



**University of Dundee**

**Identification of pathological complete response after neoadjuvant chemotherapy for breast cancer**

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

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23

24 **Short title**

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

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27

## 28 **Introduction**

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

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

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

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

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

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

#### 61 **Patients and methods**

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

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

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

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

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

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

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

## 101 **Results**

102 Complete ultrasound and MRI datasets were obtained for all 80 patients in the cohort. The mean patient  
103 age was 53yrs (range 26-79yrs). Thirty three patients had triple negative tumours, 27 were HER2 positive  
104 and 20 luminal. The mean pre NACT stiffness was 141 kPa and the mean pre-treatment US size was 29  
105 mm. pCR occurred in 21 of the 80 (26%) patients. pCR was seen in 9 of 33 (27%) triple negative cancers,  
106 10 of 27 (37%) HER2 positive cancers and 2 of 20 (10%) luminal cancers. At the end of treatment scan, a  
107 residual US-visible mass was seen in 77 of 80 (96%) women. All three patients with no US mass at the  
108 end of treatment scan had a pCR. The mean end of treatment stiffness was 83 kPa and the mean end of  
109 treatment US size was 17 mm.

110 Area under the curve (AUC) for pCR of percentage reductions in Emean, Emax, SD, and greyscale US  
111 diameter were 0.89, 0.85, 0.75, and 0.86 respectively. The combination of percentage reductions in  
112 Emean and greyscale ultrasound diameter yielded an AUC of 0.92, which is similar to the AUC for MRI of  
113 0.96 (p=0.28) (figures 3-6).

114 The associations between pCR and baseline to post-treatment changes in US, SWE and MRI parameters,  
115 based on cut-off values suggested by Youden's index derived from ROC curve analyses, are shown in  
116 Table 1. The sensitivity of percentage reductions in Emean, Emax, SD and US diameter were 73%, 78%,  
117 81%, and 78% respectively. The specificities were 95%, 81%, 67% and 81% respectively (table 1).

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

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

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

## 126 **Discussion**

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

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

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



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

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

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

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

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

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

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

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

186 axilla, potentially replacing MRI subject to replication studies. In the future, accurate imaging  
187 assessment at the end of NACT may even lead to no surgery in women with excellent imaging responses  
188 (24).

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250 **Figure Legends**

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

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

255 Figure 3

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

258 Figure 4

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

260 Figure 5

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

263 Figure 6

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

265