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Proceedings of Symposium on Ultrasonic Electronics, Vol. 32 (2011) pp. 445-446
8-10 November, 2011

Detection and Localization of Small Metastatic Foci in Human Lymph Nodes Using Three-dimensional High-frequency Quantitative Ultrasound Methods

Jonathan Mamou[‡, 1], Emi Saegusa-Beecroft[2], Alain Coron[3,4], Michael L. Oelze[5], Masaki Hata[2], Junji Machi[2], Eugene Yanagihara[2], Pascal Laugier[3,4], Tadashi Yamaguchi[6] and Ernest J. Feleppa[1]

([1]F. L. Lizzi Center for Biomedical Engineering, Riverside Research Institute, New York, NY, [2]University of Hawaii and Kuakini Medical Center, Honolulu, HI, [3]UPMC University of Paris 06, UMR 7623, LIP, Paris, F-75005 France, [4]CNRS, UMR 7623 Laboratoire d'Imagerie Parametrique, Paris, F-75006 France, [5]Dept. of Electrical and Computer Engineering, University of Illinois, Urbana, IL, [6]CFME, Chiba University, Chiba, Japan)

1. Introduction

Quantification of tissue properties using ultrasound has been sought for over three decades, and many different tissue properties have been investigated as tools to diagnose disease states [1], monitor tissue response to therapies [2], or more fundamentally, to understand better the intricate relationship between ultrasound scattering and tissue properties [3].

High-frequency ultrasound (HFU, >20 MHz) permits qunatification of tissue properties at the microscopic level with spatial resolutions below 100 μm. In this study, HFU was used to develop novel three-dimensional (3D) quantitative ultrasond (QUS) methods to detect and localize metastatic foci in lymph nodes freshly excised from cancer patients undergoing a lymphadectomy for staging purposes. In total, these QUS methods yielded 13 QUS estimates dervied from quantification of envelope signal statistics or radio-frequency (RF) backscattered spectra. The underlying hypothesis is that because these QUS estimates are related to tissue miscrostructure they should depict contrast between nodal regions containing metastases and those devoid of metastatic tissue.

2. Methods

Surgery was performed at the Kuakini Medical Center (KMC) in Honolulu, HI. Patients with histologically proven abdominal (e.g., gastric and colorectal) or breast cancers were recruited. During surgery, several lymph nodes were excised from the patient and sent to the pathology laboratory at KMC where they were grossly prepared for histology.

Individual lymph nodes were dissected, underwent removal of excess perinodal fat, and were immersed in an isotonic saline (0.9% sodium chloride) bath at room temperature. Each node was scanned in 3D using a single-element transducer (PI30, Olympus NDT, Waltham, MA) having an aperture of 6.1 mm and a focal length of 12.2 mm. The transducer had a center frequency of 25.6 MHz and a -6-dB fractional bandwidth of 67%. Ultrasound RF echo signals were digitized with a sampling frequency of 400 MHz and 8-bit accuracy. Adjacent scan vectors were 25 μm apart in cross-range directions to cover the entire node in 3D with sufficient spatial sampling.

Following 3D ultrasound scanning, each lymph node was inked to recover orientation, cut in half, embedded in a cassette, fixed, sectioned at 65 μm intervals, stained with H&E, and a fine-resolution digital image of each slide was obtained with a high-quality slide scanner (NanoZoomer, Hamamatsu, Japan) with a pixel resolution of 0.46 μm. Metastatic regions then were highlighted in each digital image.

To obtain the 13 QUS estimates, the 3D RF volume of data was analyzed in overlapping 3D cylindrical regions of interest (ROIs) having a 1-mm diameter and 1-mm length. Within each ROI, the normalized average spectrum was estimated and used to obtain four QUS estimates using two independent ultrasound scattering models [4]. Similarly, the probability-density function (PDF) of the envelope of the RF signals within the ROI provided the remaining nine QUS estimates by fitting two different envelope-statistics models to the empirical PDF and by quantifying the difference between the empirical PDF and a Rayleigh PDF [4,5]. (Rayleigh statistics are typically expected when ultrasound speckle is fully developed.)

Linear-discriminant analysis then was used to combine the 13 QUS estimates for classification and to maximize classification performance. *A posteriori* cancer probabilities were computed based on the discriminant score for each ROI of

each lymph node. Because of their structural differences, analysis of abdominal and breast cancer nodes was performed separately, and two different classification functions were obtained. Classification performance was evaluated by computing ROC curves and estimating the area under the ROC (AUC).

3. Results

In total, over 240 lymph nodes from over 100 patients were entirely processed. Data obtained from lymph nodes entirely filled or entirely devoid of metastatic tissue were used to train and test the classifiers. Classification of the abdominal nodes and breast nodes produced AUC values of 0.96 and 0.89, respectively.

To illustrate the results, **Fig. 1** shows a cross-sectional B-mode image of a colon-cancer lymph node augmented with a color-coded depiction of cancer likelihood. This node did not contain any metastatic tissue, and our QUS-derived cancer-likelihood values were below 50% over the entire lymph node volume. **Figure 2a** shows a similar cross-section from a breast-cancer lymph node. Histology (**Fig. 2b)** revealed that this node contained two metastatic foci. The metastatic foci were well detected in the cancer-likelihood image, as indicated by the red highlights corresponding to a cancer likelihood greater than 50%.

4. Conclusions

The results obtained in this study demonstrate that 3D QUS methods at high frequencies can permit detection of metastases in dissected lymph nodes with excellent sensitivity and specificity. Therefore, the results to date suggest that these methods have great potential for detection and localization of small metastatic foci that often are missed during conventional histology.

Acknowledgments

This research was supported in part by NIH grant CA100183 and the JSPS Invitation fellowship program (FY2011).

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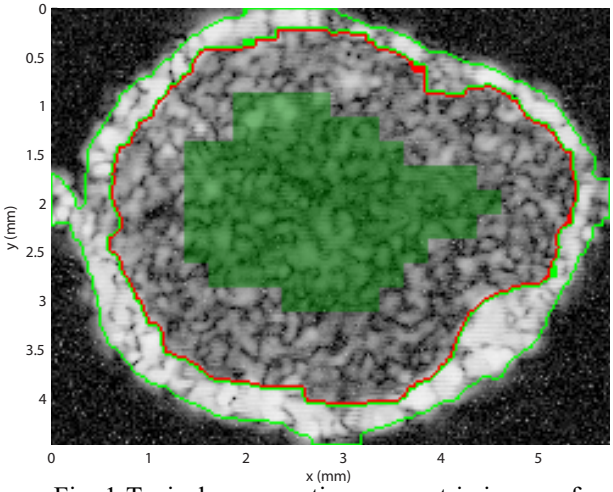

Fig. 1 Typical cross-section parametric image of a non-metastatic lymph node from a colon-cancer patient. Green highlight indicates a cancer likelihood less than 50%.

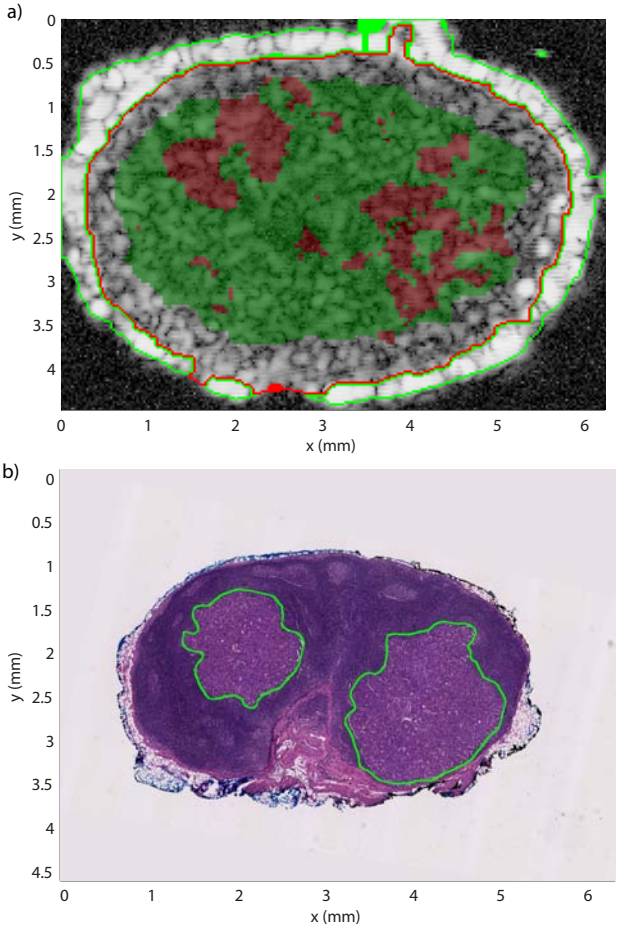

Fig. 2 (a) Typical cross-section parametric image of a partially metastatic lymph node from a breast-cancer patient. Green and red highlights symbolizes cancer likelihood smaller and greater than 50%, respectively. (b) Co-registered histology photo micrograph showing metastatic regions in green.