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Toward MR-guided High Intensity Focused Ultrasound for Pre-surgical Localization: Focused Ultrasound Lesions in Cadaveric Breast Tissue

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Abstract

Purpose—To investigate MR-HIFU as a surgical guide for non-palpable breast tumors by assessing the palpability of MR-HIFU created lesions in *ex vivo* cadaveric breast tissue.

Materials and Methods—MR-HIFU ablations spaced 5mm apart were made in 18 locations using the ExAblate2000 system. Ablations formed a square perimeter in mixed adipose and fibroglandular tissue. Ablation was monitored using T1wFSE images. MR-ARFI was used to remotely palpate each ablation location, measuring tissue displacement before and after thermal sonications. Displacement profiles centered at each ablation spot were plotted for comparison. The cadaveric breast was manually palpated to assess stiffness of ablated lesions and dissected for gross examination. This study was repeated on three cadaveric breasts.

Results—MR-ARFI showed a collective post ablation reduction in peak displacement of 54.8% ($[4.41 \pm 1.48]\mu\text{m}$ pre, $[1.99 \pm 0.82]\mu\text{m}$ post), and shear wave velocity increase of 65.5%, ($[10.69 \pm 1.60]\text{ mm}$ pre, $[16.33 \pm 3.10]\text{ mm}$ post), suggesting tissue became stiffer after the ablation. Manual palpation and dissection of the breast showed increased palpability, a darkening of ablation perimeter, and individual ablations were visible in mixed adipose/fibroglandular tissue.

Conclusion—The results of this preliminary study show MR-HIFU has the ability to create palpable lesions in *ex vivo* cadaveric breast tissue, and may potentially be used to pre-operatively localize non-palpable breast tumors.

Keywords

MR guided Focused Ultrasound; MR Acoustic Radiation Force; MRI; Breast; Non-palpable Breast Tumor; Wire Localization

Introduction

Breast conservation surgery (BCS) has become a standard of care as an accepted alternative to mastectomy in patients suffering from limited stage breast cancer (1). Partly fueling the rise in BCS are the advances in breast screening programs, detecting more early stage cancers. They have also facilitated an increased detection of otherwise occult non-palpable breast tumors. Non-palpable tumors present a challenge for surgeons performing BCS, as

palpability often locates the tumor in the breast. The most clinically accepted standard is image-guided single needle wire localization (2,3). Specifically, MR image-guided wire localizations are of significance due to the clinical value of MRI in breast tumor detection and characterization (4,5).

Wire localization techniques have several downsides, including wire dislocation between placement and surgery, wire entry site conflicting with ideal surgical site, and most importantly, the inability to delineate non-palpable tumor boundaries of irregular shape (6). These aspects can be critical since up to 30% of tumors must be re-excised for close or transected tumor at the specimen margin, and the primary cause of re-excision to prevent local recurrence after BCS is due to positive histological tumor margins (7,8). This causes significant morbidity and cost because all patients with positive margins undergo repeat surgery to remove any residual tumor that may be present. The patient burden of repeat surgery is significant, as favorable cosmetic results decrease with re-excision, and can eventually end in mastectomy. There is a manifest need for improved accuracy and flexibility in approach to breast tumor localization. This need is for all non-palpable breast tumors, not just those that are only visible on MRI. Some alternative methods to pre-operatively locate and mark the tumor include image-guided placement of radioactive seeds, radioactive injection, bracketed wires, and cryoablation lesion marking (6,9–12). In addition, intraoperative margin assessment by specimen mammography, have reported varied degrees of success in predicting margin involvement, with lower specificity and sensitivity in tumors without calcifications, or with poorly defined boundaries (13–16).

MR-Image guided High Intensity Focused Ultrasound (MR-HIFU), also known as MR-Image guided Focused Ultrasound Surgery (MR-FUS), is a non-invasive interventional technique where a highly focused ultrasound beam is used to induce thermal ablations at targets deep within the tissue, without penetrating the skin, and while sparing adjacent tissue. A recent preliminary study has proposed the use of MR-HIFU for localization by comparing excision margins between MR-HIFU and MR guided wire localizations (17). The advantage of MR-HIFU over the above-mentioned techniques is its ability to non-invasively create image-registered lesions to delineate tumor margins of any shape, and in 3 dimensions. In that study, MR-HIFU created lesions that circumscribed a mock tumor area to provide a surgical guide. The findings indicated that for the same excised volume, MR-HIFU localized lesions had fewer positive margins compared with that of MR guided wire localization. However, previous work using this technique was performed in ex-vivo turkey breast, which is comprised almost exclusively of muscle tissue. Since muscle tissue and human breast tissue, which contains a high percentage of fat and fibroglandular tissue, differ in acoustic properties, so might the palpability of resulting thermal lesions (18). A critical matter for MR-HIFU as a localization tool in BCS, is the ability to create reliable changes in palpability of actual breast tissue. Other ablative therapies such as radiofrequency (RF) ablation, have reported an increase in post ablation breast tissue stiffness upon gross examination, but the change in palpability was not quantified (19,20).

It is important to mention ongoing research in the application of MR-HIFU to treat whole tumor volumes in many areas of the body, including the brain, liver, prostate and the breast (21–25). However, when compared to current BCS procedures, long treatment times requiring numerous sonications for large tumors, and the absence of post procedure histopathology challenge the application of MR-HIFU whole tumor volume ablation in the breast (26). When used as a localization tool, MR-HIFU, with only a few sonications, could present a significant reduction in treatment time vs. whole tumor volume ablation, while preserving the benefit of histological data. Typically, ultrasound focal spots are monitored during heating using water proton resonance frequency shift (PRF) thermometry. However, PRF thermometry is currently unreliable in adipose or mixed adipose/fibroglandular tissues,

like those found in the human breast (27,28). A T1-weighted fast spin echo (T1wFSE) method has been investigated in place of PRF thermometry for focal spot visualization during heating of adipose tissue (29).

The purpose of this study was to investigate palpability of MR-HIFU thermal lesions in human breast tissue. Remote palpation, an elastography technique that uses acoustic radiation force, was used as a measure of palpability in this study (30). In our version of remote palpation, MR Acoustic Radiation Force Impulse (MR-ARFI) imaging uses MRI gradients to encode the tissue displacement that results from a non-thermal ultrasonic “pushing” pulse (31). This technique has been used to visualize the focal spot location prior to MR-HIFU ablations (32), and to measure tissue stiffness in vivo (33). We used MR-ARFI to evaluate a change in tissue displacement, or stiffness, between pre and post ablated tissue. MR-HIFU lesion palpability in human breast tissue is fundamental in substantiating the use of MR-HIFU as a localization tool for poorly palpable and non-palpable tumors prior to BCS.

Materials and Methods

Overview

The experiment was repeated on three breast specimens from two different cadavers. Each experimental setup consisted of a cadaveric breast absent the skin with no known breast pathology. The breast specimens measured approximately $14\text{ cm} \times 11\text{ cm} \times 5\text{ cm} \pm 3\text{ cm}$. The breast was placed into a 10 cm diameter cylindrical container with a mylar acoustic window at one end (Fig 1). The container was filled with degassed saline solution, and weighted down by an acoustic absorber plate. A gel pad coupled the ultrasound energy between the membrane and the breast. The bulk temperature of the breast was monitored using a fiberoptic thermocouple (Luxtron, Santa Clara, CA). A single channel 10.6 cm diameter solenoid breast coil (Invivo/MRI Devices, Waukesha, WI) designed for the ExAblateR system surrounded the container for imaging.

The experimental protocol is shown in Figure 2. Ablation spots were planned in the X-Z plane (perpendicular to the ultrasound beam) using fat saturated FSE images. This was followed by baseline remote palpation images, where MR-ARFI displacement maps were acquired for each planned ablation spot. Then, MR-HIFU ablations were performed in series, and followed by post-treatment MR-ARFI displacement maps. MR imaging parameters are given in Table 1. The rest of the experiment is described in more detail below.

Focused Ultrasound

Focused ultrasound procedures were performed using the ExAblateR 2000 system (InSightec Inc., Haifa, Israel), that pairs with a 3.0T clinical MRI scanner (Signa, GE Medical Systems, Waukesha, WI). The HIFU system is embedded in the patient table. Within the table, a concave annular array transducer is controlled by a positioning system and immersed in an oil bath. The transducer is capable of both mechanical (coarse) and electronic (fine) steering. A transparent membrane creates an acoustic window between the immersed transducer and the patient for ultrasonic coupling to the skin. The ablation spot formed in the focus has the shape of an elongated ellipsoid. A single ablation volume is approximately 2 mm diameter $\times$ 9 mm length, and can penetrate up to 20 cm inside the body.

The transducer focus was localized in the breast tissue by applying 2 lower power sonications (30W, 15s), and observing the change in T1 due to slight heating on T1wFSE

(ETL = 8) magnitude images prescribed parallel and perpendicular to the ultrasound beam (27).

Acoustic Radiation Force Imaging

For MR-ARFI imaging, the ExAblateR 2000 system was driven in a non-thermal mechanical mode, and used the same experimental setup shown above. The MR-ARFI sequence consists of a 2DFT spin-echo with repeated bipolar encoding gradients along the ultrasound beam direction (Table 1) (34). The duration of each gradient lobe was 6.1 ms, which results in a diffusion weighting imaging b-value of 42 s/mm². The HIFU system was triggered to emit ultrasound for a short duration (19 ms, 27 W acoustic power), synchronous with a portion of the encoding gradients (35). Considering a 500 ms repetition time (TR), the ultrasonic duty cycle was 3.8%. MR-ARFI displacement maps were calculated as the difference between two phase images acquired with opposite displacement encoding gradient polarity. Phase is converted to distance assuming a linear relationship and an instantaneous tissue response (31).

Ablation

Eighteen sonication locations were planned in the transverse plane (Fig 3a). The sonications circumscribed an area of the breast that crossed between both highly adipose and mixed fibroglandular tissue.

Each sonication was driven at 1 MHz, 120 W acoustic power, and a 20 s duration at continuous wave excitation (100% duty cycle). The sonications were spaced 5 mm apart to accentuate palpability in comparison to untreated surrounding tissue, and in order to evaluate individual lesion stiffness. Planned sonications formed a 24 mm × 24 mm square section of the breast. A square was chosen for simplicity in this study, but any other tumor perimeter configurations could be traced. Since breast tissue easily deforms and did not contain the skin intact, a frame of reference for orientation of the tissue would be lost after removal from the experimental setup. In order to create a transverse cross sectional cut of the tissue that included all of the ablated lesions, 4 sonications were stacked 4 mm apart in the Y plane, elongating each lesion along the beam direction (Fig 3b). The effective lesion size was approximately 2 mm × 17 mm, allowing for leniency in the precision of the cross sectional plane, and a better chance of slicing through all 18 lesions. Individual ablation heating was monitored by acquiring T1wFSE images every 5 seconds (Table 1).

Post Ablation Evaluation

MR-ARFI maps were acquired in the X-Z plane (perpendicular to ultrasound) before and after ablations, to show the change in tissue displacement due to lesion formation. Each ablation location was individually remotely palpated. To calculate the degree of displacement and the extent of the shear wave induced by radiation force, displacement profiles centered at the peak were plotted for each sonication location. The speed of shear wave is directly dependent on the shear elastic modulus, expressed by tissue stiffness (36). Distance of the shear wave was measured as the first minima from the central displacement peak. Considering the same constant encoding time, the change in shear velocity is directly proportional to change in propagation distance where, $\Delta v \propto \Delta d$. Statistical significance ($p < 0.05$) was evaluated using a matched pair t-test.

The cadaveric breast was removed from the setup and allowed to equalize to room temperature. Manual palpation (not performed by a specialist) was followed by dissection in the X-Z plane to evaluate changes in tissue appearance.

Results

HIFU Ablation Procedure

During the heating phase of ablation, the ablation location could be identified on T1w FSE images by a loss of signal intensity at the focus due to increase in T1 (Fig 4a,b). In the first cadaveric breast some T1wFSE images showed movement of the tissue during ablation. As heating progressed, tissue shrank towards the heated fibroglandular tissue. A comparison of FSE images before and after ablation showed where the tissue moved (Fig 4c,d). This was most pronounced in sonications closest to the edge of the breast, where the tissue was less restricted by the bulk weight of the breast. This effect was not obvious in the second and third cadaveric breast trials, where the ablation spots were prescribed more central in the tissue. The bulk temperature of the breast elevated by up to 16 °C over the course of the ablation sonications, then returned to room temperature before lesion evaluation.

Remote Palpation Lesion Evaluation

The remote palpation sonication focus is shown as the bright spot on pre and post ablation MR-ARFI displacement maps of the cadaveric breast (Fig 5). Figure 5 presents three remote palpations, showing reduction of post ablation displacement. The inflections in displacement surrounding the central peak (positive contrast) show a traveling shear wave (negative contrast) that is induced by the radiation force. The MR-ARFI maps of each ablation were combined into a single maximum intensity projection (MIP) image in a single cadaveric breast (Trial #2, Fig 6). The MIPs images represent the collection of all ablation locations that made up the square treatment perimeter, showing the combined result of reduced displacement in post treatment palpations. Displacement profiles of the focal spots present a decrease in peak amplitude and increase of shear wave velocity, of post ablation (red) palpations vs. pre ablation (blue) in the second cadaveric breast (Fig 7). The pre and post ablation statistics for each cadaveric breast trial are summarized in Figure 8. Combining results, the collective post ablation reduction in peak displacement was 54.8%, $[4.41 \pm 1.48] \mu\text{m}$ pre ablation vs. $[1.99 \pm 0.82] \mu\text{m}$ post ($p \leq 0.006$). The post ablation shear wave propagation increase was 65.5%, $[10.69 \pm 1.60] \text{ mm}$ pre vs. $[16.33 \pm 3.10] \text{ mm}$ post ablation ($p < 0.001$). Fiberoptic thermocouples showed no temperature rise during any MR-ARFI remote palpations.

Gross Examination

The cadaveric breast was manually palpated at room temperature prior to dissection. Although individual FUS lesion margins were not easily differentiated, the collection of lesions corresponding with primarily fibroglandular tissue were clearly stiffer than untreated areas. After dissection, all the FUS lesions were visible. However, due to the amorphous nature of the breast specimen, a purely transverse slice showing each lesion cross section was not achieved (Fig 9). Additional tissue slices were necessary to locate remaining lesions. The breast tissue showed a darkening of the ablated perimeter (Fig 9a). Lesions could be identified by oil cysts occurring in highly adipose ablations, and whitening of the thermally damaged fibroglandular tissue (Fig 9b).

Discussion

Three cadaveric breasts were ablated with MR-HIFU in 18 ablation locations along the perimeter of an arbitrary square within the breast. Tissue in each ablation location was remotely palpated using MR-ARFI before and after ablative treatments to assess changes in tissue stiffness. The principle findings of MR-ARFI showed a collective reduction of tissue displacement by 54.8% after ablation, suggesting tissue became stiffer. Manual palpation and dissection of the breast confirmed changes in palpability, and individual ablations were

visible. The stiffening of the ablated breast tissue indicates that MR-HIFU may be used for pre-surgical localization by creating a palpable tumor perimeter of any shape as a surgical guide.

The results of post ablation remote palpations showed changes in tissue stiffness compared with pre ablation by displacement amplitude, and shear wave propagation. The post ablation reduction of tissue displacement was the most pronounced measure of tissue property change for each breast trial (Fig 8). This result is consistent with a stiffening of the tissue due to ablation, since stiffer tissue displaces less for the same ultrasonic pushing force. Shear waves originating from the focus propagated 65.5% further after ablation, resulting from an increased velocity. Considering the dependence of shear velocity on elastic modulus of tissue, these results point to an increased stiffness of tissue due to ablation (33,37). This study reports palpation results where elongated lesions encompassed mixed adipose and fibroglandular breast tissue. It is unclear what the change in stiffness would be for a single lesion isolated in a volume of entirely adipose breast tissue. Studies in vivo may give more information as to how factors such as edema, contribute to palpability in those regions.

Specific to the first breast trial, the movement of the breast tissue during heating could have been the result of tissue desiccation and coagulative necrosis, as seen in RF ablation treatments (19,38). Of the 54 post ablation remote palpations, 47 had a reduced displacement. The 7 palpations that showed an increased displacement compared to pre ablation were located in the area of the breast that moved during heating (Fig 5). In that case, the prescribed locations for post ablation palpation no longer corresponded with the pre ablation locations, and were omitted from the results. This finding may be more pronounced in the ex-vivo case, since in vivo the skin could provide structural support. Additionally, focused ultrasound treatments incorporate a safety margin that requires ablations be prescribed at a minimum distance from the skin surface. No apparent movement of bulk tissue upon heating was observed in the second and third cadaveric breast trials where MR-HIFU lesions were more central to the breast. In those trials all post ablation remote palpations indicated stiffer tissue.

The darker yellow ablation perimeter shown in Figure 9 is consistent with findings of RF breast ablation studies where darker tissue presented in the area outside the zone of thermal destruction (39). Manual palpation at room temperature revealed an overall stiffening of the ablation perimeter. However, not every individual lesion margin could be palpated through untreated breast tissue. Because the surrounding adipose tissue of the breast becomes more solid with cooler temperatures, individual lesion identification may be more profound in vivo, where the ablated breast tissue would be palpated at body temperature. Nonetheless, it is important to note that the clinical significance of this technique is not in individual lesion identification, but rather, in a surgeon's ability to palpate the tumor location.

In efforts to spare healthy breast tissue, MR-ARFI could be used to non-thermally locate the focus in place of low power heating sonications. Using MR-ARFI imaging for focal spot visualization can provide increased SNR and 10 times less energy deposition than the low power sonication T1wFSE method (34).

There are two primary clinical implications in MR-HIFU lesion marking when compared to wire localization. First, creating a palpable tumor location could better inform surgical planning. Because the presence of a wire limits the options of surgical entry sites, this method may provide access to an entry site with more favorable cosmetic results. Second, is the delineation of margins of non-palpable tumors, even of irregular shape. Surgical outcomes, both cosmetic and in tumor margin status, could be improved by making these tumors less occult at the time of surgical intervention. The visibility of MR-HIFU lesions

could supply additional benefit by showing excision margins during surgery. Potential limitations of the technique include: the application to breast tumors whose boundaries are not MRI visible, patients with very small breasts or with tumors below the HIFU safety margins of the chest wall or skin surface.

The clinical utility of remote palpation may be in confirming increased stiffness boundary marker, and if necessary, re-marking immediately within the same session. This could provide a pre-surgical level of confidence in the success of the MR-HIFU treatment before the patent is removed from the treatment table. To minimize additional treatment time, the number of remote palpations could be reduced to a few MR-ARFI palpations, potentially enough to inform decisions on regional stiffness. Also, additional studies that determine the minimum MR-ARFI response corresponding to the palpation threshold would be useful.

In conclusion, this study has shown that MR-HIFU can create focal palpable, visible lesions in human breast tissue, and that these lesions can be mapped through remote palpation MR-ARFI. The ability of MR-HIFU lesions to change breast palpability is the key to its prospective use in image-registered localization of poorly palpable and non-palpable breast tumors. The impact of MR-HIFU in breast tumor demarcation is the possibility to provide reduced positive tumor margins, and in doing so potentially reduce the burden of repeated breast conservation surgeries.

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Figure 6.

Figure 7.

Figure 8.

Figure 9.

Table 1

Imaging Parameters. Focus localization and lesion monitoring used a T1wFSE sequence, planning images used a fat saturated FSE, and MR-ARFI is based on a spin echo sequence.

	Monitoring	Planning Images	MR-ARFI
Repetition Time (ms)	400	3000	500
Echo Time (ms)	12	12	41
Slice Thickness (mm)	3	2	3
Bandwidth (kHz)	15.6	122	15.6
FOV (cm)	20 × 20	20 × 20	20 × 11, 20 × 20 *
Matrix	256 × 128	256 × 192	256 × 64, 256 × 128 *

* FOV and Matrix size for the third cadaveric breast.