Accuracy of MRI in the Detection of Residual Breast Cancer after Neoadjuvant Chemotherapy

MONA A. ABUL-ENEIN, M.D.*; INAS A. KORIEN, M.Sc.*; RASHA KAMAL, M.D.** and MOHAMED A. HASSAN, M.D.*
The Department of Clinical Oncology and Nuclear Medicine (NEMROCK), Kasr El-Aini Center* and The Department of Radiology, Faculty of Medicine**, Cairo University

Abstract

Background: This study investigated the role of Magnetic Resonance Imaging (MRI) in evaluation of pathologically complete response and residual tumors in patients who received Neoadjuvant Chemotherapy (NAC).

Material and Methods: Thirty patients with locally advanced primary breast carcinoma, who presented at Kasr Al-Aini School of Clinical Oncology (NEMROCK) underwent contrast-enhanced MRI before and after treatment with neoadjuvant anthracycline-based and taxane-based chemotherapy. For each patient, the maximum extent of the MRI abnormality was measured both before and after treatment. These measurements were subsequently compared with physical examination findings and histologic results to determine the ability of MRI to accurately reveal tumor extent after neoadjuvant chemotherapy.

Results: Six patients (20%) achieved radiological CR (rCR) with complete disappearance of both breast lesions and pathological axillary lymph nodes; but only three patients (50%) of them had pCR. Three patients experienced a false positive outcome, having an rCR without a pCR, and one patient had a false negative outcome, failing to achieve an rCR but having a pCR.

Conclusion: MRI can show residual malignancy after neoadjuvant chemotherapy better than physical examination, particularly in patients who have not had a complete clinical response to therapy.

Key Words: Locally advanced breast cancer – Contrast-enhanced MRI – Pathological complete response – Neoadjuvant chemotherapy.

Introduction

BREAST cancer is the most commonly diagnosed cancer among females, with an estimated 249,260 new cases of invasive breast cancer and estimated death toll of 40,890 women with breast cancer in the United States in 2016 [1]. Neoadjuvant Systemic Treatment (NAST) of breast cancer is commonly used nowadays, either by chemotherapy (NAC) or hormonal therapy, to increase the rate of breast conservation [2]. Moreover, NAC permits for testing in vivo chemosensitivity [3]. Data from large randomized trials showed that the achievement of pathological Complete Response (pCR) in breast and/or axillary lymph nodes after completion of neoadjuvant chemotherapy is associated with favorable long-term outcome [4,5]. Therefore, pCR is used as a surrogate marker for disease free survival and overall survival [6,7].

Physical examination is the gold standard for assessing initial tumor size and response to neoadjuvant chemotherapy. Pathologic analysis is the gold standard for assessing the size of the residual tumor after surgery. Routinely, patients undergo mammography and possibly sonography for initial assessment, diagnosis, and staging of breast cancers. All of these methods (including physical examination, mammography, and sonography) have been shown to be suboptimal in the accurate assessment of response to neoadjuvant chemotherapy [8]. Some have suggested that the lack of concordance may be related to chemotherapy-induced fibrosis [9]. Contrast-enhanced MRI of the breast has been shown in a number of studies to detect breast cancers with a high degree of sensitivity ranging from 95% to 100% and with variable specificity ranging from 37% to 97% [10]. MRI enhancement patterns in predicting response to neoadjuvant chemotherapy, and functional MRI as a marker of tumor response to neoadjuvant chemotherapy [11].

Patients and Methods

This is a prospective observational cohort study carried out at Kasr El-Aini Center of Clinical
Oncology and Nuclear Medicine (NEMROCK) during the period between August 2013 and March 2015. A group of thirty female patients with locally advanced breast cancer were recruited and evaluated for pathological response, which is the primary end point of the study. Patients included were >18 years, T ≥ 2 or more, node positive with no distant metastases. Patients’ performance status was 0, 1 or 2 with adequate organ function and signed informed consent. Patients were excluded if they had positive pregnancy test, received previous chemotherapy or radiotherapy. Also; patients were excluded if they had previous malignancy. TNM stages were determined according to the American Joint Committee on Cancer Staging Manual (7th edition).

All patients received neoadjuvant chemotherapy in the form of: Anthracyclins-based regimens (Cy-clophosphamide, epirubicin and flurouracil (FEC, C 500mg/m² iv d1, E 100mg/m² iv d1, and F 500 mg/m² iv d1) repeated every 21 days provided hematological recovery or Doxorubicin plus cyclophosphamide (AC, A 60mg/m² iv d1, C 600mg/m² iv d1) repeated every 21 days), after 2 cycles of this regimen, the clinical response of patients was assessed. We continue to 4 cycles then shifted to taxanes while if the disease is stable or progressed during the 4 cycles the patient was shifted to taxanes-based regimen directly. Taxanes-based regimen used was either Paclitaxel weekly as 80 mg/m² iv for 12 weeks or Docetaxel 75mg/m² iv d1, repeated every 21 days for 4 cycles).

Response to the treatment was evaluated clinically i.e. by palpation every two cycles of chemotherapy. Radiological assessment was performed simultaneously using contrast-enhanced MRI (used in case of young patients <40 years, in mammographically dense breasts or in case of complete disappearance of the tumor by palpation. Tumor size is typically assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1) [12]. Moreover, at the time of surgery pathological assessment was performed where pCR was defined as no residual invasive cancer in the excised tumor or lymph nodes after completion of neoadjuvant chemotherapy. The presence of residual ductal carcinoma in situ in absence of an invasive element was also considered as pCR [13].

**Results**

This is a prospective observational cohort study conducted at Kasr El-Aini Center of Clinical Oncology and Nuclear Medicine (NEMROCK) during the period from August 2013 to March 2015. The study included thirty patients who had locally advanced breast cancer recruited in accordance with the inclusion and exclusion criteria. Patients were evaluated every 2 cycles clinically and radiologically to detect the response to chemotherapy. Pathological Complete Response (pCR) was used as a primary end point, correlation between pCR and radiological CR was the second end point for the study.

**Patients characteristics:**

Thirty patients were evaluated at the end of the study with an age range of 24 to 65 years (median age 45.5 years). Twenty-six patients (>85%) were stage III A, B and C. Twenty-one patients (70%) were premenopausal. Table (1) shows the clinical and pathological features of the patients.

**Clinical and radiological examination of the patients after completion of chemotherapy:**

According to the RECIST system, eleven patients (36.6%) achieved Complete Response (CR) i.e. complete disappearance of the breast mass and axillary lymph nodes, while sixteen patients (53.3%) achieved Partial Remission (PR) i.e. decrease in size of the mass more than 50%, three patients (10%) were stationary Disease (SD). When these patients had contrast-enhanced MRI as a tool of assessment of response to treatment; six patients (20%) achieved radiological CR with complete disappearance of both breast lesions and pathological axillary lymph nodes.

**Type of surgery:**

After completion of all chemotherapy patients were subjected to surgical intervention; where nine patients underwent breast conservative surgery and twenty-one patients underwent modified radical mastectomy.

**Pathological response:**

Five patients (16.66%) achieved pCR i.e. complete disappearance of cancer cells from both breast and lymph nodes while twenty-five patients (83.33%) didn’t achieve pCR.

**Correlation between the clinical and pathological response:**

Of the 11 patients that achieved cCR, only 4 patients (35.3%) achieved pCR while of the 16 patients who had cPR, 1 patients (20.8%) achieved pCR.

**Correlation between the radiological and pathological response:**

Six patients achieved radiographic CR (rCR) by contrast-enhanced MRI after completion of
chemotherapy and underwent surgery. When pCR was defined by the traditional definition of resolution of invasive disease, 4 of 6 patients (66.6%) with rCR had a pCR. Two patients experienced a false positive outcome, having a rCR without a pCR, and one patient had a false negative outcome, failing to achieve a rCR but having a pCR.

Table (1): Clinical and pathological features of the 30 patients recruited in the study.

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
</tr>
<tr>
<td>Menopausal status all (n=80):</td>
</tr>
<tr>
<td>Operability at presentation:</td>
</tr>
<tr>
<td>AJCC stage:</td>
</tr>
<tr>
<td>Histopathology:</td>
</tr>
<tr>
<td>Tumor grade:</td>
</tr>
<tr>
<td>Molecular subtypes:</td>
</tr>
</tbody>
</table>

Table (2): Correlation between rCR and pCR.

<table>
<thead>
<tr>
<th>rCR</th>
<th>pCR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>23</td>
</tr>
</tbody>
</table>

pCR: Pathologic Complete Response.
rCR: Radiographic Complete Response.

Mona A. Abul-Enein, et al. 1413

Fig. (1): Schematic diagram of sequence of protocol used for our pilot study. Patients received neoadjuvant Chemotherapy (CT). Medical examination and imaging (i.e., mammography, breast sonography, and breast MRI) were performed. Each patient received neoadjuvant chemotherapy; then physical examination and imaging examinations were repeated. Second chemotherapeutic agent was given to patient, and physical examination and imaging examinations were repeated. Patient underwent surgery, either Breast Conservative Surgery (BCS) or Modified Radical Mastectomy (MRM), and final pathology results were obtained.

Fig. (2): Magnetic resonance images of case no. (11) before (A) and after (B) Neoadjuvant therapy based on the pCR definition of resolution of both invasive disease and ductal carcinoma in situ.
Fig. (3): Pre-(A) and post-treatment (B) Magnetic resonance images of case no (45) showing radiographic complete response whereas the patient did not achieve a pathologic complete response.

Fig. (4): Pre (A) treatment and post (B) treatment magnetic resonance images of case no (64) showing incomplete radiographic responses whereas the patient achieved pathologic complete response.

Discussion

Because neoadjuvant chemotherapy followed by surgery and radiation is being used with increasing frequency in the treatment of patients with palpable breast cancer, noninvasive methods of assessing response to chemotherapy are increasingly important. A sensitive and specific method would be particularly advantageous because early recognition of nonresponse might lead to changing to a more effective agent sooner, minimize toxicity, and permit optimal timing of surgery. A lack of response to a particular agent in vivo may also help guide additional chemotherapy after surgical removal.

Physical examination serves as the gold standard for assessing clinical response to chemotherapy. In this pilot study, we compared physical examination findings with mammography, sonography, and MRI findings and compared all techniques with pathology results regarding the ability of each technique to assess tumor response to neoadjuvant chemotherapy. The presence of dense tissue on mammography likely contributed to the fact that the response agreement of mammography compared with pathology was less than that of MRI compared with pathology. Dense breast tissue often obscured the tumor on mammography making size determination difficult.

Of the non-invasive methods of tumor assessment in patients undergoing neoadjuvant chemotherapy that we measured, MRI correlated better with pathology than physical examination, mammography, and sonography. However we did find that MRI overestimated and underestimated residual
tumor in 10% of the patients. We had one case in which MRI overestimated residual tumor. It is unclear whether the specific chemotherapeutic agent altered gadolinium uptake or induced surrounding inflammation. Preliminary studies have suggested that taxanes increase vascular permeability and may induce a capillary protein leakage, thereby contributing to increased gadolinium uptake by the tumor [11]. Further study into the effects of specific chemotherapeutic agents is warranted.

Chemotherapy-induced fibrosis can be difficult to differentiate from residual disease on physical examination and conventional imaging [8]. Clinical examination potentially can overestimate residual tumor; morphologic response has been shown to be more accurately assessed using contrast-enhanced MRI [14]. In our case in which MRI overestimated residual disease, perhaps the residual enhancement was from reactive inflammation that was caused by tumor response and healing.

In two of the cases, MRI showed no residual mass or enhancement; pathology result for one of these cases showed very small foci of invasive carcinoma, including an invasive ductal carcinoma (<0.1cm). While the other case was an invasive cancer with lobular features. It has previously been shown that lobular carcinomas may have variable enhancement on MRI [15].

The radiologist was blinded to the clinical size of the tumor and the pathology results, but to provide the best clinical care for the patient, the radiologist had access to the other imaging studies, with the exception that the MRI results were not known to the radiologist at the time of the mammogram and sonogram. This study design may be associated with potential bias; however, we think that this design provided the best clinical care to the small number of patients enrolled in this study. Another potential limitation of the study is that it is possible that the chemotherapeutic agents may affect the imaging appearance, especially on MRI with regard to the gadolinium uptake [12].

In summary, MRI appears to correlate better with pathology than physical examination, mammography, and sonography in patients undergoing neoadjuvant chemotherapy. MRI is not, however, perfect. It may overestimate or underestimate residual disease in some patients. These results support the need to conduct further studies to assess the value of MRI in the prediction of in vivo morphologic and pathologic tumor response to specific neoadjuvant chemotherapeutic regimens in women with palpable breast cancer.

References

Accuracy of MRI in the Detection of Residual Breast Cancer after NAC


Dقة التصوير بالرنين المغناطيسي في الكشف عن سرطان الثدي المتبقية بعد العلاج الكيميائي (ما قبل الجراحة)

فحص التصوير بالرنين المغناطيسي للكشف عن سرطان الثدي توفر معدلات ثابتة من الكشف عن السرطان والنتائج أقل إيجابية كاذبة مع مرور الوقت. في حين أن التصوير بالرنين المغناطيسي يمكن أن يكون أكثر فعالية من التصوير الإشعاعي للثدي في تحديد المناطق المشبوهة في الثدي، فإنه ليس دائمًا قادرًا على التمييز بين الأفقتين السرطانية والحميدة، والتي يمكن أن تؤدي إلى إجراء إختبارات إضافية والنتائج الإيجابية الكاذبة التي قد تسبب الألم للمرضى.

الهدف من دراستنا التحقيق في جدوى التقييم المعززة التصوير بالرنين المغناطيسي لقياس دقيق لحجم الورم المتبقية للمرضى الذين خضعوا للعلاج الكيميائي (ما قبل الجراحة)، وتمت مقارنة أحماض الورم على صور الرنين المغناطيسي بعد فحص السرير قبل العلاج الكيميائي وبعدة.

تم تصوير 20 قبل وبعد تلقيين العلاج الكيميائي وتمت مقارنة النتائج بالفحص السريري.

الخلاصة: إن الإرتباط كبير بين القياسات التي تم الحصول عليها من المرض المتبقية على صور الرنين المغناطيسي وتلك التي حصلنا عليها من علم الأمراض يؤكّد جدوى التصوير بالرنين المغناطيسي بعد العلاج الكيميائي.