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Original Article

Diffusion weighted imaging in early prediction of neoadjuvant chemotherapy response in breast cancer

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ABSTRACT

Background: Neoadjuvant chemotherapy (NAC) has clinically important outcome. Early evaluation of the treatment response is important to avoid unnecessary therapy in non-responders. MRI is the most sensitive imaging for monitoring NAC response.
Aim of this study: Is to test the ability of DWI to detect early response to NAC.
Results: The study was performed on 20 patients, proved pathologically to have invasive breast cancer. All patients underwent breast MRI before initiation of NAC, after one cycle and after completion of the NAC protocol. Regarding the mass size, results showed no significant change in maximum mass diameters occur after the 1st NAC cycle. Absolute value of the ADC show increase all along the treatment course which has no significant correlation with the pathological response. The relative increase ADC more than 20% calculated from subtraction of the pre-treatment ADC_{mean} value from that after the first NAC, subdividing the result on the pre-treatment ADC_{mean} value and multiply it by 100 reflected significantly on the pathological response (p value of 0.011).
Conclusion: ADC value can predict responder from non-responder as early as after the first cycle of chemotherapy.

1. Introduction

Neoadjuvant (preoperative, induction) therapy has clinically important outcomes, including early treatment of micrometastatic disease, disease downstaging and feasibility of breast conservation in selected cases. Furthermore, neoadjuvant chemotherapy (NAC) may also allow an in vivo assessment of chemosensitivity, potentially allowing a regimen change that would not otherwise be made with traditional postoperative adjuvant treatment. Finally, NAC provides a platform for important biomarker and correlative studies to enhance our understanding of this disease [1,2].

Cancer drug resistance is a major obstacle in medical oncology. Resistance can arise prior to or as a result of cancer therapy. Different mechanisms can be adapted by cancerous cells to resist treatment, including alteration in drug transport and metabolism, mutation of drug targets, as well as impaired apoptosis [3].

Early evaluation of the treatment response is important to avoid unnecessary therapy in non-responders and to minimize drug-related side effects. Traditionally the efficacy of these drugs has been monitored by the extent of tumor shrinkage [4].

Contrast material–enhanced breast MR imaging is currently accepted as the most sensitive imaging technique for the diagnosis and staging of breast cancer [5].

As a general rule, any pharmacologic process –including NAC- that causes necrosis or cellular lysis will lead to an increase in water diffusion in the extracellular space, with decreases in signal

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intensity on high- b -value images and corresponding increases in ADCs. On the other hand, disease progression is displayed as new areas of abnormal signal intensity or as increases in the extent and intensity of previously documented abnormalities [6].

1.1 The aim of this study is to test the ability of DWI to detect early changes caused by neoadjuvant therapy in a trial to distinguish non-responder from responder.

2. Methods

2.1. The study was performed on 20 patients presented to our Radio-diagnosis department, from October 2015 to October 2016, with histologically confirmed invasive breast carcinoma and planned for neoadjuvant chemotherapy.

Histological confirmation was performed by core needle biopsy. Fine needle aspiration of clinically suspicious lymph nodes was performed.

All patients underwent staging evaluation which included complete history tacking, physical examination, CBC, chemistry profile, chest radiograph, echocardiography, ultrasound or CT scan of the liver, bone scan, mammography and ultrasound of both breasts.

All patients received doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles, followed by paclitaxel 80 mg/m^2 weekly for 12 doses.

Exclusion criteria included:

1. Over-weight patient in whom the breast could not fit into the breast coil or the patient was not fit into the MRI gantry.
2. Claustrophobic patient.
3. Patient with ferromagnetic implants

Ethics was followed and informed consent was obtained. All patients underwent thorough history taking, complete clinical examination and histopathological fine needle aspiration cytology or true-cut needle biopsy.

2.2. Breast MRI was done at three time points using Philips Achieva 1.5 T using dedicated breast coil. The pre-treatment (baseline) as well as the post-treatment (pre-operative) MRI include the following sequences:

(a) **T2-weighted, fat saturated sequence** with TR (5600), TE (59), FOV (270–340), matrix (320x314), slice thickness (4 mm) and gap (20% = 0.8 mm) in axial plane with extension to the axillae.
(b) **T1-weighted non-fat saturated sequence** with TR (8.6), TE (4.7), FOV (270–340), matrix (448x323), slice thickness (1 mm) and gap (-10% = -0.1 mm) in axial plane with extension to the axillae.
(c) **Diffusion weighted echo-planar imaging (EPI) sequence** before contrast media injection with TR (4800), TE (98), FOV (270–340), matrix (192x192), slice thickness (4 mm) and gap (50% = 2 mm) in axial plane. The b values (0, 400 and 800 s/mm^2) were fixed in all studies with computer generated ADC map.
(d) **3D T1-weighted fat suppression gradient echo sequence** performed before and repeated five times after IV administration of 0.1 mmol gadolinium chelate/kg in a rate of 4 mL/s, followed by 20 mL saline flush. The repeated sequences are taken with 60 s interval.

Seven to nine days after the 1st chemotherapy cycle a **second imaging setting** consisted of DWI and T2 had been done. The last imaging setting was full MRI protocol which had been done after completion of chemotherapy regimen.

Images Post processing was done to measures the maximum tumor diameters on the sequence that show maximum enhancement. In DWI, multiple ROI technique was used. In a trial to achieve standardized conditions for results analysis and avoiding data contamination by adjacent structures, multiple freehand regions of interest (ROI), with mean area of 30 mm^2 (ranging from 10 to 50 mm^2), were individually placed on the ADC map at the site of the target lesion and the minimum (ADC_{min}), mean (ADC_{mean}) and maximum (ADC_{max}) ADC values were calculated. Necrotic or cystic components were avoided.

ROI site was based on the voxels that showed most enhancements in the pre-treatment and post-treatment studies. That was well correlated with voxels that showed maximum restriction values at high b value (800 s/mm^2). On the workstation we used the cross reference to locate the chosen ROI site on ADC map that coincide with the contrast study. As for the DWI-MRI study after the 1st NAC cycle, since we confirmed the correlation between the areas of maximum enhancement and true restriction at high b value (800 s/mm^2), areas of true restriction were used and cross reference with the ADC map for ROI placement.

2.3. Surgery (breast conservative surgery or modified radical mastectomy) were done and pathological examination of the specimens to evaluate the response (pCR). Complete pathological response was defined as complete absence of invasive cancer cells –irrespective of carcinoma insitu- in the surgical specimen of the breast and axillary lymph nodes.

3. Results

Out of 20 examined patients, one decided to stop NAC after the first cycle and gone for mastectomy. Otherwise all patients underwent full MRI protocol before the starting chemotherapy.

Patient's age ranged from 24–68 years with a mean of 46.70 ± 10.86. Apart from a single patient with invasive lobular carcinoma, all the other 19 patients were invasive ductal carcinoma, of non-otherwise specified type (NOS) type. Patients were all complaining of either only breast lump or lump with skin changes.

On two MRI follow-up serials, none of the patients was progressive disease, however 6 patients were stable disease (SD) and those were classified as non-responders (Fig. 1). The other 13 patients were responders. From which 9 patients showed partial radiological response (PR) (Fig. 2) and 4 patients showed radiological complete response (CR). The latter group showed both radiological as well as pathological (pCR) complete response.

3.1. Early change of tumor size and predicting pCR

Table 1 shows the initial tumor size as well as the changes after the first cycle and at the end of scheduled NAC. One patient decided to do surgery after her second MRI study. The mean pre-treatment, after 1 NAC cycle and post-treatment size was 4.88 ± 2.19, 4.35 ± 2.33and 2.93 ± 2.41 cm respectively. No significant statistical correlation was seen between the post 1st NAC tumor size and pCR.

3.2. The use of ADC value as an indicator of pCR

On comparing the ADC values of the different patients along the three examinations, we noticed a continuous increase in values along the treatment course. The mean ADC value in the pre-treatment period was $0.98 \pm 0.09 \times 10^{-3}$ mm^2/sec, which jumped to $1.25 \pm 0.18 \times 10^{-3}$ mm^2/sec 7–9 days after the 1st NAC cycle and increased to$1.28 \pm 0.22 \times 10^{-3}$ mm^2/sec after full treatment course. No statistical significance could be seen between the