Original Article

Role of contrast enhanced spectral mammography in predicting pathological response of locally advanced breast cancer post neo-adjuvant chemotherapy

Noha Abd ElShafy ElSaid,⇑ Hebatallah G.M. Mahmoud, Asmaa Salama, Marwa Nabil, Eman D. ElDesouky

a Department of Diagnostic Radiology, Cairo University, National Cancer Institute, Egypt
b Department of Surgical Oncology, Cairo University, National Cancer Institute, Egypt
c Department of Pathology, Cairo University, National Cancer Institute, Egypt
d Department of Medical Oncology, Cairo University, National Cancer Institute, Egypt
e Department of Biostatistics and Cancer Epidemiology, Cairo University, National Cancer Institute, Egypt

Abstract

Objective: To evaluate the accuracy of CESM technique in predicting the final pathological response and residual tumor size post NAC in LABC.

Patients and methods: This study was prospectively carried on 21 female patients diagnosed with stage II and III breast cancer. CESM was done at the end of last cycle of chemotherapy and before definitive surgery.

Results: The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), false negative and false positive of the CESM were assessed by comparing the enhancement of the residual lesions and their size post neoadjuvant chemotherapy (NAC) with the final pathological response and residual tumor size in the MD Anderson system. The specificity of the CESM in predicting the tumor response to NAC in this initial study is 91%, sensitivity was 40% and the NPV and PPV were 80% and 62.5% respectively. The sensitivity of this technique for complete response detection was 100% with a specificity 83% and lowered sensitivity in detecting chemoresistant tumors (33.3%).

Conclusion: CESM is an emerging easy technique that can predict the final pathologic tumor response after NAC especially complete response acting as a good negative technique.

1. Introduction

Before the introduction of the neo-adjuvant chemotherapy as a standard of care for locally advanced breast cancer, the surgical treatment available for stage 2 and stage 3 operable breast cancers was mastectomy [1]. Neo-adjuvant chemotherapy allowed for down staging of the tumor then performance of more conservative surgeries [2], also it has allowed assessment of the chemotherapy response in vivo which correlates with the clinical outcome [3]. The tumor response to NAC influences surgical planning in the form of mastectomy or breast conserving surgery and even omitting surgery in complete responders as have been suggested recently [4].

Accurate prediction of pathological response to neo-adjuvant chemotherapy with down staging in locally advanced breast tumors as well as estimation of the residual tumor size are critical elements in determining if the patient is a good candidate for breast conserving surgery or not [5].

The complete clinical response if it corresponds to a complete pathological response represents a good prognostic indicator. The use of dual block targeted therapy anti her2 trastuzumab and pertuzumab and tailored chemotherapy regimen according to the hormonal receptor status allowed for an increase in the rate of complete pathological response [6].

Clinical as well as radiological and pathologic methods are used to assess the tumor response to NAC; clinical by comparing the size of the mass pre and during and post the course of the
chemotherapy [7], radiological using the RECIST criteria (Response Evaluation Criteria In Solid Tumors) [8] and pathological using the MD Anderson and Miller Payne systems [9].

All the available radiological methods have their limitations in predicting the final pathologic response. Mammography and complementary US are the routine methods in our center to assess the response post NAC in locally advanced breast cancer. CESM is an emerging technique that has proved to be an accurate tool in breast cancer diagnosis. The technique relies on the assessment of the vascularity of the tumor where the non-ionic iodine based contrast material injected during mammography is only taken by the viable cancer cells [10].

Different patterns of enhancement that forms images derived from subtraction of dual exposures of low and high X-rays energies are obtained [10]. In this study we investigated the use and the feasibility of the CESM as a method for assessment of chemotherapy response in a sample of locally advanced breast cancer patients. The clinical and radiological findings are compared to the final pathologic diagnosis.

2. Patients and methods

This is a prospective case series performed for 21 patients who attended the outpatient surgical and oncology clinics and diagnosed by biopsy as locally advanced breast cancer (stage II and III) at the National Cancer Institute, Cairo University.

3. Patients’ selection criteria

Inclusion criteria: locally advanced breast cancer cases scheduled for neo-adjuvant chemotherapy including T3, T4 and N1, N2 or N3 nodal disease (stages II or III).

Exclusion criteria: stage IV metastatic breast cancer, contraindications for neo-adjuvant chemotherapy or to the administration of iodine contrast agent, pregnancy, and known BRCA mutation.

Diagnosis was done using the TNM staging system for breast cancer according to the AJCC cancer staging system (American Joint Committee on Cancer). A biopsy in the form of FNAC or true cut needle was done for diagnosis. Metastatic workup was done in the form of chest X-ray, abdominal US; CT and bone scan to detect distant metastasis.

An initial bilateral mammography and a complementary US with or without contrast were done to determine the site and size of the tumor. Preoperative skin tattooing was done to localize the tumor in case of complete response.

Treatment: Neo-adjuvant chemotherapy was given in the form of eight cycles, four cycles of adriamycin and cyclophosphamide followed by four cycles of taxanes. After the last course of chemotherapy, all selected patients underwent clinical response assessment as well as CESM and complementary US. The chemotherapy response was categorized into: complete response, partial response, progression of the disease, stable disease.

Definitive surgical treatment in the form of modified radical mastectomy or breast conservative surgery was done for the patients depending on the assessment of the clinical response to chemotherapy, the presence of preoperative tattooing and the patient’s choice as well as the indications and contraindications for the breast conservative surgery.

CESM interpretation of response: interpretation was done using response evaluation criteria in solid tumors (RECIST) guide lines for evaluation of target lesions [8]:

- Complete Response (CR): complete resolution of all main lesions with reduced short axis of pathological lymph nodes to <10 mm.
- Partial Response (PR): At least a 30% decrease in the diameters of the main lesion.
- Progressive Disease (PD): At least a 20% increase in the diameters of main lesions as compared to the smallest sum diameters. The appearance of one or more new lesions is also considered progression.
- Stable Disease (SD): the lesion didn’t reduce in size to meet with PR and didn’t progress to be PD as compared to the smallest sum diameters of the original lesion.
- Contrast Agent:
  - The contrast agent used was the non-ionic solution (iohexol, Omnipaque 300; Nycomed, Roskilde, Denmark) containing 300 mg of iodine per milliliter, which is commonly used for CT. In our study, we injected 1.5 ml/kg of the agent by hand over a period of approximately 1 min.
  - Instrumentation:
    - All images were acquired with a production system (Seno-bright; GE Medical Systems, Milwaukee, Wis). GE Healthcare’s new Seno-Bright Contrast Enhanced Spectral Mammography (CESM) technology designed to allow the physician to image blood flow through angiography of the breast using a contrast agent and a dual energy acquisition technique.

3.1. Technique

This is consisted of high-energy and low-energy digital mammograms obtained after administration of iodinated contrast agent. An informed consent was obtained from all patients.

Bilateral conventional mammography both cranio-caudal and medio-lateral oblique views were taken. Contrast-enhanced digital mammographic procedure was performed in approximately 7–10 min. The lesions were analyzed by the radiologist for the presence, morphology, and pattern of enhancement of residual lesions after CTH.

The patterns of contrast enhancement of the residual tumors were interpreted as follows: Intense contrast enhancement denotes chemo-resistance (stable and progressive disease), faint uptake and homogenous background uptake denotes minimal residual disease and enhancement with reduced lesion size is considered partial response, no contrast uptake indicates complete therapeutic response.

3.2. Assessment of the pathology response

Interpretation of the pathology response was done by the pathologist using the MD Anderson system [9] for assessment of response post neo-adjuvant chemotherapy using the following parameters from pathologic examination in order to calculate Residual Cancer Burden (RCB):

1. The largest two dimensions (mms) of the residual tumor bed in the breast (largest tumor bed if multi-centric disease)
2. Submission of the entire largest cross-sectional area of the residual tumor bed for histologic mapping, with specific identification of those slides in the pathology report
   - If the residual tumor is large (i.e. largest diameter > 5 cm), then at least 5 representative cassettes from the largest cross-sectional area are sufficient, but should be identified in the original pathology report
   - Histologic assessment of the percentage of the tumor bed area that contains carcinoma (all carcinoma, i.e. invasive and in situ).
   - To assess cellularity it is helpful to scan across the sections of tumor bed and then estimate the average cellularity from the different microscopic fields.
- Expect there to be variable cellularity within the cross section of any tumor bed, but estimate the overall cellularity from the average of the estimates in different microscopic fields of the tumor bed.

3. Histologic estimate of the percentage of the carcinoma in the tumor bed that is in situ.

4. The number of positive (metastatic) lymph nodes.

5. The largest diameter (mm) of the largest nodal metastasis.

So we categorize the cases response under the following: CR (complete response), I (minimal residual disease RCB I), II (partial response RCB II), III (chemo resistance, poor response or no response RCB III).

3.3. Statistical methods

SPSS version 15.1 (SPSS Inc., Chicago, IL) was used to analyze CESM enhancement patterns and correlate it with the presence of residual disease after NAC pathologically. The positive predictive value (PPV) was calculated by dividing the number of patients with a positive test and residual disease by the total number of patients with a positive test. The CESM response and residual tumor pathological response were correlated. Specificity, sensitivity, PPV, NPV of CESM were determined. The size of the residual tumor mass was also assessed radiologically and correlated to pathology.

4. Results

Our study included 21 female patients diagnosed as having locally advanced breast cancer. Their age ranged from 30 to

<table>
<thead>
<tr>
<th>Pathology type</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC</td>
<td>18</td>
<td>85.7</td>
</tr>
<tr>
<td>IDC&amp;ILC</td>
<td>1</td>
<td>4.8</td>
</tr>
<tr>
<td>ILC</td>
<td>2</td>
<td>9.5</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 1
The different pathologies in the examined cases.

Fig. 1. The different biological types of the studied malignant breast masses.

Fig. 2. A 29-year-old female patient presented by a right breast malignant mass (T3N1M0) treated by chemotherapy. A and C conventional mammogram pre and post treatment and B and D contrast mammogram pre and post treatment. Follow-up after two months revealed reduction in the lesion size that still shows intense contrast enhancement (arrow), staging became T2N1M0 denoting partial therapeutic response.
77 years old, the mean age is 50 years and the median is 50.8 years. The pathological subtypes are illustrated in Table 1 and the biological types are shown in Fig. 1.

### 4.1. The radiological and pathological response

We had only one case (4.8% of cases) that showed partial response by MD Anderson pathological system and it showed

**Table 2**

Illustrates the CESM pattern post-chemotherapy and final pathological response.

<table>
<thead>
<tr>
<th>Response</th>
<th>Numbers of cases</th>
<th>CESM enhancement patterns</th>
<th>Final pathological response by MD Anderson</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>1</td>
<td>Intense enhancement with reduced mass size</td>
<td>Partial response (II)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Intense enhancement</td>
<td>Chemoresistant (III)</td>
</tr>
<tr>
<td>True negative</td>
<td>10</td>
<td>5 cases: no enhancement</td>
<td>Complete response (CR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 cases: faint enhancement and 1 case:</td>
<td>Minimal residual disease (I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>homogenous background enhancement</td>
<td></td>
</tr>
<tr>
<td>False negative</td>
<td>6 cases</td>
<td>Faint enhancement</td>
<td>Chemoresistant (III)</td>
</tr>
<tr>
<td>False positives</td>
<td>1 case</td>
<td>Heterogeneous residual parenchymal enhancement</td>
<td>1 complete response (CR)</td>
</tr>
</tbody>
</table>

**Fig. 3.** A 38-year old female patient presented by a left breast malignant mass (T3N1M0) treated by chemotherapy (arrow). Conventional mammogram (A) MLO view, (B) & (C) contrast mammogram MLO and CC views show retro-areolar enhancing mass. Post treatment follow-up after three months: Conventional mammogram (D) MLO view, (E) and (F) contrast mammogram MLO and CC views show no enhancement, the staging became T0N0M0 denoting complete therapeutic response.
intense enhancement in CESM with reduced lesion size (Fig. 2). Pathological response assessment by the MD Anderson system as well as its agreement with the radiological response is shown in Table 2.

Complete pathological response was achieved in 28.5% of cases (6 cases). CESM was able to identify complete response in 5 out of 6 cases by showing no enhancement pattern post NAC (Fig. 3) and one case showed contrast enhancement and had complete response elicited by pathology (false positive) (Fig. 4). The specificity of this technique for prediction of complete response is 66.6% and the negative predictive value is 100% with a 95% CI = 39.76–100.00%.

Minimal residual disease response represented 23.8% of the tumor responses and was predicted by CESM in 4 out of 5 cases by showing a faint enhancement pattern post NAC that corresponded truly to pathology response RCB I by MD Anderson system (Fig. 5) and one case showed markedly regressed lesion size with faint homogenous background enhancement on CESM and the final pathological response was also minimal residual disease (I) (Fig. 6).

The chemo resistant tumors (RCB III) represented 42.8% (9 cases) in the final pathologic tumor response assessment of the locally advanced breast cancer in this study, three cases showed intense enhancement which corresponded to the poor therapy effect or chemo resistance in the final pathology (true positive) (Fig. 7) and six cases showed faint enhancement (false negative) (Fig. 8) resulting in 33.3% sensitivity for this technique in detecting chemo resistant tumors post NAC.

Fig. 4. A 49-year old female patient presented by left breast malignant mass and edema treated by chemotherapy. Staging was (T3N1M0). Conventional mammogram MLO view (A) and post contrast MLO view (B) after treatment revealed heterogeneous residual central increased density with post contrast enhancement (arrows) and a palpable mass clinically denoting chemo-resistance however by pathology after MRM no active malignant cells detected denoting complete response (T0N0M0). Enhancing central portion of the parenchyma may be due to vascular residual fibrous stroma.

Fig. 5. A 45-year old female patient presented by right breast malignant mass treated by chemotherapy (A conventional mammogram MLO view) and (B post contrast study MLO view) staging was (T2N2M0) and shows two residual faintly enhancing lesions (arrows) and staging became T1N0M0 denoting minimal residual disease (I) by imaging and proved also by pathology in spite of that the lesion was clinically T2 due to residual fibrous stroma.
The sensitivity, specificity, PPV, NPV and accuracy of CESM for prediction of all the tumor responses are 40%, 91%, 80%, 62.5% and 66% respectively.

The correlation between the CESM lesion responses to the final surgical procedure done is illustrated in Table 3.

5. Discussion

CESM has proved recently as a more accurate method than the conventional soft tissue mammography and US for the breast cancer diagnosis [11]. CESM was able to predict pathologic response in this study accurately in 14 out of 21 (66%) of patients with locally advanced breast cancers after NAC.

Contrast agent has been used for many years in both computed tomography (CT) and magnetic resonance imaging (MRI) examinations to detect angiogenesis in breast carcinoma by detecting the uptake and washout of contrast agent in the detected lesion [11].

In a previous study done by [12] CESM revealed to be a good negative test for exclusion of the underlying breast lesions in edematous breasts in cases of metastatic axillary lymph nodes, while being a good positive test in delineation of masses obscured by condensed parenchymal tissue and they also concluded that CESM acts as a promising modality of follow-up of cases presenting by edema after conservative breast surgery and chemotherapy.

In a study done by [13] NAC caused down staging of disease in LABC making more conservative surgery feasible; however, longer follow-up is recommended.

CESM was compared to MRI in a study of 47 patients with locally advanced breast cancer received NAC. The lesion size measurements were highly correlated and in strong agreement in assessing the response to NAC [14]. In our study, the concordance of the complete pathological response with the no enhancement pattern on CESM was achieved in 83% (5 out of 6 cases). Three cases out of five that showed the agreement underwent modified radical mastectomy despite the presence of a complete response because of the original tumor site which was retro-areolar.

The discordance between the radiological response and the pathological response was shown with the chemo resistant tumors. The pattern of enhancement in (6 out of 9 cases) denoted minimal residual disease while the final pathologic response was a poor therapy effect. This fact put into question the use of this...
technique in response assessment especially in the chemo resistant group as this group of false negatives will be treated conservatively while they should have a more radical treatment especially when planning surgery so radiological finding should be correlated to clinical examination.

It was hypothesized that the residual cancer cells present as small foci in the tumor bed and receive nutrients by diffusion and not from vascular perfusion could be the reason behind the false negative enhancement pattern on CESM [15]. In our study six cases were false negative (28.5%) leading to lowered sensitivity (40%).

In our study complete pathological response was not always accompanied by disappearance of the tumor mass due to presence of residual fibrous stroma despite the loss of viable cells elicited by absence of an enhancement and proved by pathology with specificity 83% and 100% sensitivity.

Since the use of the breast conservative surgeries after neoadjuvant chemotherapy in locally advanced breast cancer depends on down staging and reduction in the tumor size to less than 5 cm, a radiological complete response determined by CESM can change the treatment strategy to conservative breast surgery even in the presence of a mass clinically.

We also reported the hormonal subtypes but we could not relate them with the CESM enhancement pattern due to small sample size.

In this study the rate of modified radical mastectomy was high 76.1% (16 cases) while breast conservative surgery was done in 5 cases despite the down staging of the tumors achieved in 12 cases ranging from PCR to minimal residual disease because we depended on the clinical and conventional mammography in assessing the response to chemotherapy and accordingly the surgical strategy was decided.

Our study limitation was mainly related to the small number of patients studied.

Finally we conclude that CESM is a simple technique, less expensive and with no claustrophobic experience like MRI.

The use of the CESM as an adjunct to the conventional mammography and the clinical method for assessment of the pathological response post NAC can give information that can help guide surgical planning. The timing of the CESM in relation to the neo-adjuvant chemotherapy cycles can be investigated also to assess the initial response to neo-adjuvant chemotherapy and after 2 or 3 cycles of chemotherapy.

Fig. 7. A 62-year old female patient presented by a left breast malignant mass treated by chemotherapy. A and B conventional and contrast mammogram MLO views and C and D show US of the mass and the axillary LNs, the case staged (T2N2M0) and shows no response after treatment denoting stable disease(Chemo-resistant [III]).
Further studies should be implemented to investigate its accuracy compared to the MRI with contrast in predicting pathological response to NAC.

Conflicts of interest

The authors declare no conflict of interests.

References


