Four-Dimensional (4D) Subharmonic Aided Pressure Estimation for Monitoring Neoadjuvant Chemotherapy Response of Breast Cancer

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Introduction

Neoadjuvant chemotherapy is a well-established treatment option for patients with non-metastatic breast cancer. The patient response is correlated with survival. However, the optimal method for monitoring neoadjuvant therapy response has not been established. One factor that may affect the response of neoadjuvant therapy is the interstitial fluid pressure (IFP). Increased IFP prevents an effective delivery of therapeutic agents and reduces the efficacy of the therapy. Recently, subharmonic-aided pressure estimation (SHAPE) using contrast-enhanced ultrasound (CEUS) has been developed and its potential was demonstrated in animals as a non-invasive technique for IFP measurements. The SHAPE method estimates IFP based on the inverse relationship between the subharmonic signal magnitude from CEUS and IFP. The purpose of this study was to determine if 4D SHAPE can predict the response of breast cancer to neoadjuvant chemotherapy.

Materials and Methods

A. Subjects

Seventeen women with breast cancer (T1 or greater locally advanced breast cancer) and scheduled for neoadjuvant chemotherapy (approximately 16 therapy cycles over 3-6 months) participated in this study and all participants provided written informed consent.

B. Ultrasound examinations

Subjects underwent 4 US exams: immediately prior to therapy, at 10%, 60%, and 100% completion of neoadjuvant therapy. Ultrasound exams were performed using a modified Logiq 9 scanner with a 4D10L probe (GE Healthcare, Milwaukee, WI, USA). Modified software enabled collection of radiofrequency (RF) data from a 4D pulse inversion subharmonic imaging mode (transmitting pulses at 5.8 MHz and receiving at 2.9 MHz). At each exam, 2D US baseline images were first acquired. Subjects then received a continuous IV infusion of 3 ml of Definity (Lantheus Medical Imaging, N Billerica, MA, USA) suspended in 50 ml saline via an antecubital vein, with infusion rates of 4 to 10 ml/min (titrated to effect). The acoustic output power used for SHAPE was optimized by running an automatic power control algorithm during the infusion. This power optimization was performed only for the exam prior to therapy for each patient and the individual acoustic output power setting selected was then maintained through the rest of the US exams. After the optimization process, the infusion was halted for about 5 minutes to allow for clearance of bubbles. Then RF data was collected with no contrast agent in the 4D SHAPE mode. Infusion was restarted for collection of 3 sets of RF data with contrast agents. The volume rates for 4D data were 0.6 to 3.2 volume/second. Note, that the infusion interruption happened only for the initial exam in which the output power optimization was performed.

C. Evaluation of neoadjuvant therapy response

Clinical response was evaluated using the change in 3D tumor volume measurements from the US baseline images after the completion of neoadjuvant therapy. Subjects with more than 90% tumor volume reduction were rated as responders, while others were rated as partial/non-responders. This relatively coarse classification scheme was applied, due to the small sample size in this pilot study.

D. Data analysis

Using baseline images, the 3D tumor size change during therapy was compared to the clinical response and corresponding SHAPE results. RF data from 4D SHAPE exams were transferred to a PC for off-line analysis using Matlab (Mathworks, Natick, MA). Two regions of interest (ROI) were selected in each elevational plane: one within the tumor and the other in the surrounding tissues. Fast Fourier Transform (FFT) was computed for each A-line within the ROI and all FFTs were averaged laterally as well as over a volume and frames to obtain a reliable frequency spectrum. The maximum magnitude from the resultant frequency spectrum was extracted from each pre-infusion and during infusion data and the ratio was calculated for each ROI. This ratio of subharmonic signal was calculated to account for possible attenuation change in the ROIs over 4 exams and to include the subharmonic signal only from the contrast agent. Finally, the difference in the obtained subharmonic signal ratios from the tumor and the surrounding area was calculated as a relative estimate of IFP. The results from 3 sets of RF data were averaged and this analysis was repeated for all 4 US exams of each patient. The obtained subharmonic signal differences between the tumor and surrounding area in all 4 exams were compared to the final Therapy response. A t-test was used to compare SHAPE results between responders and partial/non responders with a 5% significance level.

Results

A total of 17 subjects participated in the study (Fig 1). Ultrasound exams were performed in 3D modes and the tumor size change was observed through the therapy. Examples of 3D images from a subject prior to therapy and at the 10% completion of therapy are presented in Fig. 2. In this case, tumor size decreased after the therapy (from 4.2cm x 3.5cm x 3.4cm to 3.9cm x 3.5cm x 2.8cm). The tumor size change between the first two exams did not differentiate responders from partial/non-responders ($p > 0.2$, data not shown for brevity). The subharmonic signal changes related to IFP were analyzed over all 4 US exams. The subharmonic signal increase with contrast agent infusion is shown in Fig. 3 Among SHAPE results from the 4 exams, only the results after 10% completion of the therapy showed significance (Fig. 4; $p= 0.0011$). The initial and final tumor size, tumor reduction rate, and the results from SHAPE data collected after 10% completion of the therapy are presented in Table 1. Subjects 9 and 10 did not complete treatment, due to the non-responsiveness, and underwent surgery after 10% completion of the therapy. Subject 11 was also determined to be non-responsive and received additional treatment after 10% completion of the therapy. The results from the SHAPE analysis were positive (subharmonic signal increased more in the tumor than in the surrounding area) for responders and zero or negative for partial / non-responders.

Conclusions

Monitoring neoadjuvant therapy at an early stage is challenging and the optimal method has not been established. In this pilot study, the 4D SHAPE method showed potential to monitor the clinical response of breast cancer to neoadjuvant chemotherapy as early as at 10% completion of therapy. As a functional assessment tool, 4D SHAPE may be useful to predict the neoadjuvant therapy response at an early stage.

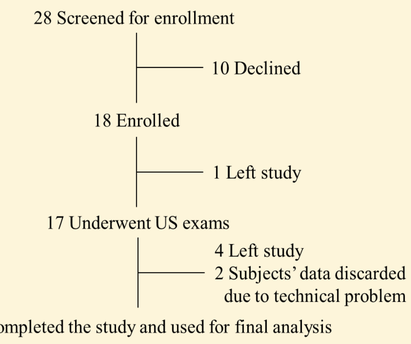

Figure 1: Flowchart of participants in this study

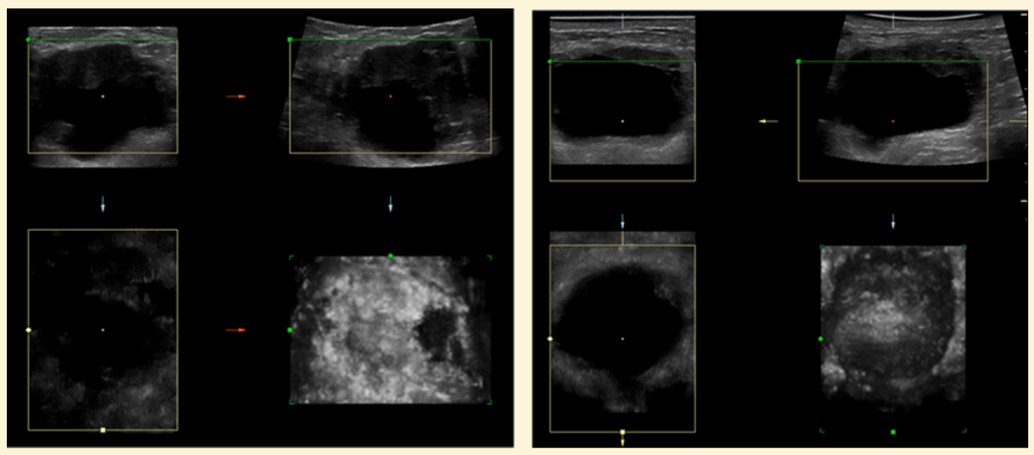

Figure 2: 3D images of breast cancer acquired at the prior to neoadjuvant therapy (a) and at the 10% completion of therapy (b) are displayed using 4D View (GE Healthcare, Zipf, Austria). This viewer shows the three orthogonal planes of sagittal (top left), transverse (top right), and coronal (bottom left) as well as a rendered volume (bottom right). The rendered volume is a semitransparent representation of all volume pixels within the ROI boxes of the top row.

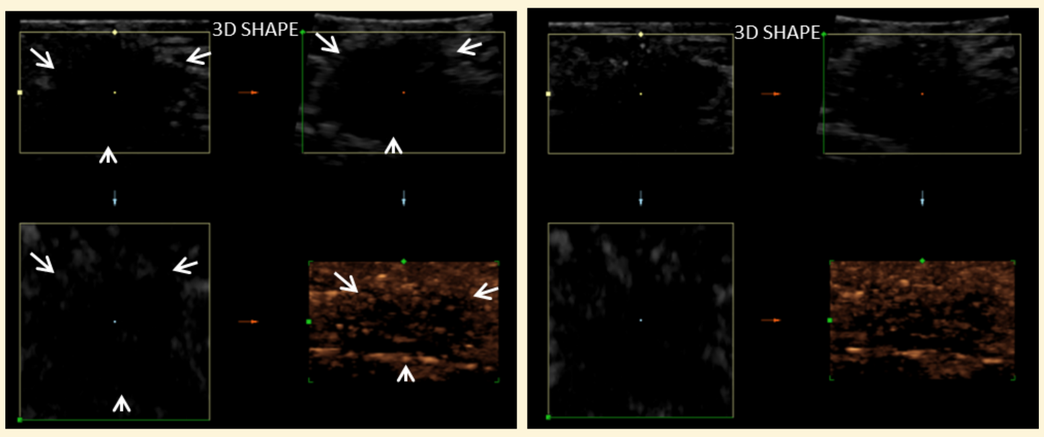

Figure 3: Subharmonic images collected before (a) and during the contrast agent infusion (b) for SHAPE (acquired from the patient after 10% completion of neoadjuvant therapy). The figure shows the three orthogonal planes of sagittal (top left), transverse (top right), and coronal (bottom left) as well as a rendered volume (bottom right). A tumor is located in the center of each view (arrows).

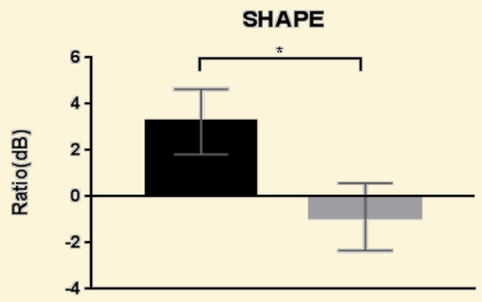

*Figure 4: 4D SHAPE results from the data collected after 10% completion of the neoadjuvant therapy for responders (black bar) vs. partial/non-responders (gray bar) based on clinical assessment. The bars and error bars show the mean and standard deviation, respectively. The symbol * represents significant differences with $p < 0.01$.*

Table 1. Tumor size change and the results from 4D SHAPE data collected after 10% completion of therapy (unit for tumor size: cm x cm x cm).

Subject number	Initial tumor size	Final tumor size	Tumor volume reduction	SHAPE result (dB)
1	2.4 x 2.1x 1.6	Undetectable in imaging	100%	2.58
2	3.4 x 2.4 x 2.7	Undetectable in imaging	100%	4.04
3	2.3 x 2.4 x 1.7	Undetectable in imaging	100%	0.88
4	4.2 x 3.5 x 3.4	0.6 x 1.1 x 0.3	99.6%	4.30
5	2.8 x 2.0 x 1.7	0.3 x 0.4 x 0.4	99.5%	4.68
6	3.2 x 2.8 x 2.2	1.0 x 1.0 x1.6	91.9%	2.88
7	1.4 x 1.1 x 1.9	1.0 x 1.0 x 0.9	69.2%	-3.23
8	3.6 x 2.3 x 3.0	2.2 x 1.7x 2.3	65.4%	-1.37
9	3.9 x 4.4 x 4.2	Not available	Not available	0.27
10	1.0 x 1.4 x 1.3	Not available	Not available	0.00
11	4.0 x 3.9 x 2.1	Not available	Not available	-0.07

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