Proceedings of Meetings on Acoustics

Volume 19, 2013 http://acousticalsociety.org/

ICA 2013 Montreal
Montreal, Canada
2 - 7 June 2013

Biomedical Acoustics
Session 5aBAa: Acoustic Characterization of Biological Media

5aBAa1. Evaluation of tumor cell death response in locally-advanced breast cancer patients to chemotherapy treatment by scattering property estimates using ultrasound backscatter

Lakshmanan Sannachi*, Hadi Tadayyon, Ali Sadeghi-Naini, Omar Falou, Zahra Jahedmotlagh, Michael L. Oelze and Gregory J. Czarnota

***Corresponding author's address: Department of Radiation Oncology and Medical Biophysics, University of Toronto, Toronto, M4N 3M5, Ontario, Canada, Lakshmanan.Sannachi@sunnybrook.ca**

Breast cancer tumor response to chemotherapy in twenty nine patients was examined using quantitative ultrasound techniques. Backscatter parameters, such as the average scatterer diameter (ASD) and average acoustic concentration (AAC), were estimated from regions-of-interest in tumors prior to treatment onset and at four times during neoadjuvant chemotherapy treatment (weeks 1, 4, 8 and prior to surgery). Gaussian and Anderson form factor models were used over an analysis bandwidth of 4.5 to 9 MHz to obtain ASD and AAC estimates. The Gaussian model did not fit with the measured data as well as Anderson model. The AAC estimates yielded significant differences with therapy times in clinically treatment responded patients. Data indicated increases of 6.6 dB/cm in acoustic concentration obtained maximum at week 8 in treatment responding tumors. Non-responding tumors didn't show any significant difference in the parameters during treatment. This study demonstrates that the scattering parameters have the potential to being used in quantifying the changes in tumors during treatment noninvasively and distinguishing treatment responders and non-responders early after of treatment initiation.

Published by the Acoustical Society of America through the American Institute of Physics

 [DOI: 10.1121/1.4800357]
Received 22 Jan 2013; published 2 Jun 2013

INTRODUCTION

One of the common types of cancer diagnosed in women is breast cancer. Women with locally advanced breast cancer (LABC) have poor long-term survival rates compared to early stages patients (5 year survival rate of ~ 50%)[1]. Early detection of treatment response to breast cancer is very important in order to guide the optimization of cancer therapy on an individual patient basis[2]. Current imaging modalities such as X-ray, mammography, and MRI are not able to evaluate therapy response early during treatment period and also they are cost expensive. Ultrasound is a fast and low cost technique that has been demonstrated to be a promising tool for prediction of changes in the biological tissues. It is highly sensitive to variation in mechanical properties of tissues at many scales. The Radio Frequency (RF) spectrum of ultrasonic backscatter contains information that can be used to noninvasively characterize the structural and mechanical properties of tissues[3]. In addition, more accurate estimates of those properties can be obtained when the product of the wave-number of the interrogating ultrasound and the prominent tissue scatterer radius (ka) is approximately equal to 1.0 [4]. Current methods for LABC treatment include aggressive neoadjuvant chemotherapy followed by mastectomy with axially nodal clearance. This cancer chemotherapy treatment can alter the structural and biomechanical properties of tumour tissues during a course of treatment. This can be linked to the fact that tumour degeneration in response to treatment exhibits considerable morpholigcal changes altering cell structure and stromal organization[5]. Therefore, cancer therapy response is expected to alter the ultrasonic backscatter parameters at tumourous regions.

Imaging techniques based on analyzing ultrasound backscatter have been successfully used to diagnose and monitor disease, such as cancer, in clinical settings. Furthermore, these imaging approaches have been used to differentiate different types of tissues[3,6]. Parametric images generated for scatterer parameters, i.e the average scatterer size and acoustic concentration (number density times the square of relative acoustic impedance), have been constructed for tissues[7]. In clinical settings, these imaging techniques have been successful in diagnosing prostate cancer, ocular tumors, and cardiac and vascular abnormalities[8,9].

In this study, ultrasonic backscatter parameters were used to monitor the histological features of breast tumour after chemotherapy treatment and to classify the breast cancer patients as treatment responder or non responder. Gaussian and Anderson form factor models were used previously to estimate scatterer parameters in many tissues[3,6,7]. Those two models were used here to extract backscatter properties from breast tumours over the frequency bandwidth of 4.5 to 9 MHz. Obtained results demonstrate the potential of backscatter parameter extracted from ultrasound data for predicting chemotherapy response, as early as 1 week after treatment initiation.

MATERIALS AND METHOD

Twenty nine patients were examined in this study in accordance with research ethics guidelines. Ultrasonic B-mode data were acquired from breast tumour region before treatment, as well as 1 week, 4 weeks, and 8 weeks after treatment and prior to operation. Following operation, patient mastectomy specimens were examined by a board-certified pathologist using whole-mount 5″×7″ in pathology slides digitized using a confocal scanner[10]. Patients were classified as responders and non-responders based on their ultimate clinical and pathological response.

All ultrasonic breast imaging and RF data acquisition were performed with a Sonix RP clinical system operating at 6.7 MHz central frequency transducer (L14-5/60, Ultrasonix, Vancouver, Canada) sampling at 40 MHz, each image frame storing 512 RF lines over a 6 cm width and 4-6 cm depth. The analysis bandwidth used with the transducer was 4.5 – 9 MHz. Regions of interest were selected from each image plane for each tumor sample and averaged for the final analysis. For backscatter parameters estimation, a sliding window had its size fixed with 10×30 times ultrasound wavelength, and the overlap between the adjacent gated RF signals was 80 %. A reference phantom was used to account for clinical system dependencies in backscatter estimation[11].

Estimates of the average scatter properties such as averaged scatterer diameter (ASD) and averaged acoustic concentration (AAC) were performed by comparing the normalized backscattered power spectrum of the RF signal gated from each ROI to a theoretically derived backscattered power spectrum. The minimum significant error (MSE) value which indicates the goodness of fit between measured and a theoretically derived backscatter power spectrum was also calculated. Gaussian and Anderson models were used to extract backscatter parameters from breast tumour and each model assumed the Born approximation (valid when there is a weak scattering and no multiple scattering). Quantitative ultrasound (QUS) images were constructed by superimposing colored pixels which represent backscatter parameter on the original grey scale B-mode image of the tumour[3].

RESULTS

Backscatter parametric images of the tumours were constructed for each patient. Figure 1 shows analysis results and a representative QUS scatterer size image of breast tumour using the Anderson model from pre-treatment ultrasound data. To compare the backscatter parameters estimated using Gaussian and Anderson models, all pre treated ultrasound data were used. Estimates of backscatter parameters from the Gaussian model were significantly lower than that obtained from Anderson model (Figure 1a). The MSE value was larger for Gaussian model indicating that the model did not fit the measured data as well as the Anderson model. So, only the backscatter parameters extracted using Anderson model were taken in to account for further analysis in this study. The range of scatterer sizes estimates from Anderson model were very close to the gland diameters estimated from microscopic images of the breast tumours (Figure 1a).

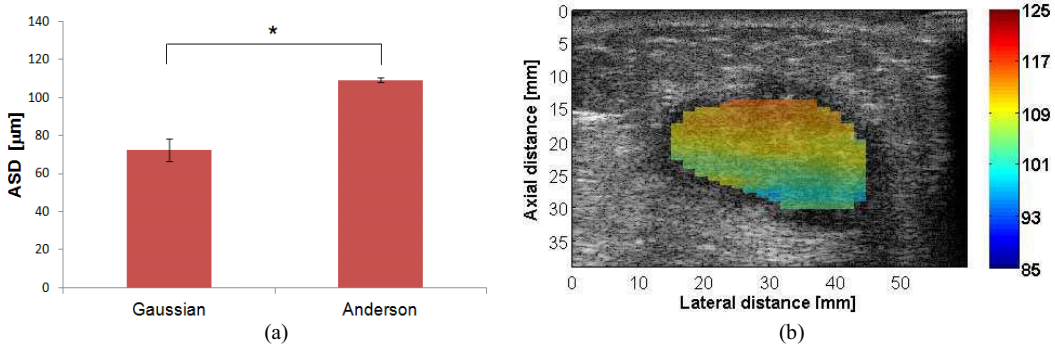

FIGURE 1. Average scatterer diameter estimates for breast cancer obtained from all pre treatment ultrasonic measurements. Error bars represent ± one standard error (a). Scatterer diameter (µm) parametric image of breast cancer patient before treatment initiation (b).

The average change in ASD and AAC measured in responders and non-responders over their treatment are presented in Figure 2a and 2b respectively. Responder and non-responder showed similar backscatter parameter values before treatment with mean ASD of 109 ± 6, 113 ± 3 µm and mean AAC of 67 ± 5, 68 ± 5 dB/cm^3, respectively. In responders, the ASD increased slightly during treatment, but were not significantly different. The ACC showed increases of approximately 6.6 dB/cm^3 and obtained maximum at week 8. Both ASD and AAC did not show any considerable changes for non-responders over treatment. Responders and non-responders were found to be significantly different at 1 weeks after treatment initiation for the AAC parameter (p = 0.036).

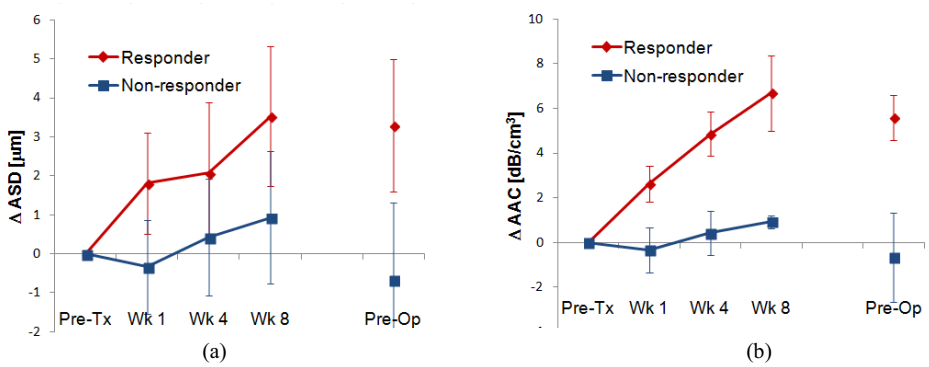

FIGURE 2. Average change in ASD (a) and AAC (b) measured in responders and non-responders over treatment time.

DISCUSSION

Ultrasonic backscatter parameter estimation is an emerging technique that provides information regarding tissue structure and tissue elastic properties at microscopic level. Previous studies have demonstrated that this technique may be used to classify tissue abnormalities from normal tissue and different type of tumour cells[3,6,7]. In this study, we demonstrated the first time the results of 29 patients with LABC receiving neoadjuvant chemotherapy whose tumour responses were monitored using QUS backscatter parameter estimates. Gaussian and Anderson models were tested to determine if estimate of scatter properties could be related to tissue microstructure and also distinguish responder and non-responder patients. Use of the Anderson model for the fluid-filled sphere model allowed the differentiation of responder and non-responders. Considerable increases of AAC were found for responder after treatment. The AAC parameter in responders exhibited an increase during the first weeks of the treatment (Figure 2b). The AAC parameter is related to scatterer distribution and its mechanical property. Examining microscopic images from responding patients suggests that, as tumours begins to respond to the treatment, invasive ductal carcinoma and affected glands begins to degenerate and fill with fibroblasts and extra cellular collagen fiber network. These changes in structural and biomechanical properties lead to increases in the tumor acoustic concentration. Compared to the ultrasonic spectral parameters investigated in our previous study[12], backscatter parameter can predict treatment response earlier during course of treatment.

Even though the Anderson model permitted the differentiation of responders and non-responders, this model did not permit the correlation of scatterer property estimates to the microstructure observed from microscopic images of tumours obtained following modified radical mastectomy surgery from responders. The microscopic image obtained from responding patients do not show any structure with sizes as estimated from QUS backscatter estimates using the Anderson model. Comparisons of microscopic images observed from responders and non-responders suggested that chemotherapy treatment affected the structural organization and properties of tumours. Our study did not however show any significant different in ASD between those two population.

In the previous studies, all the proposed form factor models were used with the hypothesis that cell or nuclei of the cells act as strong scatterer. The condition for precise scatterer size estimation is $ka \sim 1.0$ [4]. The results here suggest that the frequency bandwidth used in this study is not suitable for the use of a model like the Gaussian and fluid filled sphere models. Breast glandular tissue is very complex structure. Close examination of gland microstructure indicates that the fluid filled sphere model for scattering from gland is potentially too simplistic. So, for backscatter parameters estimation from treatment responding and non-responding breast cancer tumour, proper scatterer models have to be developed. This may require the acoustic impedance of subcellular, cellular and glandular tissue to be measured in order to understand the contribution of each structural component of tumour to the ultrasound signal at each frequency of the analysis bandwidth.

In conclusion, this study demonstrates for the first time that backscatter parameters estimates may be used to monitor chemotherapy treatment response on breast cancer tumour and discriminate between clinically responding and non-responding patients earlier during course of treatment. This is important in order to customize cancer therapy types to better treat non-responding patients early after treatment initiation.

ACKNOWLEDGMENTS

A.S.N and O.F. each hold a Canadian Cancer Foundation Postdoctoral Fellowship. G.J.C. holds a Cancer Care Ontario Research Chair in experimental therapeutics and imaging. This study was funded, in part, by the Canadian Breast Cancer Foundation – Ontario Region. Funding for this project was also provided by the Terry Fox Foundation and the Natural Sciences and Engineering Research Council of Canada. The authors thank Sara Iradji for assisting with technical support.

REFERENCES

1. S. H. Giordano, “Update on locally advanced breast cancer,” Oncologist **8**, 521–530 (2000).
2. F.J. Esteva and G. N. Hortobagyi, “Can early response assessment guide neoadjuvant chemotherapy in early-stage breast cancer?,” J. Natl. Cancer Inst. **100**, 521–523 (2008).
3. M. L. Oelze and J. F. Zachary, “Examination of cancer in mouse models using high frequency quantitative ultrasound,” Ultrasound in Med. & Biol. **32**, 1639– 1648 (2006).
4. M. F. Insana and T. J. Hall, “Parametric ultrasound imaging from backscatter coefficient measurement – Image formation and interpretation,” Ultrasonic Imaging **12**, 245– 267 (1990).

5. P. Schedin, J. O'Brien, M. Rudolph, T. Stein and V. Borges, "Microenvironment of the involuting mammary gland mediates mammary cancer progression," J. Mammary Gland Biol. Neoplasia **12**, 71– 82 (2007).
6. M. L. Oelze, W. D. O'Brien, J. F. Zachary, "High frequency quantitative ultrasound imaging of solid tumors in mice," Acoustic Imaging **28**, 301– 306 (2007).
7. F. L. Lizzi, D. L. King, M. C. Rorke, J. Hui, M. Ostromogilsky, M. M. Yaremko, E. J. Felleppa and P. Wai, "Comparison of theoretical sattering results and ultrasonic data from clinical liver examinations," Ultrasound in Med. & Biol. **14**, 377– 385 (1988).
8. E. J. Feleppa, W. R. Fair and H. Tsai, "Ultrasonic spectral parameter imaging of the prostate," Int. J. Imaging Syst. Technol. **8**, 11– 25 (1997).
9. F. L. Lizzi, M. Astor and T. Liu, "Ultrasonic spectrum analysis for tissue assays and therapy evaluation," Int. J. Imaging Syst. Technol. **8**, 3– 10 (1997).
10. G. M. Clarke, S. Eidt, L. Sun, G. Mawdsley, J. T. Zubovits and M. J. Yaffe, "Whole-specimen histopathology: a method to produce whole-mount breast serial sections for 3-D digital histopathology imaging," Histopathology **50**, 232– 242 (2007).
11. L. X. Yao, J. A. Zagzebski and E. L. Madsen, "Backscatter coefficient measurements using a reference phantom to extract depth-dependent instrumentation factors," Ultrasonic Imaging **12**, 58– 70 (1990).
12. A. Sadeghi-Naini, O. Falou, N. Papanicolau, J. Zubovits, R. Dent, S. Verma, M. Trudeau, J. F. Boileau, J. Spayne, S. Iradji, E. Sofroni, J. Lee, S. Lemon-Wong, M. Yaffe, M. C. Kolios and G. J. Czarnota, "Quantitative Ultrasound Evaluation of Tumour Cell Death Response in Locally Advanced Breast Cancer Patients Receiving Chemotherapy," Clinical Cancer Research (2013) (accepted with minor revision).