Detection of breast cancer via 3D multi-modal ultrasound tomography

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Purpose

A new 3D diagnostic imaging technology, termed Multimodal Ultrasonic Tomography (MUT), was developed for the detection of breast cancer without ionizing radiation and was compared with the current "gold standard" of X-ray mammography in 32 female volunteers who had BI-RADS 4 or BI-RADS 5 X-ray mammograms exhibiting at least one discernible lesion with maximum dimension greater than 10 mm.

Using the obtained MUT diagnostic images ("off-label" use for research purposes only), we seek to examine the hypothesis that the MUT technology with its tissue-differentiation capability can detect and classify correctly these lesions.

Methods and Materials

A clinical MUT prototype was built that performs 3D tomographic scans of the pendulant breast of female patients in water-bath using transmission ultrasound in a fixed-coordinate system. This prototype is the first implementation of a technology/methodology developed over the last 10 years [1-6] that can be used in clinical trials and has its conceptual roots in pioneering work performed at Mayo Clinic in the 1970s [7].

The patient is lying prone on a comfortable clinical bed with one breast inserted through a 16-cm circular opening leading to a cylindrical scanning chamber filled with degasified, de-ionized, filtered and sanitized water of constant temperature. The chamber contains parallel sets of transmitting and receiving ultrasound transducers that perform transmission tomography over a 16-cm field of view for multiple view-angles and elevations (see schematic configuration in Figure 1). The in-plane pixel size is 0.25 mm x 0.25 mm and the separation between adjacent coronal scans is 2-4 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 (transmission mode). 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 [1-3].

These multiple images are based on various acoustic attributes of the tissues traversed by the propagating ultrasonic pulse, such as measurements of refractivity (based on the relative speed of sound in various tissue types), frequency-dependent attenuation over multiple bands from 1 to 7 MHz (calibrated relative to water-through propagation), and estimates of dispersion (or susceptibility ratio) based on measured phase-
velocity changes relative to water-through propagation. These multiple images provide multimodal information for tissue classification based on the acoustic/mechanical attributes of individual tissue voxels that may allow reliable detection and differentiation of breast lesions ("off-label" use for research purposes only).

Thirty-two female volunteers, with median age of 59 years (ranging from 39 to 82), were selected according to their mammogram diagnosis. A total of 46 lesions suspicious for malignancy (i.e. BI-RADS 4 and BI-RADS 5) with a maximum dimension greater than 10 mm were present. After informed consent, the subjects underwent MUT scanning over 12 min per breast, prior to application of the established clinical procedure deemed appropriate in each case (biopsy and possible surgery). There were no operational complications in any of the MUT scans and all volunteers attested to the total comfort of the scanning procedure. Subsequent histological analysis of the biopsied or excised lesions determined their type and was used as "ground truth" for MUT performance evaluation.

**Images for this section:**

![Fig. 1: Schematic of the tomographic scanning configuration involving two sets of ultrasound transducers (transmitting and receiving pairs). The breast is freely immersed](image-url)
in the rotating water-bath scanning chamber through a circular bed opening. © MastoScopia S.A. 2010
Results

The obtained measurements of refractivity, frequency-dependent attenuation and phase velocity (used to estimate dispersion and susceptibility ratios) were properly analyzed and fused in order to develop composite MUT images of diagnostic value, utilizing as "ground truth" the information from the aforementioned pathology reports. Specifically the histological analysis identified 27 malignancies lesions (19 Invasive Ductal Carcinomas (IDC), 6 Invasive Lobular Carcinomas (ILC), 1 Invasive Papillary Carcinoma (IPC) and 1 Invasive Mucinous Carcinoma (IMC)) and 19 benign lesions (Fibroadenomas, Cysts, Fibrocystic lesions, Lipoma and Epithelial Hyperplasia).

All lesions were clearly identified on the MUT images and also correctly classified into benign and malignant based on their respective multimodal information. The malignant lesions exhibited higher values of refractivity, frequency-dependent attenuation and dispersion (or susceptibility ratio) in a manner that made possible their unambiguous delineation from benign lesions and normal tissues. 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, de-ionization etc.) and, therefore, retain global numerical validity for comparative diagnosis across subjects and time.

Illustrative examples of MUT "composite" and "diagnostic" sets of images containing malignant and benign lesions are shown below (two cases of malignant lesions and one case of benign lesion). In all cases, the field of view is 150 mm by 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. The ten most relevant coronal slices are shown in each case, although the MUT system can generate any number of coronal slices/scans 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 of 10 coronal slices (4 mm apart) of the right breast of a 74 year-old female volunteer (No. 22) with a BI-RADS 5 lesion (greatest dimension 20mm) is shown in Figure 2. The malignant portions of the lesion are depicted on slices 3-5 in dark red because they correspond to the highest values of the MUT composite index (greater than 2). The corresponding mammogram is shown in Figure 3. The location and size of the lesion on the MUT images correspond to the lesion seen on the mammogram. Histological analysis of the biopsy sample proved the lesion to be an Invasive Lobular Carcinoma (ILC). Low MUT index values (blue/green areas of MUT composite images) correspond to normal tissues (glandular, connective and fatty - both subcutaneous and interlobular), with slightly higher values (yellow and light red) appearing occasionally in the peripheral zone and the glandular space. Somewhat higher
values correspond to fibrocystic changes and hyperplasia, while even higher values correspond to malignant lesions. Occasional ambiguity in differentiating malignant from benign lesions with MUT index values in the gray zone separating the two classes of lesions is resolved by use of other modes of MUT images.

Utilizing all MUT results so far and the corresponding pathology reports from histological analysis of biopsy samples or mastectomy specimens, we have developed a tentative tissue-classification algorithm that employs the quantitative information in the various modes of MUT images to differentiate among tissue/lesion types by classifying them in 7 tissue classes. Obviously, this algorithm is bound to evolve as the aggregate database of MUT results expands. Furthermore, this algorithm cannot replace the radiologist but simply seeks to provide some quantitative advisory assistance with statistical significance in a clinical diagnostic setting. An illustrative example of the obtained "diagnostic" MUT image for volunteer No. 22 is shown in Figure 4, where the malignant lesion is depicted with dark red on slices 3-5. Fibrocystic changes are depicted in light blue and green, while epithelial hyperplasia is depicted in yellow.

A second example of 10 coronal slices (4 mm apart) of composite MUT images of the right breast of a 64 year-old female volunteer (No. 04) with a large malignant lesion (Grade 3 Invasive Ductal Carcinoma, maximum dimension of ~35 mm) is shown in Figure 5. The corresponding X-ray mammogram is shown in Figure 6. Again, the malignant portions of the lesion are depicted in dark red on slices 1-7 of the MUT composite images and have values of the composite MUT index >2. Subsequent histological analysis of the mastectomy specimen identified extensive necrosis in the central region of the lesion, corresponding to the blue/green areas of the lesion interior in the MUT images. As in the previous example, we observe elevated values of the MUT index within a peripheral zone that corresponds anatomically to subcutaneous fatty tissue interwoven with connective tissue, vessels and Cooper's ligaments.

An example of MUT composite images of a large benign lesion (cyst and fibrocystic changes) in the right breast of an 82 year-old female volunteer (No. 16) and the corresponding mammogram are shown in Figures 7 and 8 respectively. The cyst and the surrounding fibrocystic changes are depicted as an area with elevated MUT index values (but not as high as in the case of a malignant lesion) on slices 1-10 with a maximum dimension of ~40 mm. The cystic lesions were found to be characterized by high refractivity, low attenuation and medium dispersion.

Note that the MUT images allow also 3D reconstruction for whole breast imaging in a known (fixed) coordinate system, which may prove useful in assisting biopsy of difficult cases and may facilitate the diagnostic comparison of MUT imaging results over time (i.e. assessing the possible growth of lesions).
The MUT classification results for this initial set of 32 volunteers are summarized in Table 1 below. Normal tissues (fatty, connective, glandular) are classified under MUT Classification Index C1 corresponding to the lowest values of the MUT composite index.

**Table 1:** Summary of malignant and benign lesions found in the initial set of volunteers and the corresponding MUT Classification Indices.

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Number of Lesions</th>
<th>MUT Classification Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Ductal Carcinoma (High Grade)</td>
<td>14</td>
<td>C7</td>
</tr>
<tr>
<td>Invasive Lobular Carcinoma (High Grade)</td>
<td>4</td>
<td>C7</td>
</tr>
<tr>
<td>Invasive Ductal Carcinoma (Low Grade)</td>
<td>5</td>
<td>C6</td>
</tr>
<tr>
<td>Invasive Lobular Carcinoma (Low Grade)</td>
<td>2</td>
<td>C6</td>
</tr>
<tr>
<td>Invasive Papillary Carcinoma</td>
<td>1</td>
<td>C6</td>
</tr>
<tr>
<td>Invasive Mucinous Carcinoma</td>
<td>1</td>
<td>C5</td>
</tr>
<tr>
<td>Epithelial Hyperplasia (atypical or simple)</td>
<td>7</td>
<td>C5 or C4</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>3</td>
<td>C4 or C3</td>
</tr>
<tr>
<td>Fibrocystic Lesion</td>
<td>4</td>
<td>C3 or C2</td>
</tr>
<tr>
<td>Cyst</td>
<td>4</td>
<td>C2</td>
</tr>
<tr>
<td>Lipoma</td>
<td>1</td>
<td>C2</td>
</tr>
</tbody>
</table>

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**Images for this section:**
**Fig. 1:** Schematic of the tomographic scanning configuration involving two sets of ultrasound transducers (transmitting and receiving pairs). The breast is freely immersed in the rotating water-bath scanning chamber through a circular bed opening. © MastoScopia S.A. 2010

**Fig. 2:** Ten coronal slices (4 mm apart) of composite MUT images of the right breast of 74 year-old volunteer (No. 22) depicting in dark red a large Invasive Lobular Carcinoma on slices 3-5 (see text). © MastoScopia S.A. 2010
Fig. 3: X-ray mammogram of the right breast of volunteer No. 22 (left panel: R-CC view, right panel: R-MLO view) depicting in the upper outer quadrant a BI-RADS 5 mass with spiculated margins. © Department of Radiology, Hippokration Hospital, Athens, 2010.

Fig. 4: Ten coronal slices of "diagnostic" MUT images of the right breast of volunteer No. 22 that are generated by the MUT classification algorithm and depict a large malignant lesion (Invasive Lobular Carcinoma) in red on slices 3-5 (see text). © MastoScopia S.A. 2010
Fig. 5: Ten coronal slices (4 mm apart) of composite MUT images of the right breast of 64 year-old volunteer (No. 04) with a large Grade 3 Invasive Ductal Carcinoma on slices 1-7. © MastoScopia S.A. 2010

Fig. 6: X-ray mammogram of the right breast of volunteer No. 04 (left panel: R-CC view, right panel: R-MLO view) depicting a BI-RADS 5 mass with indistinct, partially spiculated margins. © Department of Radiology, Hippokration Hospital, Athens, 2010.
Fig. 7: Ten coronal slices (4 mm apart) of composite MUT images of the right breast of 82 year-old volunteer (No. 16) with a large cyst and fibrocystic changes depicted on slices 1-10. © MastoScopia S.A. 2010

Fig. 8: X-ray mammogram of the right breast of volunteer No. 16 (left panel: R-CC view, right panel: R-MLO view) depicting a round high-density radiopaque lesion with partially, ill-defined margins (BI-RADS 0). On follow-up B-scan ultrasound examination, a complicated cyst was diagnosed. © Department of Radiology, Hippokration Hospital, Athens, 2010.
Conclusion

The preliminary results summarized in Table 1 suggest that:

(1) MUT Classification Indices C7 and C6 may detect/classify high-grade and low-grade malignant lesions respectively;

(2) MUT Index C5 may detect/classify non-aggressive carcinomas and advanced pre-cancerous conditions, such as atypical hyperplasia;

(3) MUT Index C4 may detect/classify advanced-stage fibroadenomas and mild conditions of hyperplasia;

(4) MUT Index C3 may detect/classify early-stage fibroadenomas and fibrocystic lesions; and

(5) MUT Index C2 may detect/classify early-stage fibrocystic lesions, cysts and lipomas.

Obviously, these initial observations are preliminary and require far more clinical data and careful analysis before they can attain the requisite scientific credibility and clinical acceptance. These results are offered simply as initial confirmation of the ability of MUT technology to detect all 46 suspicious lesions (BI-RADS 4 and 5) with at least one dimension greater than 10 mm that are discernible in the mammograms of 32 female volunteers. Furthermore, the tissue-differentiation capability of the MUT technology (based on the proper combination of various measured acoustic/mechanical attributes of tissue voxels) was initially confirmed by classifying correctly all 46 lesions into 27 malignant and 19 benign, as corroborated by the pathology results from histological analysis of biopsy samples or surgical specimens.

These capabilities of the MUT technology are currently evaluated in cases with smaller lesions (where all dimensions are smaller than 10 mm). The results to date are rather encouraging.

References


**Personal Information**