (32.1%); 6/26 (23%) showed complete response and 20/26 (77%) showed concentric shrinkage pattern. *Grouped lesions* constituted 13/81 (16%); 5/13 (38.5%) showed complete response, 1/13 (8%) showed concentric shrinkage with surrounding lesions, 5/13 (38.5%) showed residual nodular lesions, and 2/13 (15%) showed residual diffuse enhancement. *Separated lesions* were the commonest lesions constituting 32/81 (39.5%); 8/32 (25%) showed complete response, 4/32 (12.5%) showed concentric shrinkage pattern, 14/32 (43.7%) showed concentric shrinkage with residual lesions, and 2/32 (6.3%) showed residual multi-nodular lesions. All 4 lesions showing no response were *separated lesions* in the baseline CESM (4/32(12.5%)). Replaced lesions constituted 10/81 (12.4%); 1/10 (10%) showed complete response, 2/10 (20%) showed residual multi-nodular lesions, and 7/10 (70%) showed residual diffuse enhancement.

### CESM assessment of response to neo-adjuvant chemotherapy

#### A. RECIST 1.1 evaluation

In reference to the (RECIST 1.1) criteria, progressive disease (PD) was not identified in any of the cases. Stable disease (SD) was seen in 28/81 (34.6%) of lesions, partial

**Table 2** Results review

	Number	Percentage
Baseline patterns of contrast uptake		
– Solitary Lesion	26/81	32.1
– Grouped lesion	13/81	16
– Separated lesion	32/81	39.5
– Replaced lesion	10/81	12.4
Post-NAC shrinkage patterns		
– Type I (concentric)	24/81	29.6
– Type II (concentric with surrounding lesions)	15/81	18.5
– Type III (residual multi-nodular)	9/81	11.1
– Type IV (diffuse enhancement)	9/81	11.1
– No residual lesion (complete response)	20/81	24.75
– No appreciable change (stationary course)	4/81	4.95

**Table 3** The correlation between the initial pattern of enhancement in the baseline study and the post-NAC shrinkage patterns

	Solitary (n = 26/81, 32.1%)		Grouped (n = 13/81, 16%)		Separated (n = 32/81, 39.5%)		Replaced (n = 10/81, 12.4%)	
	N	%	N	%	N	%	N	%
Complete response (n = 20/81, 24.75%)	6/26	23%	5/13	38.5%	8/32	25%	1/10	10%
Type I: concentric (n = 24/81, 29.6%)	20/26	77%	–	–	4/32	12.5%	–	–
Type II: concentric with surrounding lesions (n = 15/81, 18.5%)	–	–	1/13	8%	14/32	43.7%	–	–
Type III: residual multi-nodular (n = 9/81, 11.1%)	–	–	5/13	38.5%	2/32	6.3%	2/10	20%
Type IV: diffuse enhancement (n = 9/81, 11.1%)	–	–	2/13	15%	–	–	7/10	70%
No response (n = 4/81, 4.95%)	–	–	–	–	4/32	12.5%	–	–

response (PR) was seen in 33/81 (40, 7%) of lesions, and complete response (CR) was seen in 20/81 (24.7%) of lesions.

In total, 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.

#### B. Combined quantitative and qualitative evaluation

In reference to the combined evaluation that was proposed by the involved researchers, *progressive disease* was not seen in any of the lesions, *stable disease* was seen in 4/81 (4.9%) of the lesions, *poor response* was seen in 12/81 (14.8%) of the lesions, *moderate response* was seen in 21/81 (26%) of the lesions, *marked response* was seen in 24/81 (29.6%) of the lesions, and *complete response* was seen in 20/81 (24.7%) of the lesions.

In total, 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.

#### Histopathology and Immuno-histochemistry

##### Initial Histopathology and Immuno-histochemistry

Results of histopathology and surgical specimens showed that 67/81 (82.7%) of the lesions were IDC, 8/81 (9.8%) were invasive lobular carcinoma, 3/81 (3.7%) were mixed invasive ductal and lobular, and 1/81 (1.2%) of the lesions were each of mucinous, tubular, and invasive papillary carcinomas.

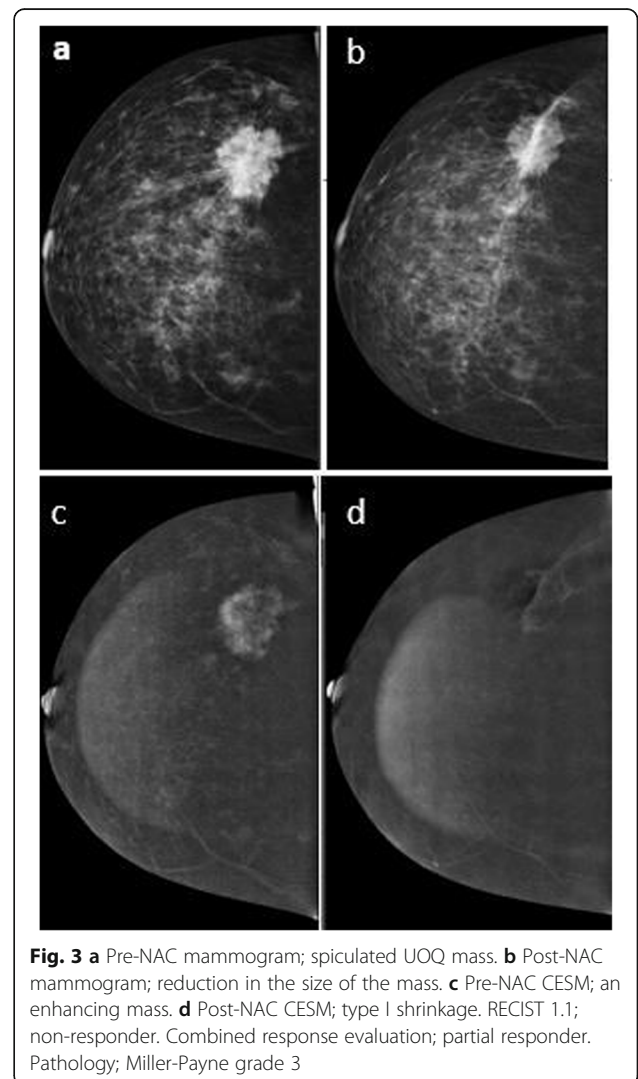
According to the immunohistochemistry results, these lesions were classified into 29/81 (35.8%) luminal A, 28/81 (34.6%) luminal B (22/81 (27.2%) luminal B1 and 6/81 (7.4%) B2), 7/81 (8.6%) Her2 over-enriched, and 17/81 (21%) basal-like (triple negative).

##### Pathological response evaluation

Tumor regression was semi-quantitatively graded using surgical biopsy in reference to Miller-Payne grading as

follows; grade 1: 6/81 (7.5%), grade 2: 15/81(18.5%), grade 3: 18/81(22.2%), grade 4: 21/81 (25.9%), and grade 5: 21/81 (25.9%) (Fig. 3).

In reference to *Miller-pane grading*, 21/81 (26%) were *non-responders* and 60/81 (74%) were *responders*; out of which, 21/81 (25.9%) showed pathological complete response (PCR).



**Fig. 3** a Pre-NAC mammogram; spiculated UOQ mass. b Post-NAC mammogram; reduction in the size of the mass. c Pre-NAC CESM; an enhancing mass. d Post-NAC CESM; type I shrinkage. RECIST 1.1; non-responder. Combined response evaluation; partial responder. Pathology; Miller-Payne grade 3

Both methods of radiological evaluation coincided with postoperative pathology in predicting PCR in 20/21 (95.2%) lesions, with an additional 1 false-positive and 1 false-negative case (Table 4) (Fig. 4). The calculated sensitivity, specificity, PPV, and NPV were 95.2%, 98.3%, 95.2%, and 98.3% respectively.

#### Correlation between pathological responders and non-responders and the shrinkage patterns

Responders (Miller grades 3, 4, and 5) constituted 60/81 (74.1%); 20/60 (33.3%) showed complete radiologic response and 17/60 (28.3%) showed concentric shrinkage pattern (Table 5).

#### Correlation between the radiological response (using the RECIST criteria and the combined response evaluation) and the pathological response

Evaluation of response using the combined approach showed significantly better agreement with histopathology results than the evaluation based on RECIST 1.1 alone (Table 6).

According to histopathology results, 60/81 patients (74%) were responders (Miller-Payne grades III, IV, and IV). Using the combined evaluation approach, 57/60 patients (95%) were classified as responders, while by using RECIST 1.1 alone, only 46 /60 were classified as responders (76.7%) (Table 7, Fig. 3).

On the other hand, according to histopathology results, 21/80 patients (26%) were non-responders (Miller-Payne grades I and II). Using the combined evaluation approach, 13/ 21 patients (61.9%) were non-responders while using the RECIST, 14/21patients (66.7%) were non-responders (Figs. 5 and 6).

#### The overall accuracy of CEM in the evaluation of response to neo-adjuvant chemotherapy

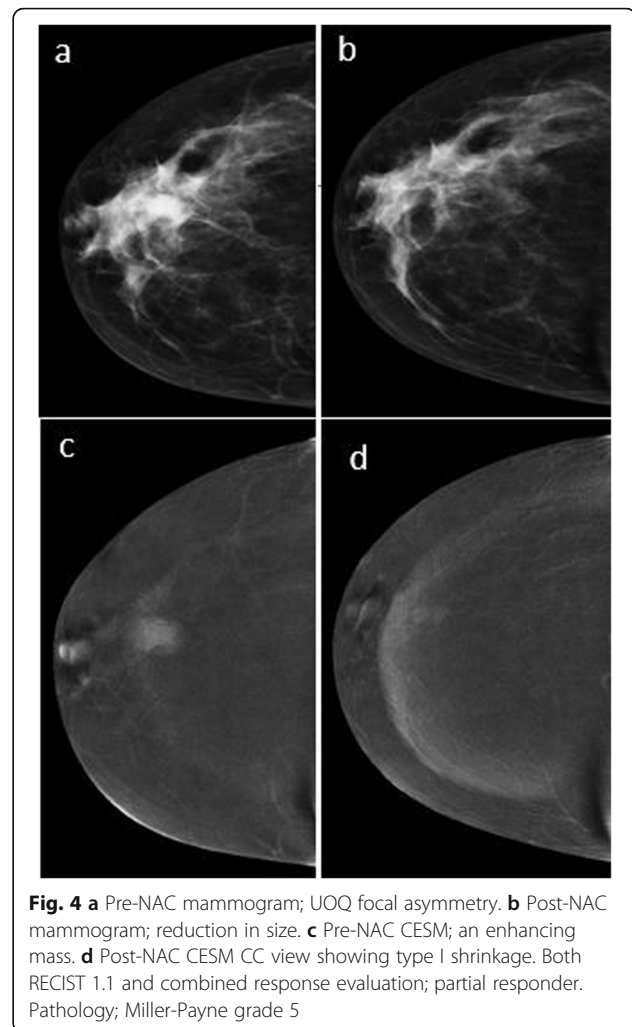
The combined response evaluation approach showed higher diagnostic indices as compared to the evaluation based on RECIST 1.1 alone (Table 7, Fig. 7).

#### Correlation between the residual tumor size in CEM and histopathology specimens

A strong correlation ( $R: 0.921$ ,  $P$  value  $< 0.001$ ) was found between the size of residual mass lesions on

**Table 4** CEM in predicting pCR

		Pathologic response			
		Complete responder		Incomplete responder	
		Count	%	Count	%
RECIST 1.1 evaluation	CR	20/21	95.23%	1/60	1.7%
	ICR	1/21	4.76%	59/60	98.3%
Combined response evaluation	CR	20/21	95.23	1/60	1.7%
	ICR	1/21	4.76%	59/60	98.3%



**Fig. 4** a Pre-NAC mammogram; UOQ focal asymmetry. b Post-NAC mammogram; reduction in size. c Pre-NAC CEM; an enhancing mass. d Post-NAC CEM CC view showing type I shrinkage. Both RECIST 1.1 and combined response evaluation; partial responder. Pathology; Miller-Payne grade 5

CEM (mean size:  $3.12 \text{ cm} \pm 2.95\text{SD}$ ) and histopathology specimens (mean size  $3.33 \text{ cm} = /- 3.22\text{SD}$ ) in the total 81 lesions. The overall mean size discrepancy was  $0.85 \text{ cm} \pm 1.04\text{SD}$  (Table 8, Figs. 8 and 9).

The size of the lesions showing types I, II, and IV shrinkage patterns showed a significant correlation with the histopathology size. The mean CEM–pathologic size discrepancy was least in types I, II, and IV shrinkage patterns and greatest in type III (Table 8).

The mean CEM–pathologic size discrepancy was least with the triple-negative tumors and HER2-positive tumors as shown in Table 8.

#### Discussion

With the development of new lines of cancer treatment options, various diagnostic imaging modalities are emerging accompanied by new strategies and guidelines to predict early tumor response to NAC and to assess the burden of residual disease [9–12].



**Table 5** Correlation between shrinkage pattern and pathologic response

	Pathologic response				P value
	Responder 60/80 (75%)		Non-responder 20/80 (25%)		
	Count	%	Count	%	
Complete response (n = 20/81, 24.75%)	20/60	33.3%	0	0%	0.002
Type I: concentric (n = 24/81, 29.6%)	17/60	28.3%	7/21	33.3%	0.666
Type II: concentric with surrounding lesions (n = 15/81, 18.5%)	7/60	11.7%	8/21	38.1%	0.018
Type III: residual multi-nodular (n = 9/81, 11.1%)	8/60	13.3%	1/21	4.8%	0.434
Type IV: diffuse enhancement (n = 9/81, 11.1%)	7/60	11.7%	2/21	9.5%	1
No response (n = 4/81, 4.95%)	1/60	1.7%	3/21	14.3%	0.052

The current study included 81 patients who have completed the full NAC course. Assessment of response was performed in reference to the previously described MRI shrinkage patterns by Kim et al. [6].

The combined response evaluation proposed by the authors showed significantly better agreement with histopathology than the evaluation based on *RECIST 1.1* alone. Contrast-enhanced mammography is less expensive and less time consuming and may even have a chief advantage over MRI as it can assess the true extent of residual tumors associated with microcalcifications [1, 13, 14].

After NAC, some histopathological changes may occur in the tumor bed with an overall reduction in size and the amount of viable tumor cellularity giving the different post-NAC shrinkage patterns described by Kim et al. [6, 15]. Some tumors may show concentric shrinkage patterns, while others may disintegrate or fragment into discrete foci which are difficult to measure. In some other tumors, a fibrous stroma may persist in the original tumor bed. This fibrous stroma may show subtle enhancement giving a false impression of poor response to NAC as there will be no change in tumor diameter [16]. Knowing the shrinkage pattern helps in the accurate assessment of residual disease before conservative surgery [6, 17].

Goorts et al. stated that a possible explanation for the better prediction of pathological response by MRI half-way through NAC than after NAC is that taxanes might suppress MRI enhancement irrespective of the cytotoxic

activity, as reported by Schrading et al. And since in Goorts et al. patient's cohort, taxanes were also only given during the second half of treatment, this could be a plausible explanation; however, their study also showed that this might be false negative, especially when lobular carcinomas are classified as complete responders. Furthermore, the two triple-negative tumors classified as type 0 were both true negatives [16].

Kim et al. stated that types III and I shrinkage patterns were more frequently observed in the pathological responder group, and type IV was more frequently noted in the non-responder group [6]. Our results were in agreement with Kim et al., where 17/24 (70.8%) of type 1 shrinkage pattern and 8/9 (88.8%) type 3 shrinkage pattern were responders. On the other hand, solitary lesions showed the most favorable response to NAC where 6/26 (23%) lesions showed a complete radiological response and even the remaining 20/26 (77%) with the residual disease showed type 1 concentric shrinkage pattern making conservative surgery more amenable. On the other hand, replaced lesions showed the least favorable response where 7/10 (70%) lesions showed persistent diffuse enhancement ending up with a modified radical mastectomy (MRM).

We then assessed the accuracy of CESM in the evaluation of residual disease; once using the *RECIST 1.1* and another time using the combined response evaluation approach (Table 4). This was performed in correlation with the postoperative histopathology results.

**Table 6** Correlation between the radiological response and the pathological response patterns using the *RECIST* criteria and the combined response evaluation

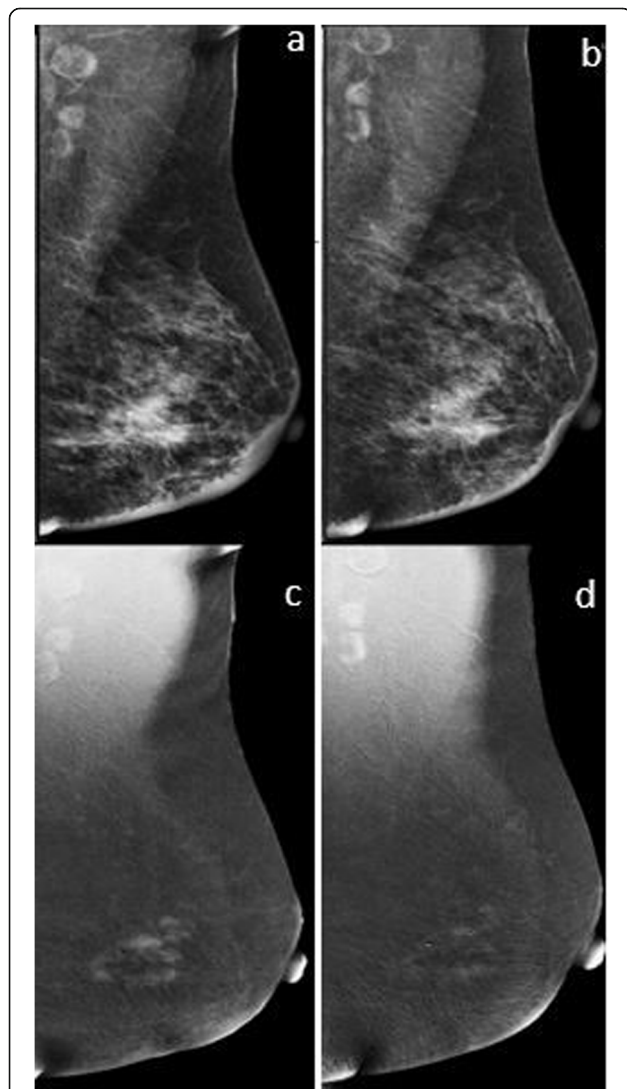
		Pathologic response				P value
		Responder		Non-responder		
		Count	%	Count	%	
RECIST 1.1 evaluation	Responder	46	76.7%	7	33.3%	< 0.001
	Non-responder	14	23.3%	14	66.7%	
Combined response evaluation	Responder	57	95.0%	8	38.1%	< 0.001
	Non-responder	3	5.0%	13	61.9%	

**Table 7** Comparison between the evaluation of response based on RECIST 1.1 and the evaluation of response based on the combined response approach

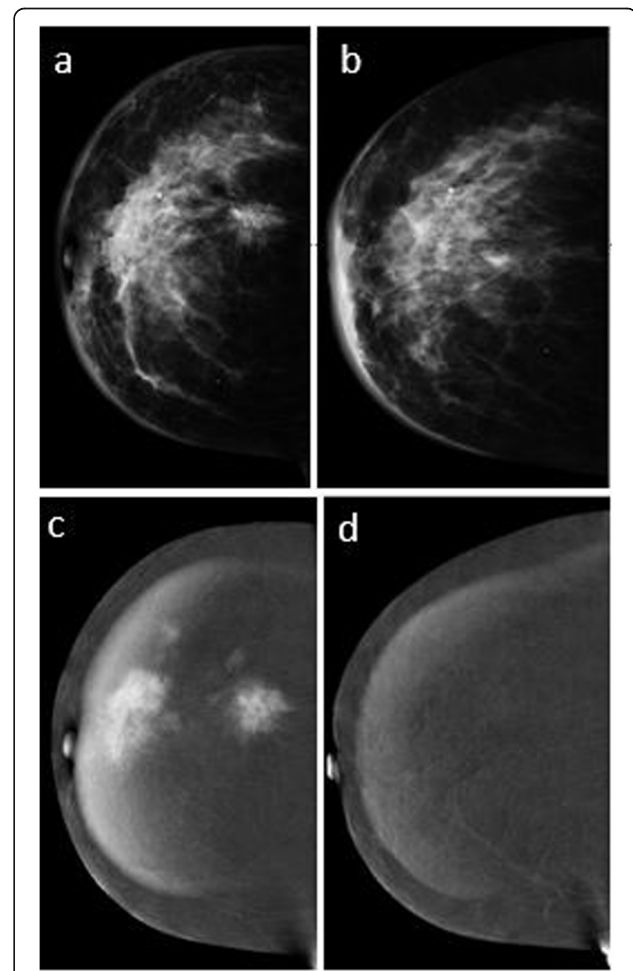
	Sensitivity	Specificity	PPV	NPV
RECIST 1.1 evaluation	76.67% (46/60) 95% CI 63.9–86.6	66.67% (14/21) 95% CI 43.03–85.4	86.79% (46/53) 95% CI 77.9–92.4	50% (14/28) 95% CI 36.6–63.4
Combined evaluation	95.00% (57/60) 95% CI 86.08–98.9	61.90% (13/21) 95% CI 38.4–81.9	87.69% (57/65) 95% CI 80.4–92.5	81.25% (13/16) 95% CI 57.7–93.2

Morphologic measurement of change in tumor size in response NAC helps assess therapeutic effectiveness through the use of the RECIST 1.1 [7]. Since the publication of the RECIST, several reports have been published regarding its low reliability in evaluating responses. The RECIST 1.1 mainly depend on tumor

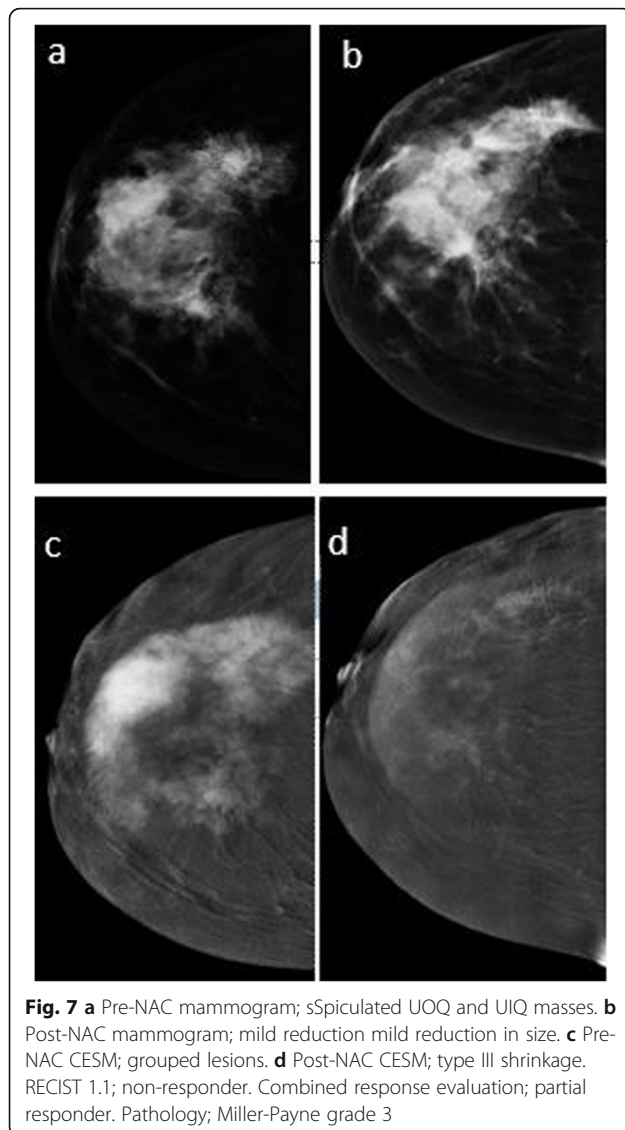
size alterations and they do not express other morphologic (tumor necrosis, hemorrhage, and cavitation), functional, or metabolic changes that may occur with NAC [10]. Forner et al. stated that when applying RECIST alone in the assessment of response to NAC, tumor necrosis and partial tumor response can be missed [18]. Magnetic resonance imaging has long been considered the most promising imaging modality in assessing response NAC, as it not only provides accurate tumor size



**Fig. 5** **a** Pre-NAC mammogram; spiculated LIQ mass. **b** Post-NAC mammogram; no change in size. **c** Pre-NAC CESM; lesions. **d** Post-NAC CESM; decreased enhancement without size change. Both RECIST 1.1 and combined response evaluation; non-responder. Pathology; Miller-Payne grade 1



**Fig. 6** **a** Pre-NAC mammogram; spiculated LOQ mass. **b** Post-NAC mammogram; marked reduction in size. **c** Pre-NAC CESM; separated lesions. **d** Post-NAC CESM CC view showing no residual enhancing lesions. CESM classified this patient as a complete responder. Pathology; Miller-Payne grade 5

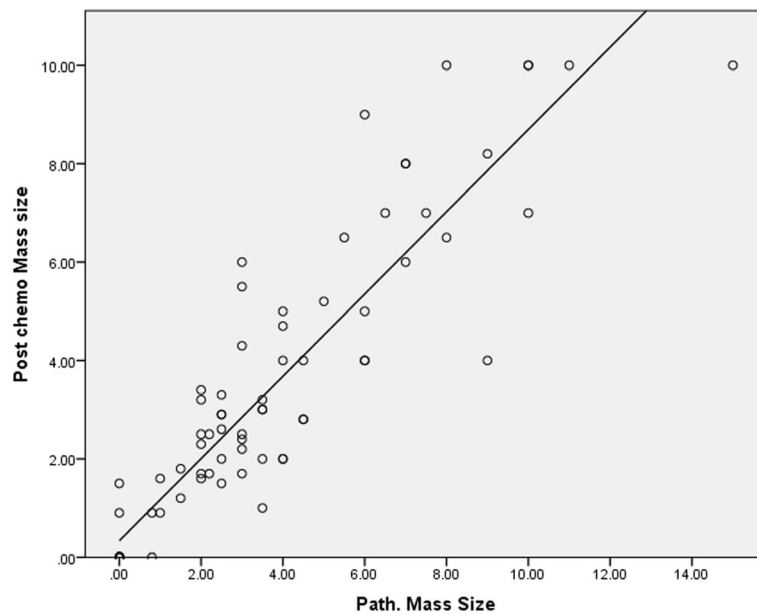


assessment but also gives us information about the change in tumor enhancement pattern reflecting the functional change in tumor cells [19]. However, since breast MRI and CESM show similar performance and are based on similar principles, we proposed a new assessment approach based on both size assessment and enhancement pattern using CESM.

In reference to the postoperative histopathology results of the 81 patients included in the current study, 60/81 lesions were responders (Miller-Payne grades 3, 4, and 5). Using the combined response evaluation approach, 57/60 patients (95%) were classified as responders, while by using RECIST 1.1 alone, only 46/60 patients (76.7%) were classified as responders. The combined response evaluation approach showed higher sensitivity and positive and negative predictive values compared to the evaluation based on RECIST alone (95%, 87.6%, and 81.2% compared to 76.6%, 86.7%, and 50% respectively). The specificity of the RECIST evaluation was slightly higher than the combined approach (66.9% as compared to 61.6%). Both methods of radiological evaluation coincided with postoperative pathology in predicting PCR in 20/21 (95.2%) lesions, with an additional 1 false-positive and 1 false-negative case. Pathology of the false-positive responder showed areas of fibrosis and hyalinosis entangling breast lobules leading to a decreased contrast uptake, yet with residual viable tumor cells. False-negative responders were significantly more in the RECIST 1.1 evaluation than in the combined approach (14 compared to 3 non-responders respectively) as the overall loss of tumor cells was not always expressed as a change in tumor size. Another explanation to the false-positive cases was also suggested in previous studies stating that the residual tumor may shrink when fixed in formalin after surgical removal giving a false impression of size reduction [20, 21].

**Table 8** Correlation of tumor diameter obtained from CESM with histological tumor diameter according to the shrinkage patterns and biomarker status of the tumors

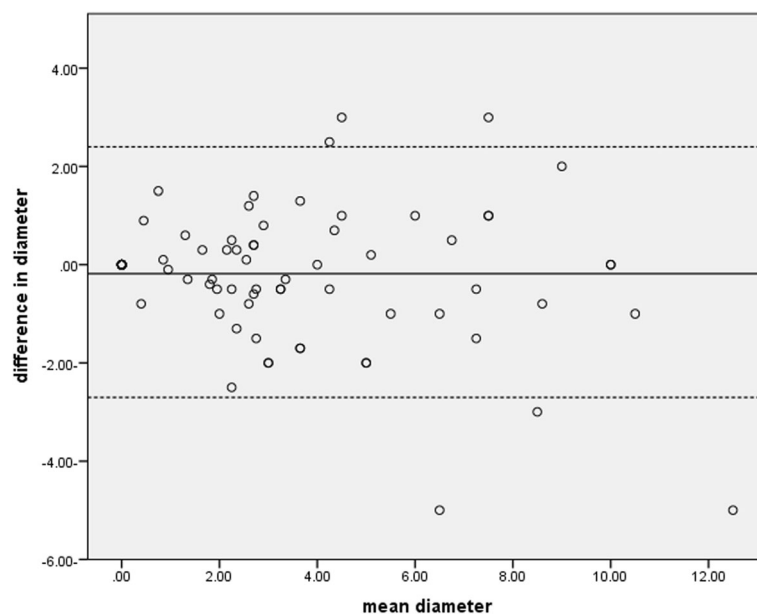
	Histology diameter mean	CESM diameter mean	Mean size discrepancy	Correlation coefficient	P value
Shrinkage pattern					
Type I	2.8 cm	2.7 cm	0.89 cm	0.615	0.001*
Type II	3.1 cm	2.5 cm	0.89 cm	0.768	0.001*
Type III	7.4 cm	6.6 cm	1.95 cm	0.640	0.063
Type IV	8.0 cm	8.2 cm	1.37 cm	0.714	0.031*
All types	3.3 cm	3.1 cm	0.85 cm	0.921	< 0.001
Biomarker status					
HER2-positive	3.6 cm	3.5 cm	0.56 cm	0.988	< 0.001
Triple negative	1.6 cm	1.5 cm	0.44 cm	0.932	< 0.001
Luminal A	3.8 cm	3.5 cm	1.13 cm	0.834	< 0.001
Luminal B	4.2 cm	3.5 cm	1.17 cm	0.840	0.036
HER2-positive	3.6 cm	3.5 cm	0.56 cm	0.988	< 0.001



**Fig. 8** Scatter plots of maximum tumor diameter measurement between CESM and histopathology

The overall reported diagnostic indices of the combined approach matched some reported results for MRI in the same context and mismatched others. For example, in a meta-analysis performed by Yuan et al., MRI showed a high specificity (90.7%) and relative lower sensitivity (63.1%) in predicting pathologic complete remission after NAC while in another study, MRI showed a sensitivity of 100%, a specificity of 50%, a PPV of 83.3%, and an NPV of 100% [22, 23]. Thus, both overestimation and underestimation were previously observed and reported [24].

Many studies have presented correlation coefficients between size measurements assessed by MRI compared to pathological tumor size measurement [25–27]. In an analysis of these studies by Lobbes et al., the median correlation coefficient was calculated and found to be 0.698, with a range of 0.21–0.982 [24]. In the current study, the overall correlation between size measurements assessed by CESM compared to pathological tumor size was 0.921 ( $P < 0.001$ ). The correlation coefficient achieved by CESM in our study was significantly higher



**Fig. 9** Bland-Altman plots for comparison of maximum tumor diameter measurement by CESM and histopathology

than that recorded for MRI in the meta-analysis by Lobbes et al [24].

In recent studies, it was observed that the accuracy of breast MRI to assess residual disease and predict pCR depended on breast cancer subtypes. For example, it was observed that MRI was able to predict pCR more accurately in patients having HER2-positive tumors when compared to HER2-negative tumors. In the latter case, a higher false-negative rate was observed [24].

HER2-negative and hormone receptor-positive cancers and lesions showing non-mass-like enhancement are more likely to show residual disease as small foci or scattered cells after NAC, leading to underestimation of residual disease extent at MR imaging, and the diagnostic results of MR imaging should be used with caution in surgical planning [28].

Loo et al. also concluded that response monitoring using breast MRI is accurate in patients having triple-negative or HER2-positive tumors. However, they found it was inaccurate in ER-positive/HER2-negative subtypes [29].

In the current study, the overall accuracy of CESM in assessing the 41 patients with hormone receptor-positive/HER2-negative tumors was 88.9%. Five out of these 41 patients achieved pCR; CESM was able to predict pCR in 4 out of 5 patients with only one false positive case.

In a study by Chen et al., the results indicated that the diagnostic accuracy of MR imaging is better in HER2-positive than in HER2-negative cancers, with a size discrepancy of  $0.5 \pm 0.9$  cm versus  $2.3 \pm 3.5$  cm ( $P = .009$ ) [28]. These results suggest that patients with HER2-negative hormone receptor-positive disease are the poorest candidates for MR imaging evaluation [28].

In the current study, the mean size discrepancy for the HER2-positive tumors was  $0.5 \pm 0.7$  cm versus  $1.1 \pm 1.2$  cm for HER2-negative tumors ( $P < 0.001$ ). Note the smaller size discrepancy achieved by using CESM in evaluating the residual disease in Her2-negative tumors compared to the MR evaluation in the Chen et al. study [28].

The present study had some limitations. The combined response evaluation approach carries the limitation of being subjective, which raises the need for the introduction of non-subjective methods in the evaluation of the change in the intensity of enhancement by CESM. However, the inter-observer variability between the different readers was excellent (kappa 0.960). Patients were only evaluated by CESM before and after completion of NAC. During the course, the evaluation was based on clinical and ultrasound assessments. The authors did not want to subject the patients to unnecessary irradiation before validating the efficiency of CESM to assess response. In a future application, it is necessary to do a limited CESM examination of the affected breast to predict early response.

## Conclusion

Contrast-enhanced spectral mammography can be readily used to assess tumor response to NAC. It showed high sensitivity and positive and negative predictive values in this study. One main advantage of CESM is that it allows the assessment of functional changes in residual tumor cells in addition to size discrepancy. Assessment based on size discrepancy alone as stated in the RECIST criteria does not reflect morphologic, functional, or metabolic changes that may occur with NAC especially in non-mass forming tumors. Using the combined assessment that was proposed by the authors, CESM can accurately assess residual disease after NAC.

## Abbreviations

CESM: Contrast-enhanced spectral mammography; NAC: Neo-adjuvant chemotherapy; RECIST 1.1: Response evaluation criteria in solid tumors 1.1; MRI: Magnetic resonance imaging; DCIS: Ductal carcinoma in situ; PD: Progressive disease; PPV: Positive predictive value; NPV: Negative predictive value; MRM: Modified radical mastectomy; PCR: Pathological complete response

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## Authors' contributions

RK wrote the manuscript. AM is responsible for correspondence to journal. SM collected patient data, image processing, and collection of patient's images. MG participated in the design of the study and performed the statistical analysis. IG was responsible for arrangement of pathology data. SM and OM conceived of the study, and participated in its design and coordination and helped to draft the manuscript. AH, AH, and AZ were responsible of revision of the draft from clinical point of view. All authors have read and approved the manuscript.

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## Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

The study was approved by the ethical committee of the Faculty of medicine, Cairo university with ethical committee approval number 20151509.3 and approval date 15/9/2015. An informed written consent was taken from all subjects.

## Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

## Competing interests

The authors declare that they have no competing interest.

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