Monitoring breast masses with ultrasound tomography in patients undergoing neoadjuvant chemotherapy

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ABSTRACT

The purpose of this study was to correlate changes in biomechanical properties of breast cancer lesions in response to neoadjuvant chemotherapy. Nine patients were examined repeatedly throughout their treatment, using an experimental prototype based on the principles of ultrasound tomography. The study was HIPAA compliant, approved by the Institutional Review Board, and performed after obtaining the requisite informed consent. Images of reflection, sound speed and attenuation, representing the entire volume of the breast, were reconstructed from the exam data and analyzed for time-dependent changes during the treatment period. It was found that changes in tumor properties could be measured in all cases. Furthermore, changes in sound speed were found to vary strongly from patient to patient. A comparison of the sound speed response curves with pathological findings suggests that complete responders exhibit distinctly different responses as measured by sound speed. These preliminary results were used to define a cut-point for predicting response. Subsequently, a prospective prediction of the treatment response of a new patient was made correctly. We hypothesize that changes in the biomechanical properties of breast cancers, as measured by sound speed, can predict response. Future studies will focus on testing this hypothesis and defining and quantifying markers of response.

Keywords: Breast imaging, breast masses, neoadjuvant chemotherapy, ultrasound tomography

1. INTRODUCTION

Neoadjuvant chemotherapy increases the ability to control locally advanced breast carcinomas, and promotes breast-conserving surgery (BCS)[1-5]. In inoperable breast cancer patients, neoadjuvant chemotherapy may provide an effective cytoreduction, thereby, rendering the disease operable. In contrast, in operable patients, the neoadjuvant chemotherapy can further downstage the tumor and facilitate BCS. It has become the standard of care for patients who have locally advanced and inflammatory breast cancer or who wish to pursue breast-conserving surgery in the US[1]. However, there remain a number of limitations. Not all patients respond to chemotherapy and, when they do, they respond in different degrees while clinically, there has not been a technology or technique that helps accurately assess and monitor individual patient response to neoadjuvant chemotherapy. It is important to identify patients who are responding to chemotherapy from non-responders early on, to guide implementation of alternative regimens or to abort an unsuccessful regimen and to avoid patients' suffering from unnecessary chemotherapy-induced side effects by advancing to surgery before progression to inoperable disease in a small portion of patients.[6-11] Among the patients who have been treated with neoadjuvant chemotherapy, overall clinical response rate at more or less around 70%, up to one third of which might achieve complete pathological remission (pCR) at the time of their surgery. In a phase III GeparTrio study, Minckwitz, et al[3]. observed 622 patients (29.8%) out of 2,090 total patients failed to show clinical response after first two cycles of TAC regimen. The pCR rate for these nonresponders dropped to 5.3%. Effort has been made to predict tumor response in patients after neoadjuvant chemotherapy. The accuracy of tumor measurement from 162 breast cancer patients after neoadjuvant chemotherapy was compared with the pathologic residual tumor size after surgery. The best concordance of 67% (benchmark) was observed when standard mammography was combined with breast sonography[8]. Accurate and frequent evaluation of a tumor's response to therapy is needed in order to minimize side effects, optimize treatment and plan for surgery.[12-21] Some patients exhibit complete pathological remission from receiving neoadjuvant chemotherapy

(no cancer cells at time of surgery). Predicting such response early in the process may not only help reduce the duration of the chemotherapy and thereby obviate the morbidity associated with it in community breast cancer treatment, but also provide a reliable pharmacodynamic endpoint to assess or compare the clinical efficacy of a new therapeutic agent or regimen versus treatment approach under standard care.

Cost-effective imaging technology for closely monitoring the response to breast cancer treatment is needed. Such a technology would be instrumental in evaluating emerging new local treatments and would be of immediate benefit for monitoring the outcomes of whole-body, or systemic treatments, such as chemotherapy. Perspectives on breast imaging have markedly changed in the past year with the recommendation of magnetic resonance imaging (MRI) as the screening modality of choice for women at high risk for breast cancer[22-23]. This has effectively made MRI the "gold standard" for breast imaging, but is too costly and has too limited access in the community to be used as a general screening tool. Nevertheless, several recent articles confirm that dynamic contrast enhanced (DCE) MRI remains very useful as both a prognostic tool before treatment, as well as measuring response to chemotherapy[12-21]. MRI again becomes the emerging gold standard, but with a high price that becomes prohibitive for repeating several exams during the course of chemotherapy. Positron Emission Tomography (PET) similarly has shown great promise in predicting response to chemotherapy[6-7] which may have direct correlates to the higher tumor blood flow seen by MRI, yet appears more expensive than MRI for repeated use. Additionally, the high costs of verifying thorough outcomes has impeded the acceptance of new treatments for localized breast cancer that do not require tissue removal. Imaging that rivals MRI in accuracy, but with lower cost and greater convenience, could markedly improve treatment options for ALL women with breast cancer.

Our group has been exploring an alternative imaging technique[24]. based on the concept of ultrasound tomography (UST)[24-41]. Our approach combines reflection and transmission ultrasound imaging to provide operator independent 3-D images of the breast. We have developed a prototype that scans the breast in about 1 minute while providing data that yield tumor characteristics related to its biomechanical properties. We have applied this technique to a group of 9 patients undergoing chemotherapy. Preliminary results, presented below, suggest that UST has the potential to measure and, through frequent scans, accurately track the volume and internal properties of tumors.

2. METHODS

The UST Prototype

We have constructed a UST prototype (Figure 1) and deployed it in a clinical environment. The prototype has been housed at the Karmanos Cancer Institute, in a dedicated exam room, measuring 15 x 10 feet, in the Alexander J. Walt Comprehensive Breast Center. The installation was accomplished without special build/or construction code requirements. The prototype is therefore very community and patient-friendly which facilitates its use for cycle-by-cycle treatment response monitoring when necessary. Nine patients were recruited under an existing IRB approved protocol at Wayne Sate University. Patients were examined with the UST prototype on the days when they were receiving chemotherapy. Generally, they were imaged approximately every 1-3 weeks for a total number of visits of up to 20 each. The principles and techniques of the device were described in detail in previous papers (e.g., Duric, Littrup *et al.* [24]). A UST exam begins with a patient positioning themselves face down on a flexible bed made of sailcloth (Figure 1). The patient's breast is immersed in a small water bath through a hole in the middle of the bed, where it is positioned in the center of a ring-shaped transducer. The ring is fixed to a gantry and moves in a downward vertical path, during which sonographic signals are transmitted and received by each of the elements. The ring's vertical imaging path allows the entire volume of the breast to be imaged, up to the chest wall through the nipple region. The data acquisition process takes approximately 1 minute, and the entire exam, including setup, takes about 5 minutes. The imaging product consists of stacks of 2-D images of the acoustic parameters of reflection, sound speed and attenuation.

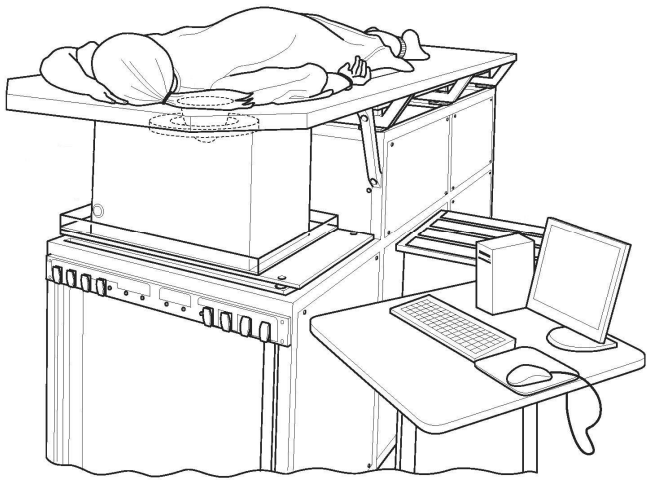

Figure 1: The UST clinical prototype. A patient lies in the prone position such that the breast is suspended inside a water tank that contains the ultrasound sensor. The water acts as a coupling medium to ensure that the acoustic waves can penetrate the breast efficiently.

Data Accrual and Analysis

Nine patients undergoing neoadjuvant chemotherapy for locally advanced breast cancer were imaged with UST at multiple times during their treatment. The exams were performed at each cycle of chemotherapy. The data set from each scan was used to reconstruct tomographic images representing the whole breast of each patient. Image manipulations and calculations were performed with *ImageJ*, a public domain, java-based image processing program whose development was supported by the National Institutes of Health. UST images are constructed from the same data and can be fused together without any geometric discrepancies. Image fusion allowed for improved visualization so that changes in tumor properties could be more easily followed.

The images were used to render the tumors' sound speed morphology in 3-D. The volume averaged sound of the primary tumor was determined using techniques previously described[38]. The resulting values were normalized and graphed to observe the change in the average sound speed of the tumors during chemotherapy.

3. RESULTS AND DISCUSSION

Figure 2 shows the changes in relative sound speed of the primary tumor in the first eight patients. The x- and y-axes represent the number of days from the start of treatment and the relative value of the sound speed of the tumor, respectively. The black lines indicate patients who had a partial or no response to treatment, while the white lines indicate the patients who had a complete pathological response to treatment. This representation appears to separate the partial responders and the complete responders. This separation is characterized by two factors: (i) The overall decline in relative sound speed is greatest for the complete responders and (ii) the rate of decline during early stages of treatment (first 20 days) is much greater for the responders relative to the non-responders.

Our hypothesis, based on these observations, is that rate of decline is a predictor of complete pathological response (pCR). To test the hypothesis, data from a new (ninth) patient (labeled patient 258 in the graphs) was analyzed in order to predict their response prospectively. After the first two UST exams, the relative change in sound speed was calculated and the results superimposed (Figure 3).

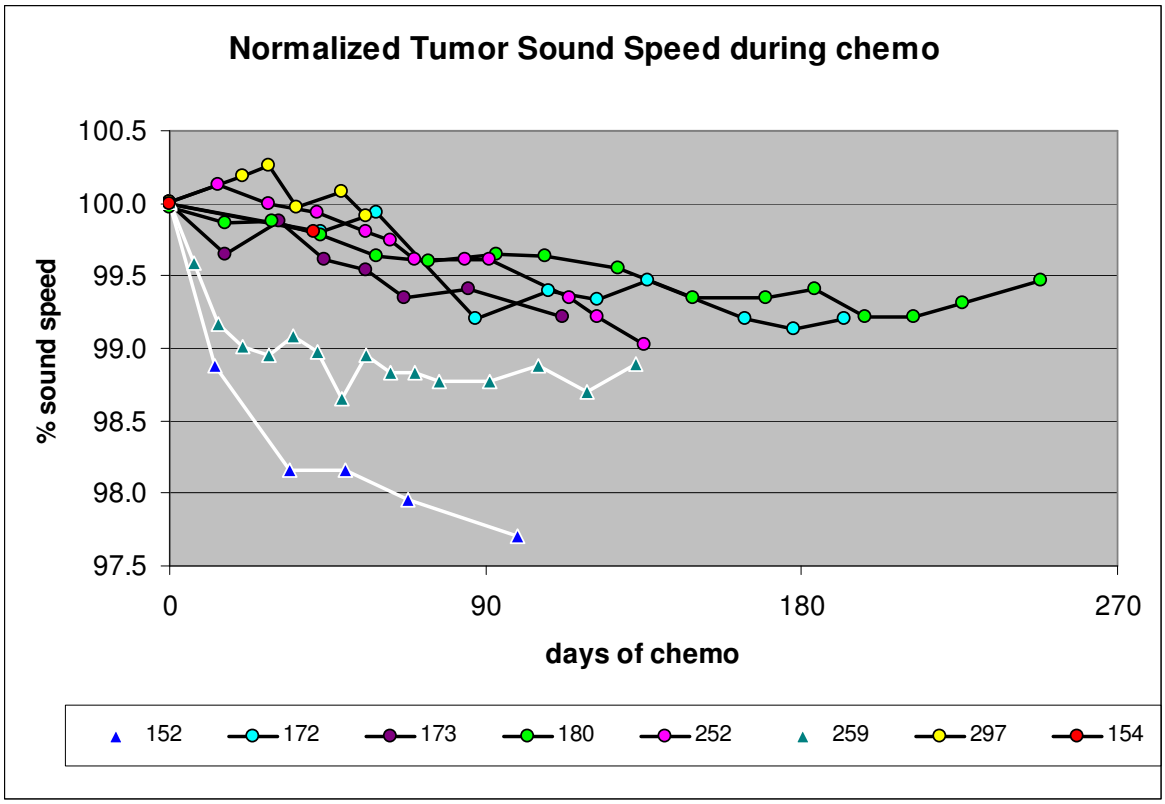

Figure 2: Relative sound speed values during neoadjuvant chemotherapy for 8 patients.

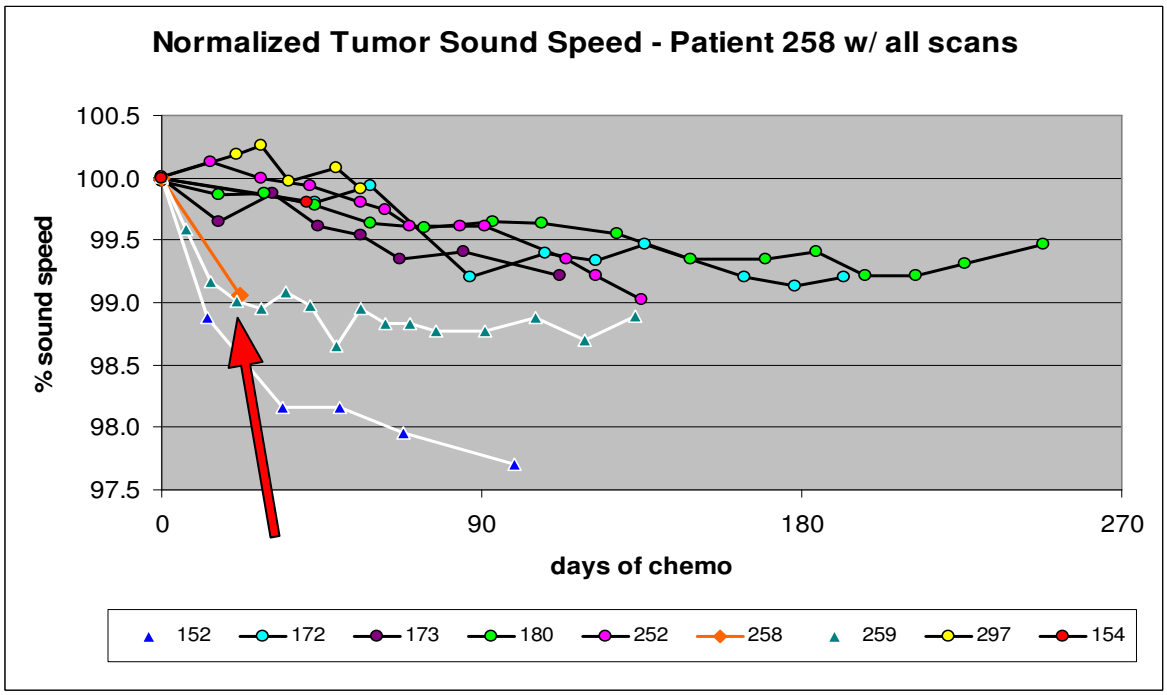

Figure 3: Relative sound speed values during neoadjuvant chemotherapy for 8 patients with new patient data superimposed. The arrow indicates when the prediction of complete response was made.

The change in sound speed for Patient 258's primary tumor is shown in orange. It was apparent that even in the early stages of chemotherapy, the rate of decline is comparable to that of the known responders and much steeper relative to the partial responders. This observation was made on day 21 of the patient's therapy, which is indicated by an arrow (Figure 3). According to our hypothesis this patient is a complete responder.

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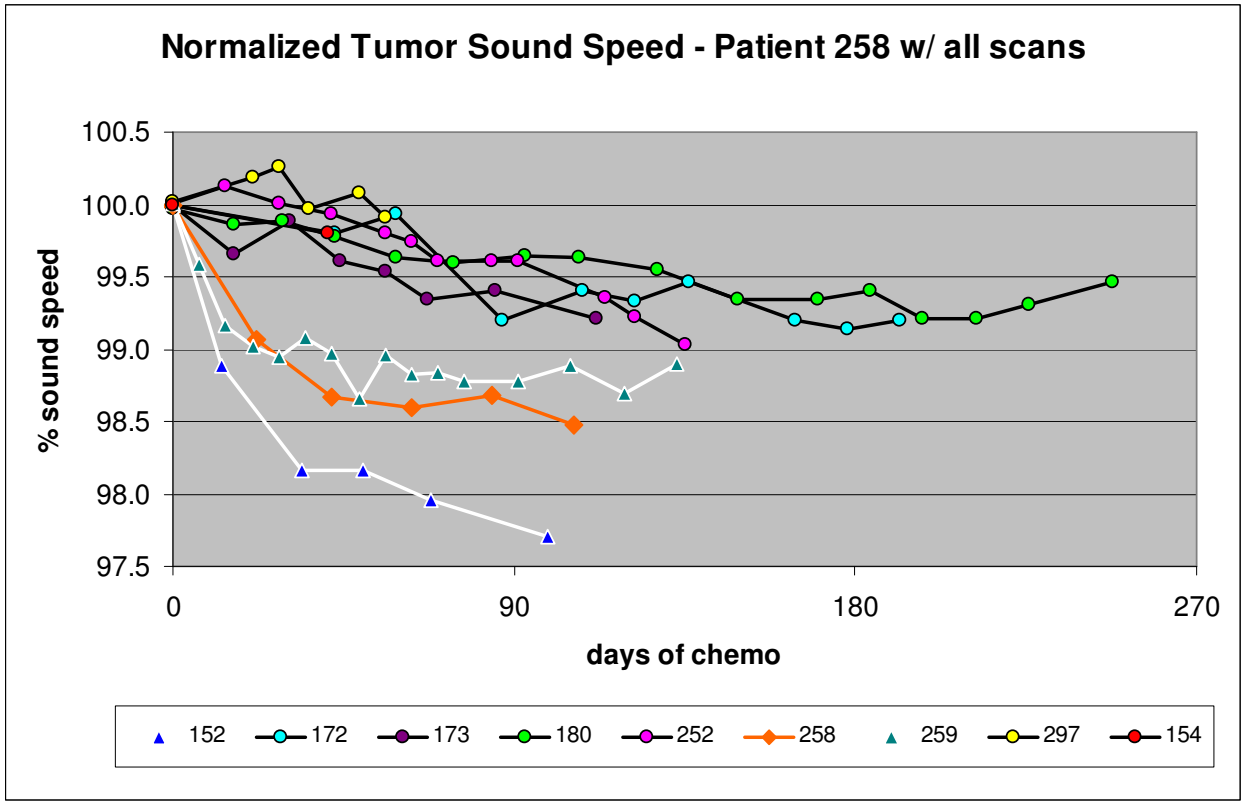

Figure 4: Relative sound speed values during neoadjuvant chemotherapy for 8 patients with all the new patient data superimposed.

After Patient 258 completed chemotherapy (over approximately 100 days), the trend in relative sound speed change was consistent with our early assessment (Figure 4). The response curve was squarely in the region of the previous complete responders. This overall response was in accordance with the prediction made on day 21 of the patient's therapy.

The patient was scheduled for surgery a month after the last treatment. *In the pathology and postoperative reports it was confirmed that there was no remaining cancer and that the patient achieved pathological complete response (pCR).*

4. CONCLUSIONS

We have demonstrated the feasibility of measuring changes in tumor properties with ultrasound tomography. For nine patients scanned with a UST prototype, the results suggest that quantification of tumor response is possible. It was found that changes in tumor properties could be measured in all cases. Furthermore, changes in sound speed were found to vary strongly from patient to patient. A comparison of the sound speed response curves with pathological findings suggests that complete responders exhibit distinctly different responses as measured by sound speed. These preliminary results were used to define a cut-point for predicting response. Subsequently, a prospective prediction of the treatment response of a new patient was made correctly. We hypothesize that changes in the biomechanical properties of breast

cancers, as measured by sound speed, can predict response. We further hypothesize that the rate of sound speed decline is a potential marker of breast cancer response to neoadjuvant chemotherapy. Future studies will focus on testing this hypothesis and defining and quantifying such markers of response. The ability to predict response early in the treatment process would have a major impact on clinical decision making. Early identification of non-responders would lead to alternative treatment strategies, including advancement of surgery in order to abandon futile treatment strategies, minimizing morbidity and preventing further progression of the disease.

Future Studies

The limitation of this study is the small number of patients studied, which limits the statistical significance of our results and prevents analyses of confounding factors such as the role of differing chemotherapy drugs. Future larger studies are therefore needed. Figure 5 illustrates the hypothesis that would be tested. It illustrates responses that have been averaged into two categories, based on the partial and complete pathological responders. The data corresponding to the time sequence of treatment were averaged to create trend-lines for each group of patients. The complete responder line (blue) represents data from the two previous patients known to have achieved pCR. Similarly, the red curve is the average response of the 5 patients who did not achieve pCR. The midpoint between the two trend-lines is shown as a dashed line. The dashed line represents a potential cut-point for analyzing these future studies. Response curves above the line will predict partial response while those that fall below the dashed line will be predicted to be compete responders. Patient 258 is shown in light blue as an example of how such a prediction would be carried out.

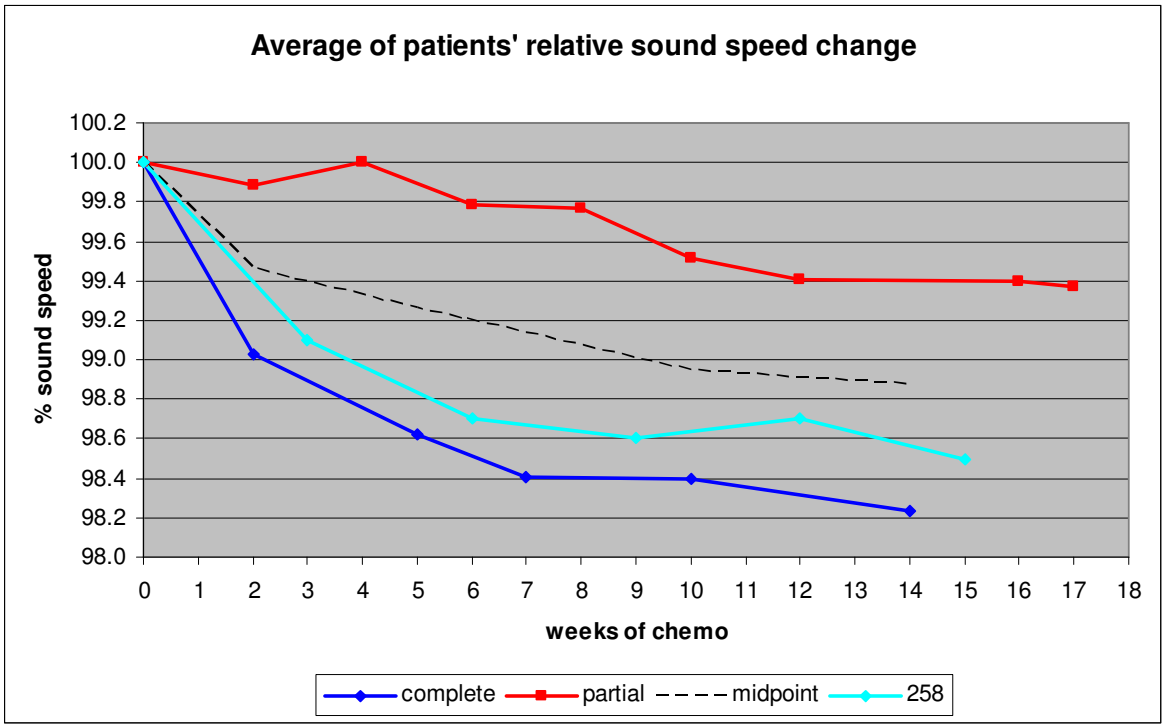

Figure 5: Average response curves for complete responders and partial responders.

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