Non-invasive differentiation of small breast lesions via 3D MT imaging

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Purpose

The new 3D non-ionizing diagnostic imaging technology of Multimodal Ultrasound Tomography (MUT) was developed for the early detection of breast cancer using a unique lesion-differentiation capability. MUT was introduced in ECR2011 [1] through initial clinical results from 32 female volunteers with clearly discernible lesions in their X-ray mammograms ("off-label" use for research purposes only). This report presents further MUT results from 103 BIRADS-4 volunteers (who were subjected to biopsy after the MUT scan) presenting breast lesions down to 2 mm in size that were not discernible in the respective X-ray mammograms. Using the obtained MUT diagnostic images and the confirmed lesion diagnosis by histopathology performed on the biopsy samples, we seek to test the hypothesis that MUT can detect and classify correctly these lesions.
Methods and Materials

The clinical MUT prototype performs 3D tomographic scans of the pendulant breast in water-bath using transmission-mode ultrasound in a fixed-coordinate system, according to the methodology developed over the last 10 years [2-8]. The patient is lying prone on a comfortable clinical bed with one breast immersed in water-bath through a circular opening (the cylindrical scanning chamber is filled with continuously degasified, de-ionized, filtered and sanitized water). Parallel sets of transmitting and receiving ultrasound transducers perform transmission tomography over a 16-cm field of view for multiple view-angles and elevations (Figure 1). The in-plane pixel size is 0.25 mm x 0.25 mm and the separation between adjacent coronal scans can be set at 1-4 mm depending on the clinical requirements. Specially designed sequences of broadband ultrasonic pulses are transmitted from one side of the scanning chamber and received at the opposite side in standard tomographic manner. The received pulses are analyzed with reference to their transmitted counterparts and changes in waveform are utilized to construct multiple tomographic images for each coronal slice of the breast scan [3-6]. These multiple images are based on various acoustic attributes of the tissues traversed by the propagating ultrasonic pulse, such as refractivity (based on the relative speed of sound), frequency-dependent attenuation from 1 to 5 MHz (calibrated to water-through propagation), and frequency-dependent dispersion (based on phase-velocity changes relative to water-through propagation). These multiple images provide multimodal information for tissue classification based on the acoustic/biomechanical attributes of individual tissue voxels, which are subsequently fused via an appropriate algorithm to achieve reliable detection and differentiation of breast lesions.

In this study, 103 BIRADS-4 female volunteers, with average age of 54.7 years (range: 39 to 79), were selected and signed the Informed Consent Form prior to MUT scanning. All subjects subsequently underwent biopsy and the results of histopathology were used as "ground truth" to validate the obtained MUT diagnostic images. The identified malignant lesions identified had average maximum dimension of 7.1 mm. There were no operational complications in any of the MUT scans and all volunteers attested to the total comfort of the scanning procedure.
Fig. 1: The MUT system (left) and scanning configuration (right) involving two sets of ultrasound transducers (transmitting and receiving pairs). The breast is freely immersed in the rotating water-bath scanning chamber through the circular bed opening. © MastoScopia S.A. 2011

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Results

The obtained measurements of refractivity, frequency-dependent attenuation and dispersion were fused to form "composite" MUT images for visualization purposes and were processed through our proprietary clustering classification algorithm to generate the MUT "diagnostic" images. The latter were evaluated in the biopsied region against the "ground truth" provided by histopathology reports on the biopsy samples. Utilizing MUT and histopathology results from our first study reported in ECR 2011 [1-2], we have developed a lesion differentiation (clustering classification) algorithm that employs the quantitative information in the various modes of MUT images to detect and classify each lesion in the MUT images using 7 tissue classes: C1 (normal tissue), C2-C4 (benign fibrocystic changes or lesions, e.g. cysts, hyperplasia and fibroadenomas), C5 (precancerous lesions, e.g. intraductal papillomas or atypical hyperplasia), C6-C7 (malignant lesions: low/high grade). Obviously, this algorithm cannot replace the radiologist but simply seeks to provide some useful quantitative advisory assistance in a clinical diagnostic setting. In the illustrative examples of "diagnostic" MUT images provided below, the malignant lesions are depicted in red (dark red: high-grade C7, light red: low-grade C6), the precancerous lesions (C5) in yellow, the normal tissue (C1) in dark blue and the benign lesions in the remaining three colors.

Note that the stack of MUT coronal images allows 3D reconstruction of whole breast imaging in a known (fixed) coordinate system, which can provide versatile visualization to assist diagnosis of difficult cases (e.g. assessing possible growth of lesions) and may also prove useful in assisting biopsy and monitoring the effects of neo-adjuvant therapy for staging of surgery.

All subjects with malignant lesions except one (33 subjects out of 34 with malignant histopathological findings) were clearly identified by the MUT diagnostic images. Only one subject of the remaining 69 with benign findings exhibited a very small (2 mm) malignancy at the edge of a benign lesion in the region of biopsy.

Among the 33 subjects with detected malignant lesions, 15 (45%) had lesions with maximum dimension < 5 mm. The malignant lesions exhibited higher values across all measurements of refractivity, frequency-dependent attenuation and dispersion. It should be emphasized that the values of the aforementioned classification attributes are calibrated relative to water-through transmission (under precisely controlled conditions of water temperature, degasification etc.) and, therefore, retain global numerical validity for comparative diagnosis across subjects and time. The importance of this observation is further amplified by the fact that the MUT images are obtained in a repeatable 3D fixed-coordinate system, thus allowing comparative evaluation and monitoring over time.
Illustrative examples of MUT "composite" and "diagnostic" sets of coronal images containing malignant and benign lesions are shown below in two cases (one malignant and one benign). In all coronal images, the field of view is 150 mm x 150 mm and the pixel size is 0.25 mm x 0.25 mm. The separation between successive coronal breast slices/scans is 4 mm in these cases - although it can be set anywhere between 1 and 4 mm depending on the clinical requirements. The most relevant coronal slices are shown in each case, although the MUT system can generate any number of coronal slices that is deemed clinically desirable. The corresponding X-ray mammograms are also shown in the customary cranio-caudal (CC) and medio-lateral oblique (MLO) views.

The first example of MUT composite images (10 coronal slices, 4 mm apart) of the right breast of a 42 year-old BIRADS-4 volunteer (No. 50) is shown in Figure 2 and depicts two small malignant lesions in dark red: an Invasive Ductal Carcinoma (IDC) with maximum dimension of 5 mm on slice 5 and a very small Ductal Carcinoma in situ (DCIS) with maximum dimension of 2 mm on slice 4. Note that dark red is color-coding of the highest numerical values in an actual numerical scale according to the color spectrum of visible light (not pseudo-coloring). Both lesions were confirmed by histopathology of biopsy samples. The corresponding mammograms are also shown in Figure 2 and are clearly unable to provide similar diagnostic information. The location of the lesions in the MUT images corresponds to the region of a micro-calcifications cluster seen in the mammogram. The resulting MUT diagnostic images (upon application of the classification algorithm) are shown in Figure 3 and depict the two small malignant lesions in dark red (C7: high-grade malignancy) marked by arrows. Note that slice 4 had to be zoomed in order to make the DCIS visible in this figure. The light blue areas signify benign fibrocystic tissue changes.

The second example concerns small benign and precancerous lesions (intraductal papilloma and atypical hyperplasia). Seven coronal slices (4 mm apart) of composite MUT images of the right breast of a 54 year-old volunteer (No. 19) are shown in Figure 4. The resulting diagnostic MUT images are shown in Figure 5 and depict an intraductal papilloma (~5 mm) and atypical hyperplasia in yellow on slices 6-7 where the biopsy was performed, as well as small benign changes in green (simple endothelial/ductal hyperplasia). These MUT findings were in agreement with the results of histopathology on the biopsy sample. The corresponding X-ray mammogram is also shown, with the biopsied lesion location (small mass) marked by arrows. Another possible lesion was depicted in the MUT diagnostic images (slices 2-5), away from the region of biopsy. This lesion was classified by the MUT algorithm also as intraductal papilloma and atypical hyperplasia, but it was not biopsied (thus we lack direct means of validation of this possible lesion). This issue of possible validation of additional lesions detected by MUT will be addressed in future studies in the context of appropriate ethical and professional standards and procedures.
Fig. 2: Ten coronal slices (4 mm apart) of composite MUT images of right breast of 42 year-old volunteer No. 50 depicting in dark red small IDC (slice 4) and DCIS (slice 5). The mammogram is also shown with corresponding location marked by arrows. © MastoScopia S.A. 2011

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Fig. 3: Ten coronal slices of "diagnostic" MUT images of volunteer No. 50 generated by the MUT classification algorithm that depict two small malignant lesions in red: a 3mm x 5mm IDC on slice 5 and a tiny (2mm) DCIS on slice 4. © MastoScopia S.A. 2011

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Fig. 4: Seven coronal slices (4 mm apart) of composite MUT images of right breast of 54 year-old volunteer No. 19 depicting (in red) small benign lesion in slices 6-7 (biopsied) and possible lesion in slices 2-5 (non-biopsied) not evident in the mammogram (also shown). © MastoScopia S.A. 2011

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Fig. 5: Seven coronal slices of diagnostic MUT images of right breast of volunteer No. 19 generated by the MUT classification algorithm that depict two small benign lesions in yellow and green: one biopsied (~5mm Intraductal Papilloma (IP) and Atypical Hyperplasia(AH) on slices 6-7) and a possible lesion (non-biopsied) on slices 2-5, classified also as C5/C4. © MastoScopia S.A. 2011

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Conclusion

Initial clinical validation results from 103 BIRADS-4 female volunteers have shown that MUT can correctly diagnose 33 out of 34 subjects with malignant lesions (confirmed via histopathology of the biopsy samples). Among the 33 correctly diagnosed subjects with malignant lesions, 15 (45%) had lesions with maximum dimension < 5 mm (mostly DCIS). The smallest detected malignant lesions (DCIS) had maximum dimension of 2 mm. There was only one false-positive diagnosis out of 69 subjects with benign lesions, whereby MUT detected a very small (2 mm) malignancy at the edge of a benign lesion in the biopsy region. These initial results suggest that MUT has **97.1% sensitivity and 98.5% specificity among BIRADS-4 subjects** (including lesions down to 2 mm in size), where X-ray mammography has much lower performance. Since these results are viewed only as initial validation of the MUT capabilities, more clinical data and analysis are required before MUT can attain the requisite scientific credibility and clinical acceptance. An important issue for future study is the examination of additional lesions identified by MUT far away from the region of biopsy.