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Identification of Pathological complete response after Neoadjuvant chemotherapy for breast cancer: comparison of greyscale ultrasound, shear wave elastography, and MRI

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Short title

Identification of pCR after NACT: comparison of US, SWE and MRI

Introduction

Pathological complete response (pCR) is increasingly seen after neoadjuvant chemotherapy (NACT) for invasive breast cancer. Identification of pCR at the end of NACT but prior to surgery may influence surgical decision making regarding both the breast and axilla. Confident identification of pCR may lead to less radical breast surgery and to sentinel node biopsy rather than axillary clearance in women with pre-treatment positive nodes (1).

Response to NACT is routinely assessed by MRI, greyscale US and mammography (2). In some studies, MRI has been shown to be superior to ultrasound (3,4). MRI assessment is usually carried out using RECIST criteria which are based on unidimensional measurements. Alternative MRI parameters, such as volumetric, functional and texture measurements, show promise for improving NACT response assessment both during and at the end of treatment, particularly in luminal and hybrid subgroups where standard MRI prediction tends to be less accurate (4-7). However, MRI has the disadvantages of being time-consuming, expensive, requiring intravenous contrast agent administration, and being infeasible or contraindicated for some patients.

Shear wave elastography (SWE) is an ultrasound imaging method which allows reproducible quantification of lesion and peri-lesional tissue stiffness (degree of elasticity). The parameters Emax, Emean and SD, where E is defined by Young's modulus and measured in kilopascals and SD gives an indication of heterogeneity, refers to the elasticity values of the tissue within a region of interest outlined on the US image.

SWE has been shown to improve discrimination of benign from malignant breast masses during US examinations (8,9). Higher stiffness at SWE has also been shown to be an independent predictor of axillary lymph node metastasis and resistance to NACT (10-13). SWE is quick, can be utilised in outpatient/ office situations and is straightforward to interpret.

One previous study has assessed the value of SWE in predicting pCR at the end of NACT (14). The authors found that SWE in combination with greyscale US performed similarly to MRI and better than greyscale US alone. That study was a retrospective, non-consecutive case series which evaluated Emax in one plane only and did not have pre-treatment SWE measurement for comparison, so percentage reduction in stiffness values could not be assessed. Cancers often display considerable anisotropy on SWE examination (15) so we hypothesised that SWE data acquired in two orthogonal planes may lead to more accurate assessment of post NACT response.

The aim of this project was to assess the value of changes in orthogonal Emax, Emean and standard deviation between baseline and end of treatment SWE, compared to greyscale US and to MRI, for identifying pathological complete response to NACT.

Patients and methods

Consecutive patients receiving NACT for invasive breast cancer were invited to participate in this prospective cohort study. The study was approved by the local Ethics Committee and by the host institution's Research and Development office. All participants provided written informed consent.

Eighty patients consented to participate between May 2013 and August 2017 and completed NACT. The imaging protocol included baseline (pre-treatment) and end of treatment US, SWE and MRI examinations. End of treatment imaging examinations were performed after six cycles of NACT. The first three cycles of chemotherapy in all patients consisted of 5-fluorouracil, epirubicin and cyclophosphamide (FEC). Subsequent cycles were dependent on the molecular subtype of the tumour. All US scans were performed by one of five breast radiologists or an advanced radiography practitioner trained to perform and interpret breast ultrasound. These practitioners had between 7 and 22 years of breast ultrasound experience and at least 12 months experience of performing SWE of solid breast

lesions prior to commencement of the study. The Aixplorer® ultrasound system (SuperSonic Imagine, Aix en Provence, France) was used throughout.

Four SWE images in two orthogonal planes were obtained at each time point. The ROI utilized in all cases was 2 mm in diameter (Figure 1 and 2). Maximum tumour diameter was measured on the greyscale US images. Emean, Emax and SD values used in the analysis were the average of the measurements taken from the four SWE images acquired in two orthogonal planes. As this was a prospective study, imaging was performed and associated measurements recorded without knowledge of the final pathological outcome. If the lesion was not seen on US at the end of treatment, then the US diameter was set to 1 mm, while SWE readings were taken in the region of the previous abnormality. Percentage reductions, between baseline and post-NACT imaging, in tumour diameter, Emean, Emax and SD were calculated. Cut-off values for percentage reduction in tumour diameter, Emean, Emax and SD were set from the Youden's index values derived from ROC curves. The percentage reduction in Emean and greyscale US diameter were combined and entered into the analysis as an additional parameter.

All MRI examinations were performed on a 32-channel 3.0 Tesla (T) Siemens Magnetom Trio scanner (Erlangen, Germany) with a 7-channel open breast biopsy coil. Patients were imaged in a head-first prone position. Early post contrast subtracted T1 weighted sequences (acquired approximately 90 seconds post contrast injection) were used to obtain measurements of the maximal enhancing lesional diameter on the pre-and post NACT scans. In cases of multifocality, the summed diameters were recorded. The absence of any enhancement above background parenchymal enhancement on the end of treatment scan was taken as MRI evidence of an imaging complete response.

pCR was classified as an absence of any invasive cancer cells in the tumour bed at surgical resection after six cycles of NACT, and an absence of lymph node metastases at axillary surgery.

Receiver Operating Characteristic (ROC) curve analysis was performed on the entire cohort and on immune-phenotypic subgroups, using MedCalc software, and the areas under the ROC curves (AUC) were compared with the DeLong method. The chi-squared test was used to assess the statistical robustness of calculated sensitivity, specificity and accuracy for pCR, with Youden's index defining the negative/positive test threshold.

Results

Complete ultrasound and MRI datasets were obtained for all 80 patients in the cohort. The mean patient age was 53yrs (range 26-79yrs). Thirty three patients had triple negative tumours, 27 were HER2 positive and 20 luminal. The mean pre NACT stiffness was 141 kPa and the mean pre-treatment US size was 29 mm. pCR occurred in 21 of the 80 (26%) patients. pCR was seen in 9 of 33 (27%) triple negative cancers, 10 of 27 (37%) HER2 positive cancers and 2 of 20 (10%) luminal cancers. At the end of treatment scan, a residual US-visible mass was seen in 77 of 80 (96%) women. All three patients with no US mass at the end of treatment scan had a pCR. The mean end of treatment stiffness was 83 kPa and the mean end of treatment US size was 17 mm.

Area under the curve (AUC) for pCR of percentage reductions in Emean, Emax, SD, and greyscale US diameter were 0.89, 0.85, 0.75, and 0.86 respectively. The combination of percentage reductions in Emean and greyscale ultrasound diameter yielded an AUC of 0.92, which is similar to the AUC for MRI of 0.96 ($p=0.28$) (figures 3-6).

The associations between pCR and baseline to post-treatment changes in US, SWE and MRI parameters, based on cut-off values suggested by Youden's index derived from ROC curve analyses, are shown in Table 1. The sensitivity of percentage reductions in Emean, Emax, SD and US diameter were 73%, 78%, 81%, and 78% respectively. The specificities were 95%, 81%, 67% and 81% respectively (table 1).

When percentage reductions in Emean and percentage US diameter were simply summed, sensitivity for pCR was 93% and the specificity was 81% (table 1).

Using the Youden's index as a cut-off, the sensitivity and specificity of MRI were 91% and 95% (table 1).

The numbers of pCR's in the HER2 positive and triple negative subgroups were sufficient to perform ROC analysis. The AUC for triple negative cancers assessed using the combination of greyscale US diameter and Emean was 0.89 compared to 0.96 when using MRI. These were not significantly different. The AUROC for the combination of greyscale US diameter and Emean in the HER2 positive group was 0.97 and for MRI it was 0.94. These were not significantly different.

Discussion

We have shown that percentage change in Emean between baseline and end of treatment SWE examinations is associated with pCR. Percentage changes in greyscale US diameter gave very similar results. Combining these two parameters with equal weighting significantly improved identification of pCR, yielding an AUC of 0.92, close to the 0.96 achieved by MRI., The percentage change in the combination of US diameter and Emean was not significantly inferior to the performance of MRI.

It is of note that both these methods combine functional information (enhancement or stiffness) and anatomical assessment of lesion size.

Greyscale US is routinely used in many centres for monitoring patients undergoing NACT for breast cancer. It has the advantages of being quick and cheap to perform. US can however give misleading results when a mass of residual scar tissue is seen on US in women who have had pCR but the scar tissue is taken to represent residual tumour. Alternatively, a round mass of tumour can develop into a plaque-like area where the volume of tumour has reduced but the diameter remains unchanged.

SWE is usually used as an add-on to a routine US examination and it takes approximately 2 minutes to perform and 2 more minutes to extract the data (8). The main advantage of SWE in the setting of women undergoing NACT is that residual tumour appears to be stiffer than fibrous tissue left after a pCR. These changes in stiffness indicating response can also be detected on interim scanning after 2 or 3 cycles of NACT (17,18). It is not yet known whether SWE can predict outcome of NACT after just a single cycle. SWE has the advantage of being highly reproducible (8). Previous studies assessing the value of SWE in women undergoing NACT have not compared the three different SWE parameters routinely produced when using an ROI on a SWE image. We have shown that the mean stiffness (Emean) gave slightly superior results when compared to maximum stiffness (Emax) and standard deviation (SD), although these differences were small and not significantly different.

The performance of SD in benign/malignant differentiation improves when the ROI is enlarged (19). It is therefore possible that when assessing response to NACT, using a larger ROI may also lead to improved performance of SD.

With modern NACT regimens it is now common to see a pCR which means that many women undergo surgical resection of the tumour bed with only scar tissue being present histologically (20). Because of this, some have advocated clinical studies using percutaneous sampling of the tumour bed using vacuum assisted biopsy devices in those women who appear to have had a complete response at end of treatment by imaging and clinical assessment (21). Before such an approach can be realised, imaging prediction of response to NACT has to become more accurate. It has become apparent over recent years that solely delineating the size of the mass in women undergoing NACT gives inadequate assessment of the pathological response of the tumour. Assessing functional characteristics using MRI, PET/CT or SWE offers the chance of measuring the changing biological characteristics of cancer and its associated peritumoural stroma, and such an approach is yielding promising results (6,7,22). It has been shown that that different tumour types have different sensitivities to NACT and that some tumours retract into a

spiculated scar while others resolve without contraction into a central scar. This means an individualised approach by the radiologist is required in this clinical setting (4,6).

The response of the cancer to NACT also has potential value when selecting what axillary procedure should be performed, since tumour response in the axilla is often similar to that seen in the breast primary. In patients who have proven axillary metastases, some authors are suggesting sentinel node biopsy may be appropriate in the subgroup of women whose end of NACT imaging suggests the presence of a pCR (1). It is therefore clear that accurate imaging assessment of response to NACT could change surgical management of the breast and the axilla to the benefit of patients.

One of the limitations of the study is that it took place in a single centre, however SWE is a straightforward technique which has been shown in a number of studies to have excellent reproducibility (16, 23). MRI assesses response to NACT better in certain subtypes of breast cancer than others (4). The limited data from the current study suggests response assessment using the combination of US size and stiffness is similar in HER2 positive and triple negative tumours and that such assessments give similar results to MRI in both subtypes.

One previous retrospective study has assessed the value of assessing response to NACT with SWE at the end of NACT (14). It showed that a threshold of Emax 30 kPa was useful in identifying response. In this previous study, patients had either pre-treatment MRI or SWE so percentage reduction in stiffness, US diameter and MRI diameter were not compared. This previous study did not compare the value of serial Emax, Emean and SD measurements, unlike the current study.

In conclusion, **SWE in combination with greyscale US shows promise as a method of end of treatment identification of response to NACT in women with breast cancer**. This combination gives both anatomical and functional information analogous to the information derived from MRI. This quick and reproducible assessment technique could be used to inform surgical decision making in the breast and

axilla, potentially replacing MRI subject to replication studies. In the future, accurate imaging assessment at the end of NACT may even lead to no surgery in women with excellent imaging responses (24).

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Figure Legends

Figure 1. SWE image of a breast cancer showing the colour map. Red is very stiff, yellow is stiff and blue is soft.

Figure 2. SWE image of a breast cancer with a 2mm ROI over a stff part of the lesion. On the right of the image is the quantitative read out of SWE parameters.

Figure 3

ROC curve showing the relationship between % reduction in mean stiffness at SWE and pCR after NACT (AUC 0.89)

Figure 4

ROC curve showing the relationship between % reduction in US size and pCR after NACT (AUC 0.86)

Figure 5

ROC curve showing the relationship between % reduction in combination of US size and mean stiffness pCR after NACT (AUC 0.92)

Figure 6

ROC curve showing the relationship between % reduction in MRI size after NACT (AUC 0.96)