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Quantitative mathematical objective evaluation of contrast-enhanced spectral mammogram in the assessment of response to neoadjuvant chemotherapy and prediction of residual disease in breast cancer

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Abstract

Background: The aim of the study is to initiate a new quantitative mathematical objective tool for evaluation of response to neoadjuvant chemotherapy (NAC) and prediction of residual disease in breast cancer using contrast-enhanced spectral mammography (CESM). Forty-two breast cancer patients scheduled for receiving NAC were included. All patients underwent two CESM examinations: pre and post NAC. To assess the response to neoadjuvant chemotherapy, we used a mathematical image analysis software that can calculate the difference in the intensity of enhancement between the pre and post neoadjuvant contrast images (MATLAB and Simulink) (Release 2013b). The proposed technique used the pre and post neoadjuvant contrast images as inputs. The technique consists of three main steps: (1) preprocessing, (2) extracting the region of interest (ROI), and (3) assessment of the response to chemotherapy by measuring the percentage of change in the intensity of enhancement of malignant lesions in the pre and post neoadjuvant CESM studies using a quantitative mathematical technique. This technique depends on the analysis of number of pixels included within the ROI. We compared this technique with the currently used method of evaluation: RECIST 1.1 (response evaluation criteria in solid tumors 1.1) and using another combined response evaluation approach using both RECIST 1.1 in addition to a subjective visual evaluation. Results were then correlated with the postoperative pathology evaluation using Miller–Payne grades. For statistical evaluation, patients were classified into responders and non-responders in all evaluation methods.

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Results: According to the Miller–Payne criteria, 39/42 (92.9%) of the participants were responders (Miller–Payne grades III, IV, and IV) and 3/42 (7.1%) were non-responders (Miller–Payne grades I and II). Using the proposed technique, 39/39 (100%) were responders in comparison to 38/39 patients (97.4%) using the combined criteria and 34/39 (87.2%) using the RECIST 1.1 evaluation. The calculated correlation coefficient of the proposed quantitative objective mathematical technique, RECIST 1.1 criteria, and the combined method was 0.89, 0.59, and 0.69 respectively. With classification of patients into responder and non-responders, the objective mathematical evaluation showed higher sensitivity, positive and negative predictive values, and overall accuracy (100%, 97.5%, 100%, and 85.7% respectively) compared to RECIST 1.1 evaluation (87.2%, 97.1%, 28.6%, and 54.8% respectively) and the combined response method (97.4%, 97.4%, 66.7%, and 85.7% respectively).

Conclusion: Quantitative mathematical objective evaluation using CESM images allows objective quantitative and accurate evaluation of the response of breast cancer to chemotherapy and is recommended as an alternative to the subjective techniques as a part of the pre-operative workup.

Keywords: Contrast-enhanced spectral mammogram, Neoadjuvant chemotherapy, Breast cancer

Background

Pre-operative neoadjuvant chemotherapy (NAC) is being continuously more employed in the control of locally advanced breast cancers and even in lower tumor stages enabling breast-conserving surgery in patients that would otherwise undergo mastectomy [1–3]. The use of NAC also enables physicians to assess tumor response in vivo. Pathological complete response after NAC may be considered an independent good prognostic factor. In fact, a pathological complete response has been associated with significantly improved disease-free survival and overall survival rates [1, 4].

A modality that enables the assessment of tumor response and accurately detects any residual disease has been always pursued [1]. Conventional methods, including clinical examination, ultrasonography (US), and mammography, have been proved to be of limited efficacy. MRI has been always looked at as the modality of choice in evaluating response to NAC as it allows assessment of both change in the tumor size and change in its morphology characteristics [4–6]. In addition to these MRI merits, studies assessing the response to neoadjuvant chemotherapy using semi-quantitative and quantitative MRI techniques allow early prediction of response even after one or two cycles. Identifying non-responders early allows amending treatment plans and facilitates the setting of tailored treatment regimens for each specific breast cancer patient [7–12].

The aim of this study is to initiate a new quantitative mathematical objective tool for evaluating the response of malignant breast mass lesions to neoadjuvant chemotherapy and allows accurate assessment of residual disease using contrast-enhanced spectral mammography (CESM) in comparison with response evaluation criteria in solid tumors 1.1 (RECIST 1.1) and a combined evaluation method (quantitative and qualitative). To our knowledge, this work is the first research that uses objective and quantitative mathematical evaluation using CESM. Previous published articles in literature in the same setting have only used subjective qualitative assessment methods and quantitative assessments only relied on measuring change in tumor size based on RECIST and measuring size of residual disease which is liable to over or under estimation [2, 13]. None of these researches discussed quantitative change in intensity of contrast uptake which reflects actual change in tumor cell activity.

Methods

Patients

Forty-two patients with pathologically proved breast cancer based on the tumor tissues obtained by core needle biopsy were enrolled in this study. They were all scheduled to receive NAC according to the decision of the multidisciplinary breast cancer tumor board. All patients underwent two separate CESM examinations; pre and post neoadjuvant chemotherapy.

The maximum interval between the post-NAC study and surgery was 10 days.

The study protocol was approved by the Institutional Review Board and informed written consent was applied for the used data of the enrolled individuals.

Patients who were not candidates for NAC, patients with distant metastases, pregnant females, those with a history of allergy, or renal impairment were excluded from the study.

Examinations were performed using the GE Senographe Essential mammography unit.

Assessment of response to neoadjuvant chemotherapy using CESM

A. RECIST 1.1 evaluation

- Quantitative assessment was performed by measuring the longest dimension of the target lesions (two lesions per organ) 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) [14, 15]. For statistical analysis, lesions showing stable or progressive response were classified as non-responders while lesions showing partial or complete response were classified as responders.

B. Combined quantitative and qualitative assessment

- The combined assessment was previously proposed by the involved researchers [16]. It depends on a combination of measuring the largest diameter of the target lesion together with subjective identification of the difference in intensity of contrast uptake before and after NAC. For statistical analysis, patients showing progressive, stable, or poor response were classified as non-responders while patients showing moderate, marked, or complete response were classified as responders (Table 1).

C. Quantitative mathematical objective evaluation

- A new objective mathematical tool for evaluation of response to neoadjuvant chemotherapy and assessment of residual disease was introduced depending on a combination of the summation of the number of pixels and their intensity within the area of interest before and after NAC. A mathematical image analysis software (MATLAB and Simulink) (Release 2013b) is used in the following steps:

Pre-processing: Applying the step of preprocessing plays a vital role to remove artifacts, labels, and increase the quality of the image [17]. The pre-processing of the images is prepared to reduce the computational rate and exploit the probability of accuracy [17]. It also involves denoising and improving the contrast of the images by removing artifacts. This is followed by resizing all the images to a fixed size [17–20]. Input images were converted to grayscale intensity image. The main target of conversion to grayscale is to eliminate the hue and saturation information while retaining the luminance.

1. Image segmentation: The breast contour is first separated from the image back ground. Then a draggable rectangular is generated manually to select the area which involves the malignant mass (region of interest) both in the pre and post NAC images. Automatic thresholding was then applied to extract the malignant mass in the images before and after taking chemotherapy as shown in Fig. 1.
2. Image thresholding is an effective method of splitting an image into a foreground and background and also is the most effective in images with high levels of contrast. This division into parts is often based on the characteristics of the pixels in the image. Automatic thresholding was done by Singh AK and Gupta B.2015 [21] that was used to separate pixels of malignant mass from the normal region. A white patch covering the malignant mass was obtained.
3. Finding the ratio of response: Executing mathematical operations are performed to deduce the response of cancerous lesions to NAC. After applying thresholding, the number of pixels within the region of interest (ROI) is summed up both in the pre and the post NAC images to

Table 1 The combined evaluation response approach

Type	Tumor largest diameter	Intensity of enhancement
• Progressive disease	Increase	+/− change in the intensity
• Stable disease	No change in size	No change
• Poor response	Up to 30% decrease	Decrease in intensity
• Moderate response	30–60% decrease	Decrease in intensity
• Marked response	> 60% decrease	Residual faint enhancement
• Complete Response	No residual lesion seen	

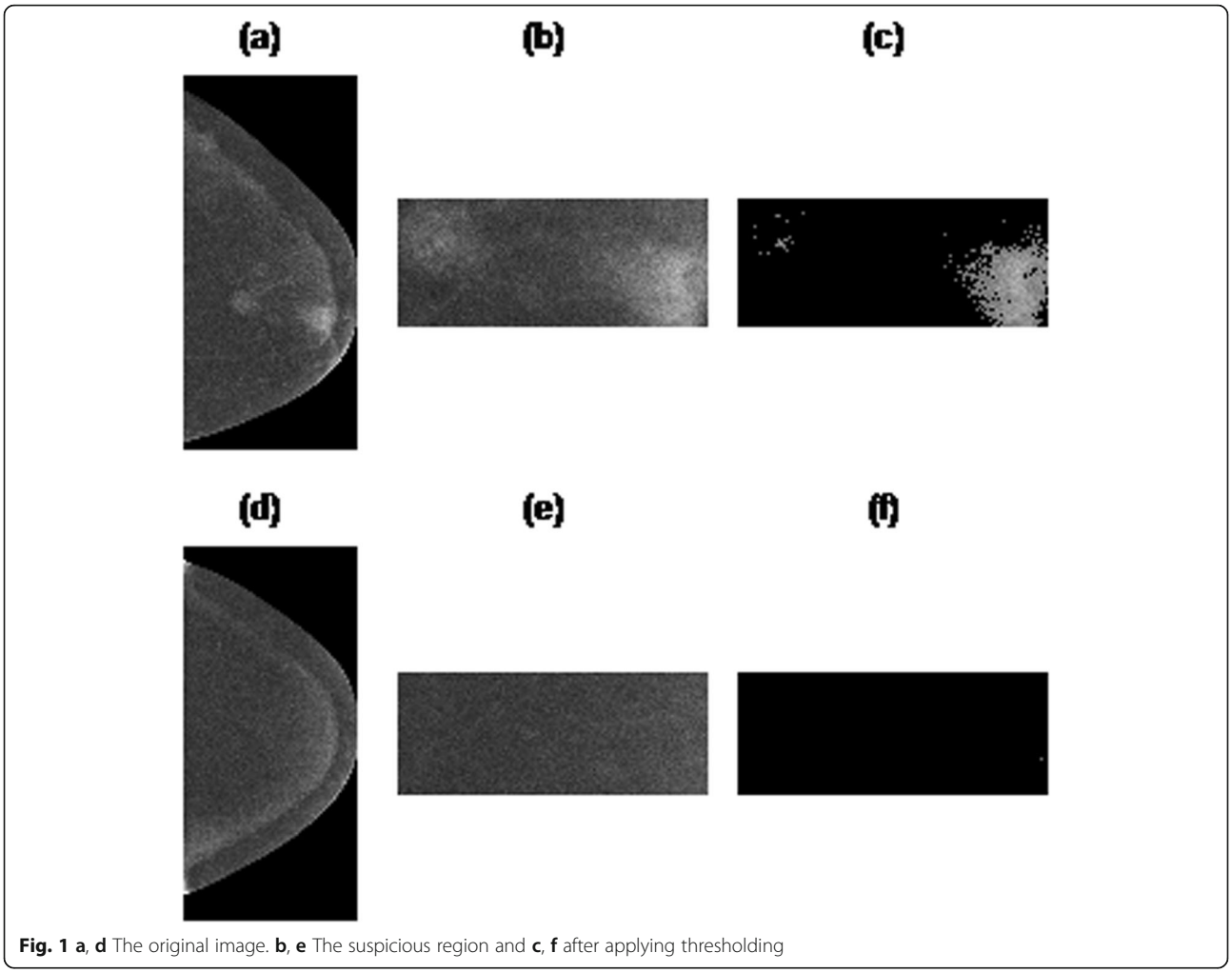

Fig. 1 **a**, **d** The original image. **b**, **e** The suspicious region and **c**, **f** after applying thresholding

identify the intensity of enhancement. The size of each region can be determined by counting the enclosed pixels according to the following equation:

$A = \Sigma$ Pi (where: Pi is the intensity value of pixels)

Then the response to NAC is measured by calculating the ratio between the areas in the pre and post NAC images to according to the following equation:

$$R = \frac{\sum_{i=0}^{n} Pi \text{ After chemo}}{\sum_{i=0}^{n} Pi \text{ Before chemo}}$$

Table 2 Miller-Payne grading system

Grade	Histopathology findings
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, DCIS may be present

Table 3 Histopathological and molecular subtypes of the patients enrolled in the study

Histological Subtype:	Number and percentage
• Invasive ductal carcinomas (IDC).	• 36/42 tumors (85.7%)
• Invasive lobular carcinomas (ILC).	• 4/42 tumors (9.5%)
• Mixed invasive ductal and lobular carcinomas.	• 1/42 tumor (2.4%)
• Invasive tubular carcinoma (ITC).	• 1/42 tumor (2.4%)
Biomarker s status of the tumors:	Number and percentage
HER2 over-enriched cancers.	9/42 were (21.4 %)
HER2-negative/HR–positive cancer	17/42 (40.45%)
Triple-negative cancers.	12 /42 (28.6%)
Luminal A cancer.	4/42 (9.5 %)

Table 4 Correlation between the results of the three different evaluation methods and the Miller–Payne Grading of the lesions

RECIST 1.1		Combined response evaluation approach		Quantitative objective evaluation approach		Pathological response (Miller–Payne grading)	
Stable disease (< 30% decrease in longest tumor diameter) (= Miller–Payne grade 1and 2)	7/42 (16.7%)	Stable disease	2/42 patients (4.8%)	Stable disease	0 patients (0%)	Grade 1	1/42 patient (2.4%)
		Poor response	1/42 patients (2.4 %)	Poor response	2/42 patients (4.76%)	Grade 2	2/42 patients (4.8 %)
Partial response (at least 30% decrease in longest tumor diameter) Correspondent to Miller–Payne grade 3and 4)	19/42 (45.2%)	Moderate response	7/42 patients (16.7%)	Moderate response	7/42 patients (16.67%)	Grade 3	8/42 patients (19%)
		Marked response	16/42 patients (38.1%)	Marked response	15/42 patients (35.71%)	Grade 4	14/42 patients (33.3%)
Complete response (complete disappearance of the lesion; Miller–Payne grade 5)	16/42 (38.1%)	Complete response	16/42 patients (38.1 %)	Complete response	18/42 patients (42.86%)	Grade 5	17/42 patients (40.5%)

Finally, we converted this ratio to fit with the correspondent pathology based Miller–Payne grades (Table 2).

Histopathology

Tumor regression was quantitatively graded by two independent pathologists in the surgical biopsy specimens based on the Miller–Payne grading system by identifying residual tumor cellularity NAC [22] (Table 2).

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 was coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Standard diagnostic indices including sensitivity, specificity, positive and negative predictive values (PPV and NPV), and likelihood ratios were calculated. For comparing categorical data, Chi-square (χ^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 Pearson correlation coefficient. A *P* value less than 0.05 was considered statistically significant.

Results

The study included 42 patients with pathologically proved breast cancer. The histopathological and molecular subtypes of the 42 malignant lesions are demonstrated in Table 3.

The correlation between the results of the three different evaluation methods and the Miller-Payne grading of the lesions is demonstrated in Table 4 and Figs. 2, 3, and 4.

The highest correlation coefficient was between the values obtained from the quantitative objective evaluation method (*r*: 0.8944) as demonstrated in Table 5.

Patients were then classified as responders and non-responders as shown in Table 6 to facilitate the calculation of the diagnostic indices of the three evaluation methods. Response was best evaluated using the quantitative objective evaluation were 39/39 lesions matched the Miller–Payne evaluation. There was only one false positive responder by the three evaluation methods.

The last step was to calculate the diagnostic indices and overall accuracy of the three evaluation methods as demonstrated in Table 7. The objective evaluation method again scored the highest indices (Fig. 5).

Discussion

Neoadjuvant chemotherapy permits in vivo testing of response and thus allows monitoring of individual tumor

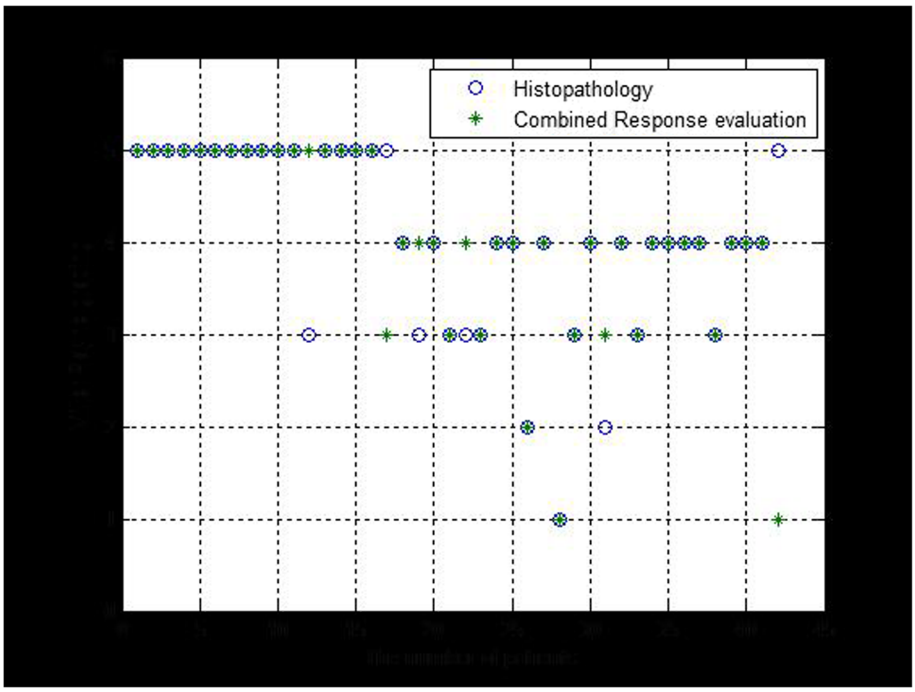

Fig. 2 The correlation between the combined response evaluation and the corresponding Miller–Payne grading

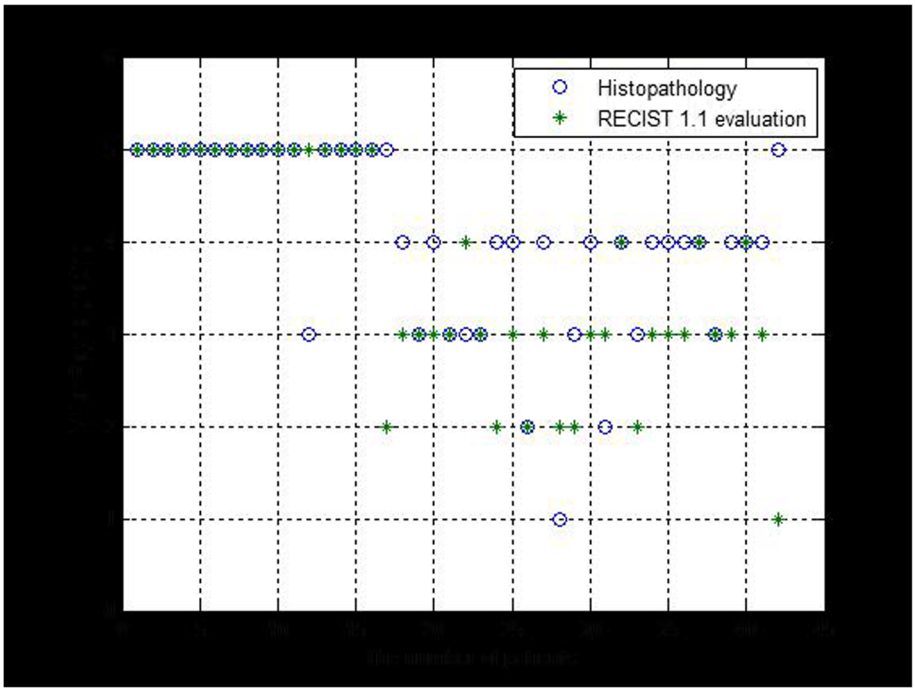

Fig. 3 The correlation between RECIST1.1 evaluation and the corresponding Miller–Payne grading

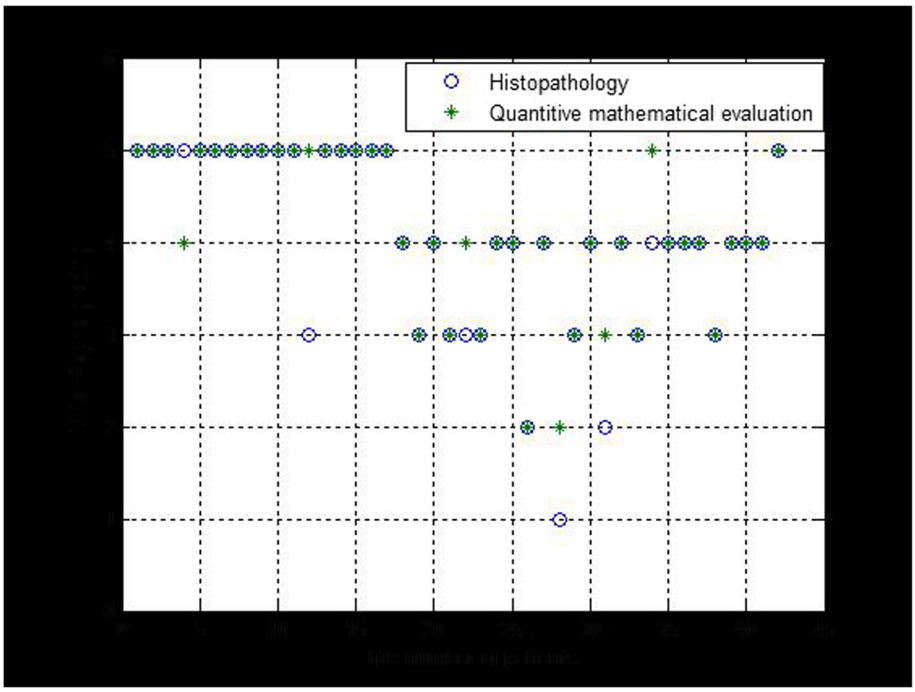

Fig. 4 The correlation between the quantitative mathematical evaluation and the corresponding Miller–Payne grading

Table 5 Correlation coefficient between the different evaluation methods and the Miller–Payne Grade of the malignant lesions

	Correlation coefficient	Accuracy
Combined response evaluation	0.6899	85.7%
RECIST 1.1 Evaluation	0.5950	54.8%
Quantitative mathematical objective evaluation	0.8944	85.7%

response. Down staging malignant lesions allows reduction in surgical complications, more conservative surgeries, and safer axillary dissections [23, 24].

The utilization of noninvasive imaging in monitoring the response of malignant breast lesions to NAC has become crucial. It may help distinguish patients who are expected to achieve a pathologic complete response from those who show no appreciable response early in the treatment course. Identifying non-responders early enough allows the planning of alternative treatment options and avoids unnecessary toxicity [7]. Many modalities have been suggested to evaluate tumor response to NAC but all of which were accused of having an unpretentious accuracy [1]. Dynamic contrast MRI has long been considered the best imaging modality for both monitoring tumor response to NAC and for the assessment of residual disease extent without competition.

CESM has emerged as one of the most promising imaging modalities with comparable sensitivity and specificity to MRI. In the neoadjuvant setting, a few studies compared the utility of CESM and MRI. In the study performed by Lotti et al., the size of residual disease after NAC was measured by both modalities based on the RECIST 1.1 criteria. They reported good correlation between both modalities (agreement: 0.76) and thus they concluded that CESM is as reliable as MRI and may be used as an adequate alternative [2]. In another study, Patel et al. concluded that the accuracy of CESM was equivalent to MRI in assessing residual disease after NAC [13]. However, these two studies depend on residual tumor size assessment. None of these studies discussed change in tumor functions which was previously investigated by quantitative MRI techniques. Another major disadvantage of the methods used in these studies is that to identify changes in tumor sizes, neoadjuvant therapy first induces cell changes that end by cell death which is then followed by size changes. In a systematic review by Lobbes et al., they stated that there is tendency of over and under estimation of response depending on tumor size alone which may both affect cosmetic outcomes and amount free margin status after operative intervention [25, 26].

To overcome these disadvantages, quantitative measures have also been tested and validated as reliable early predictors of response [8]. In the current study, we assessed a new quantitative objective tool in comparison to the previously used RECIST 1.1 criteria and a proposed combined quantitative and subjective qualitative approach in assessing the response to NAC using CESM.

The current cohort study included 42 patients who were diagnosed with breast cancer and were scheduled to receive neoadjuvant chemotherapy. Patients underwent two CESM studies (pre and post NAC) and were followed up along their treatment course. According to histopathology revision of core and surgical biopsy specimens, the commonest histopathology subtype was invasive ductal carcinomas (IDC) grades 2 and 3 (36/42, 85.7%) and the commonest molecular subtype was hormone receptor positive tumors (17/42, 40.45%) followed by triple-negative tumors (12/42, 28.6%). Complete pathological response was achieved in 17/42 (40.45%) lesions; ten triple-negative tumors and seven Her2-positive lesions. This coincides with what is stated in literature that compared with hormone receptor-positive tumors, HER2-overexpression, and triple-negative subtypes are more sensitive to NAC [23, 27] (Fig. 6).

We started by classifying the response; using the three assessment modalities, into grades that parallel the

Table 6 Comparison between the numbers of patients classified as responders/non-responders using each of the three evaluations versus pathology base Miller–Payne grading

		Pathologic Response			
		Responder		Non-responder	
		Count (n = 39)	%	Count (n = 3)	%
Quantitative objective evaluation	Responder (n = 40)	39	100%	1	33.3%
	Non-responder (n = 2)	0	0%	2	66.7%
RECIST 1.1 Evaluation	Responder (n = 35)	34	87.2%	1	33.3%
	Non-responder (n = 7)	5	12.8%	2	66.7%
Combined response evaluation	Responder (n = 39)	38	97.4%	1	33.3%
	Non-responder (n = 3)	1	2.6%	2	66.7%

Table 7 Comparisons between the diagnostic indices of the three evaluation methods

	Sensitivity	Specificity	PPV	NPV	+LR	−LR	Accuracy
Quantitative Objective Evaluat.	100% 95% CI 90.9–100	66.7% 95% CI 9.43–99.1	97.5% 95% CI 88.7–99.4	100%	3.00 95 CI:0.61–14.8	0.00	97.6% 95% CI 72.5–95.7
RECIST 1.1 Evaluation	87.2% 95% CI 72.5–95.7	66.7 % 95% CI 9.4–99.1	97.1% 95% CI 87.2–99.4	28.6% 95% CI 11.3–55.6	2.62 95% CI 0.5–13	0.19 95% CI 0.1–0.6	85.7% 95% CI 87.4–99.9
Combined Response Evaluation	97.4% 95% CI 86.5–99.9	66.7% 95% CI 9.43–99.1	97.4% 95% CI 88.4–99.4	66.7% 95% CI 19.7–94.2	2.92 95% CI 0.59–14.4	0.04 95% CI 0.00–0.31	95.2% 95% CI 83.8–99.4

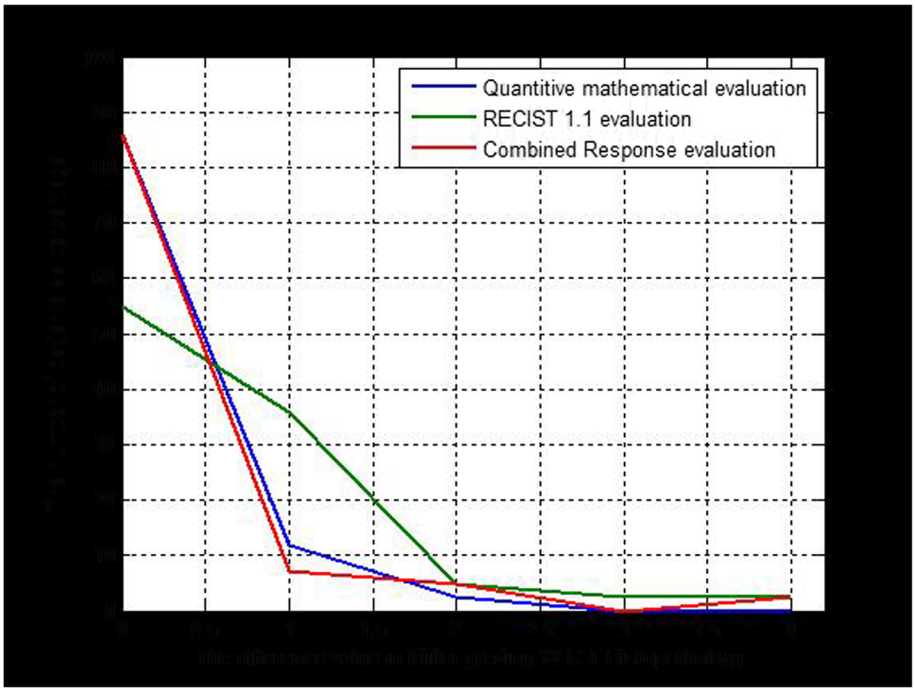

Fig. 5 Comparison between the quantitative mathematical objective evaluation, RECIST 1.1 method, and the combined method in correlation to the corresponding histopathology Miller–Payne grading

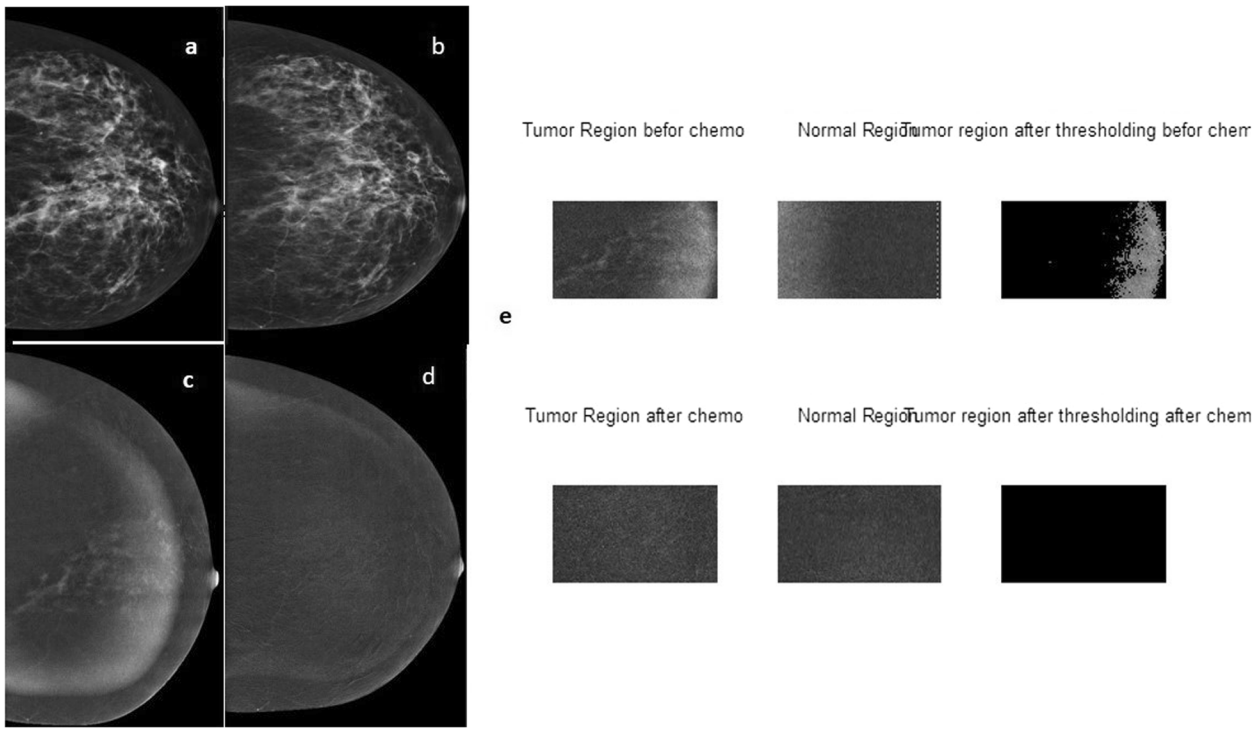

Fig. 6 A 56-year-old patient with ILC of the left breast received neoadjuvant chemotherapy. **a** Pre NAC mammogram CC view showing a left breast focal asymmetry. **b** Post NAC mammogram CC view showing reduction in size. **c** Pre NAC CESM CC view grouped enhancing lesions. **d** Post NAC CESM CC view showing no residual pathological enhancement. **e** Quantitative mathematical objective evaluation. RECIST 1.1 classified the patient as partial responder. Combined response evaluation classified this patient as a complete responder. Quantitative mathematical objective evaluation showed 99% regression. Pathological evaluation confirmed this patient as acomplete responder (Miller–Payne grade 5)

Miller Payne Grades. The quantitative objective evaluation scored the highest correlation (*r*: 0.89) with the corresponding Miller–Payne Grade. This was followed by the combined evaluation (*r*: 0.68) and the lowest scored value was for the RECIST 1.1 criteria (*r*: 059). In the study performed by Iotti et al., CESM and MRI measurements were highly correlated [2]. They even found that CESM can better predict complete pathological response better than MRI (Lin's coefficient: 0.81 for CESM and 0.59 for MRI). In another study, performed by Barra et al., they also proved that CESM measurements showed a strong, steady correlation with the pathology residual tumor size (*R*: 0.76), a value which is slightly higher than that scored by the RECIST 1.1 criteria in the current study [28] (Fig. 7).

To facilitate the calculation of the diagnostic indices of the three assessment methods, patients had to be re-grouped into either responders or non-responders. Using the three methods, only one case was considered a false positive responder. Errors in contrast administration or timing of the imaging could not be excluded. No false negative cases were reported by the quantitative objective evaluation as compared to 1 case by the combined evaluation and 5 cases for the RECIS1.1 evaluation.

The reported sensitivity, specificity, and accuracy of DCE-MRI for residual disease evaluation are 86–92%, 60–89%, and 76–90%, respectively [29–35]. The quantitative mathematical objective evaluation showed higher sensitivity, positive and negative predictive values, as well as overall accuracy compared to the evaluation based on RECIST 1.1 alone and combined response evaluation. (100%, 97.5%, 100%, and 97.6% respectively compared to 87.2%, 97.1%, 28.6%, and 85.7% for RECIST 1.1 and 97.4%, 97.4%, 66.7%, and 95.2% for combined response evaluation). Previous studies reported nearly similar indices, although they were mainly based on residual tumor size assessment. Barra et al. [28] reported no false positive cases and the calculated sensitivity, specificity, PPV, and NPV was 83.33%, 100%, 100%, and 66% respectively. On the other hand, Iotti et al. [2] reported no false negative cases with a calculated sensitivity and specificity of 100% and 84%, respectively.

Conclusion

CESM can be readily used to assess tumor response to NAC with the mathematical objective evaluation and

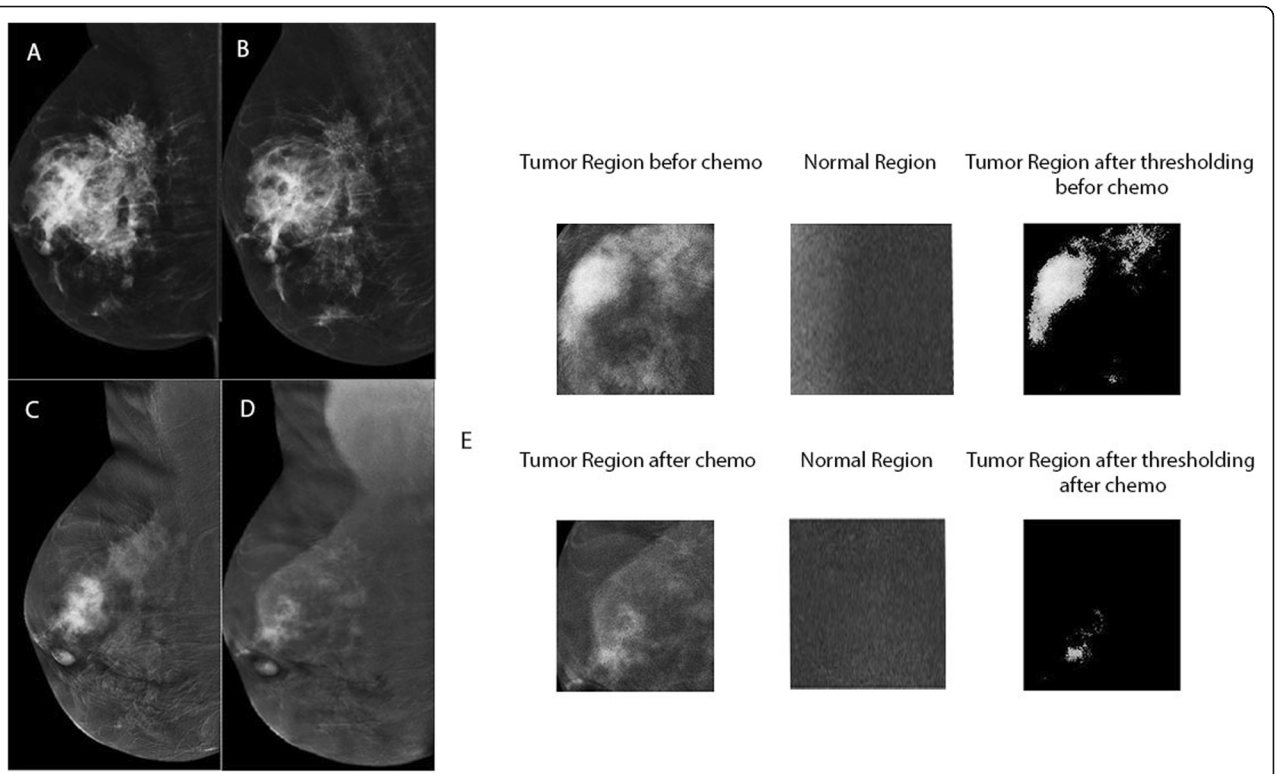

Fig. 7 A 47-year-old patient with IDC of the right breast. Biomarker status of the tumor was ER-positive, PR-positive, and HER-2 positive. **a** Pre NAC mammogram MLO view showing right breast UOQ speculated mass with micro-calcific clusters. **b** Post NAC mammogram MLO view showing mild decrease of the size of the mass. **c** Pre NAC CESM MLO view separated lesions; multi-centric masses. **d** Post NAC CESM CC view showing residual multi-nodular lesions. **e** Quantitative mathematical objective evaluation showed 84% percentage of regression. Combined evaluation response classified this patient as moderate response with 30–60% decrease in longest dimension of the dominant mass and decrease in intensity (partial responder). RECIST 1.1 classified her as partial responder. Pathological evaluation confirmed this patient as a pathological responder (Miller–Payne grade 3)

combined response evaluation providing efficient tools for evaluation of response and residual tumor. They not only allowed size discrepancy assessment but provided information about the functional changes in the residual tumor. The extra-merit of mathematical objective evaluation is avoiding bias in the evaluation.

Abbreviations

CESM: Contrast-enhanced spectral mammogram; IDC: Invasive ductal carcinomas; ILC: Invasive lobular carcinomas; ITC: Invasive tubular carcinoma; NAC: Neoadjuvant chemotherapy; RECIST 1.1: Response evaluation criteria in solid tumors 1.1; ROI: Region of interest

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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.

Authors' contributions

AM wrote the manuscript and responsible for correspondence to journal. SM collected patient data and participated in its design. MG image processing and collection of patient's images. RM and ME participated in the design of the study and performed the statistical analysis. RK conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Competing interest

The authors declare that they have no competing interests .

Ethics approval and consent to participate

The study was approved by the ethical committee of "Baheya Foundation for Early Detection & Treatment of Breast Cancer" with ethical committee approval number R-17-10-28 and approval date 12/2017. 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.

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