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Optimized Echo Decorrelation Imaging Feedback for Bulk Ultrasound Ablation Control

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Abstract

Feasibility of controlling bulk ultrasound (US) thermal ablation using echo decorrelation imaging was investigated in *ex vivo* bovine liver. The first of two ablation and control procedures used a sequence of constant-intensity sonication cycles, ceased when the minimum echo decorrelation within a control region of interest (ROI) exceeded a predetermined threshold. The second procedure used a variable-intensity sonication sequence, with spatially averaged decorrelation as the stopping criterion. US exposures and echo decorrelation imaging were performed by a linear image-ablate array. Based on preliminary experiments, control ROIs and thresholds for the minimum-decorrelation and average-decorrelation criteria were specified. Controlled trials for the minimum-decorrelation and average-decorrelation criteria were compared with uncontrolled trials employing 9 or 18 cycles of matching sonication sequences. Lesion dimensions, treatment times, ablation rates, and areas under receiver operating characteristic curves were statistically compared. Successfully controlled trials using both criteria required significantly shorter treatment times than corresponding 18-cycle treatments, with better ablation prediction performance than uncontrolled 9-cycle and 18-cycle treatments. Either control approach resulted in greater ablation rate than corresponding 9-cycle or 18-cycle uncontrolled approaches. A *post hoc* analysis studied the effect of exchanging control criteria between the two series of controlled experiments. For either group, the average time needed to exceed the alternative decorrelation threshold approximately matched the average duration of successfully controlled experimental trials. These results indicate that either approach, using minimum-decorrelation or average-decorrelation criteria, is feasible for control of bulk US ablation. In addition, use of a variable-intensity sonication sequence for bulk US thermal ablation can result in larger ablated regions compared to constant-intensity sonication sequences.

Keywords

Echo decorrelation imaging; unfocused ultrasound; bulk thermal ablation; real-time control

I. Introduction

MINIMALLY invasive bulk thermal ablation, including laser interstitial thermotherapy [1], radiofrequency ablation (RFA) [2], microwave ablation (MWA) [3], and high-intensity ultrasound (US) (e.g., interstitial [4], [5], focused [6], [7] and unfocused [8]) ablation, is an important treatment approach for unresectable primary and secondary liver tumors (e.g.,

hepatocellular carcinoma and colorectal metastases) treatment [9], [10]. All thermal ablation techniques aim to rapidly elevate the tissue temperature above 60 °C, resulting in thermal coagulative necrosis within a zone encompassing all tumor margins, to avoid incomplete treatment and cancer recurrence. However, uncontrolled ablation of large regions may also damage nearby critical liver structures (e.g., the hepatic artery and portal vein). Therefore, real-time monitoring and control methods, capable of providing consistent thermal ablation in minimal treatment time, could improve bulk thermal ablation treatments.

In clinical practice, RFA [11] and MWA [12] electrodes are typically placed in the target region under US or X-ray image guidance. Most ablation devices offer only crude automatic control, based on tissue electrical impedance or temperature measured at one or more antenna tines [13], but cannot provide detailed spatial feedback on all points in the ablation volume. As a result, RFA and MWA procedures rely heavily on operator skill, increasing the risk of untreated tumor and therefore local cancer recurrence. Alternative image-guided thermal ablation methods have been incorporated with US imaging [14], [15], computed tomography (CT) [16], and magnetic resonance imaging (MRI) [17], [18] for accurate therapy guidance and control. Although MRI provides precise 3D temperature mapping [3], it requires MR compatible tools [19], increasing treatment cost and complexity compared to US imaging. CT has the additional disadvantage of ionizing radiation.

Currently, B-mode US is the most common imaging modality for guidance of bulk thermal ablation, including RFA and MWA. Ultrasound imaging has advantages of being portable and inexpensive, while its high frame rate is suitable for real-time monitoring of moving organs like the liver [14]. Recent research efforts have used real-time US image fusion [20] with MRI or CT images, as well as contrast-enhanced US (CEUS) imaging [21], aid tumor margin visualization during treatment planning and assessment. However, the ability of B-mode US to predict the extent of thermal ablation is limited by the formation of heat-induced microbubble clouds (hyperechoic activity), causing acoustic shadowing and making tumor boundaries difficult to visualize [22].

Recently, Toshikuni et al. [23] have clinically demonstrated an RFA monitoring approach using a real-time image fusion (RTIF) system. Tumor boundaries were manually marked on a reference image (CT/CEUS/MRI), then automatically co-registered with real-time US images used to monitor the RFA ablation. Fused B-mode images were used to manually control the RFA, such that treatments were ceased when the hyperechoic region covered the spherical marker boundaries in all directions. RTIF-controlled trials achieved more effective treatment than uncontrolled trials. However, this approach is limited by its use of local echogenicity as an ablation predictor, which can lead to inaccurate prediction of RFA therapeutic effects [24], [25].

Echo decorrelation imaging [24] exploits the phenomenon of heat-induced echo signal decorrelation to locally map heat-induced tissue changes, including irreversible structural changes as well as transient microbubble activity, on millisecond time scales [26], [27]. This approach has been successfully employed to monitor bulk US thermal ablation [8] and RFA [24], [25], [27] both *ex vivo* and *in vivo*, and has been shown to predict local ablation more effectively than changes in echogenicity (e.g., integrated backscatter). A method to extract

heat-induced decorrelation from artifactual motion- and noise-induced decorrelation has been shown feasible for monitoring of *in vivo* RFA [26]. Notably, the same heat-induced decorrelation limits the utility of several other pulse-echo US imaging methods such as elastography [28] and echo strain imaging [29], [30] to accurately characterize tissue during thermal ablation [26], [31], [32]. Although such approaches have been demonstrated feasible for control of multiple-focus ultrasound heating [33] as well as ultrasonic hyperthermia [34], heat-induced decorrelation may limit their applicability to control of bulk thermal ablation.

Recently, 2D echo decorrelation imaging has been successfully employed to control high-intensity focused ultrasound (HIFU) thermal ablation. One study employed a large control region of interest (ROI) ($10 \times 10 \text{ mm}^2$), with the average decorrelation within that ROI as a stopping criterion for HIFU ablation in *ex vivo* chicken breast [35]. However, this approach can potentially lead to false alarms, due to any decorrelation artifacts outside the focal ablation region. In another previous study [36], HIFU thermal ablation was successfully controlled using the minimum cumulative echo decorrelation inside a small ROI ($1 \times 1 \text{ mm}^2$), placed at the focal zone in *ex vivo* bovine liver [36]. The present study extends the applicability of echo decorrelation imaging to control of bulk ultrasound ablation [37], which is of interest not only as a potential minimally invasive cancer treatment [4], [5], [8], but also as an analog to bulk ablation by RFA and MWA, with comparable lesion sizes and heating rates [4].

In this study, two approaches for controlling bulk thermal ablation using echo decorrelation imaging were implemented and assessed in *ex vivo* bovine liver. An optimization method was applied to determine control ROI dimensions and ablation control thresholds (treatment end points) for two different echo decorrelation feedback predictors, based on results of preliminary ablation and imaging experiments. Bulk US thermal ablation was performed by the same image-ablate array used in previous HIFU experiments [36], [38], allowing accurate image registration with treated tissue histology. The array was used to generate unfocused ultrasound, a configuration mimicking other bulk thermal ablation techniques (e.g., RFA and MWA) by ablating larger volumes with slower heating rates, compared to HIFU ablation. Results of controlled ablation experiments and matching uncontrolled experiments were analyzed to compare the effects of the different control criteria and sonication schemes on ablation outcomes, including lesion dimensions, treatment duration, and local ablation prediction.

II. Materials and Methods

A. Feedback Control Algorithm

To utilize echo decorrelation imaging feedback for controlling bulk US ablation, a real-time control algorithm was implemented using an integrated real-time US imaging and therapy system, similar to a previous study on control of focused ultrasound ablation [36]. A flow chart of the closed-loop control algorithm is shown in Fig. 1(c).

Local echo decorrelation per millisecond (y, z, t) was computed as described previously [8], where y and z are azimuthal and range coordinates. Derivation and analysis of echo decorrelation imaging has been published previously [24]-[26], [36]. Here, the local echo

decorrelation was computed between consecutive pulse-echo image frames, recorded immediately after each unfocused sonication cycle. Ensemble-averaged echo decorrelation maps for each cycle were computed as

$$\bar{\Delta}(y, z, m) = \frac{1}{K-1} \sum_{k=1}^{K-1} \Delta(y, z, k\tau), \quad (1)$$

where m is the sonication cycle index, K is the number of frames recorded per cycle, k is the frame index, and τ is the inter-frame time. Cumulative echo decorrelation (Δ_{cum}) maps were defined as the temporal maximum of the ensemble-averaged echo decorrelation map for each pixel position (y, z):

$$\Delta(y, z, m)_{\text{cum}} = \max(\bar{\Delta}(y, z, m-1), \bar{\Delta}(y, z, m)) \quad (2)$$

The minimum (Δ_{min}) and average (Δ_{avg}) cumulative echo decorrelation inside a control ROI (ROI in Fig. 1c) were used as feedback parameters for closed-loop ablation control during two series of ablation experiments. Therapy cycles were repeated until Δ_{min} or Δ_{avg} exceeded a prespecified control threshold Δ_{th} or the sonication cycle index m exceeded a prespecified maximum number of sonication cycles.

B. Bulk US Ablation Experiments

Using a custom image-treat array transducer (64-element, $4.8 \times 24.4 \text{ mm}^2$ aperture, 5.0-5.4 MHz; Ardent Sound, Mesa, AZ, USA), pulse-echo US imaging ($> 40\%$ bandwidth, transmit focal depth 3.5 cm, F-number 4) and bulk US ablation (unfocused, maximum acoustic power 35 W) were performed. The transducer was integrated with a 23 mm standoff filled with deionized, degassed ($< 30\%$ dissolved O_2) water. Both US treatment and imaging were controlled by the Iris 2 imaging and therapy system (Ardent Sound, Mesa, AZ, USA) [39].

Fresh bovine liver was obtained from a local slaughterhouse, cut to fit an open-top acrylic cuvette ($85 \times 85 \times 60 \text{ mm}^3$) as shown in Fig. 1(a), and immersed in deionized, degassed 0.01M phosphate-buffered saline (PBS). All tissue was treated within 12 hours *post mortem*. The tissue baseline temperature prior to ablation was 19.0-21.5 °C.

For bulk US treatments, high-intensity sonication cycles were performed, following the timing sequence shown in Fig. 1(d). The array fired full-aperture, continuous-wave, unfocused 6 s pulses with an estimated [40] range of *in situ* spatial-peak, temporal-peak intensity (I_{SPTP}) from 24 to 54 W/cm^2 (5% less than the range used in [8]), followed by rest periods of 2.2-2.5 s. The corresponding estimated pressure amplitude range (0.85-1.30 MPa, 5.0 MHz) was less than the threshold of subharmonic emissions (1.68 MPa, 5.0 MHz) for resonant-sized bubbles in blood [41], which ensured minimal acoustic cavitation in tissue, although some cavitation and other gas activity likely occurred as tissue was heated [42].

Immediately after each sonication cycle, 20 frames of beam-formed radiofrequency echo data were acquired at a frame rate of 116 Hz. Frames were digitized by a PC-based data

acquisition card (14-bit, 33.3 MHz sampling rate; Compuscope 14200, Gage Applied). In-phase and quadrature (IQ) complex components of the digitized frames were computed by applying a Hilbert-transform filter, then demodulated using a 5.0 MHz carrier frequency and decimated by a factor of 6. Processed IQ frames were used to compute B-mode and echo decorrelation images, as described previously [8].

After experiments, treated liver tissue was stored overnight in a -80°C freezer in the same cuvette to maintain tissue shape and orientation for registration with US images. The tissue was sectioned through the imaging/therapy plane, stained with 2% triphenyl tetrazolium chloride (TTC) vital stain [8], [25], and optically scanned at 1200 dpi (CanoScan 8800F, Canon, Japan). Using a custom MATLAB (The Math-Works, Natick, MA, USA) application, scanned sections were manually segmented into ablated (partial or no TTC uptake) or unablated (full TTC uptake) regions and registered with corresponding B-mode US images [24], [36], using a 2D rigid registration method. Estimated root-mean-square (RMS) image registration error for this method is approximately 0.7 mm [36].

C. Experiments Using Minimum-Decorrelation Criterion

The first series of controlled ablation experiments used the minimum cumulative echo decorrelation inside a control ROI as a stopping criterion. This control approach was motivated by the success of echo decorrelation in locally predicting ablation with high specificity [8], [25], potentially enabling echo decorrelation feedback to ensure ablation of the entire control ROI. This control approach also matched that used in a previous series of experiments on HIFU ablation control using echo decorrelation imaging [36]. In these experiments, a constant-intensity sonication scheme was used, similar to the *in vivo* bulk ablation experiments reported by Fosnight et al. [8]. In those previous *in vivo* experiments, the sonication sequence was chosen to ensure successful tissue ablation in all cases, while potentially exceeding the minimum number of treatment cycles required.

In order to specify an appropriate decorrelation threshold and control ROI dimensions, an optimization approach was applied to a preliminary series of uncontrolled bulk US ablation experiments ($N=30$) on fresh bovine liver tissue, using the experimental setup shown in Fig. 1(a) and the ablation methods described in section II.B. For all 30 trials, nine sham cycles (zero acoustic power) were followed by 7-18 (mean 11.4) identical sonication cycles, covering the ranges of 5.0-5.4 MHz in frequency, 70.6-73.1% in duty cycle, and 24-54 W/cm^2 I_{SPTP} .

The guiding principle of the optimization approach was to seek control criteria such that ablation of an ROI would be confirmed by the minimum value of echo decorrelation in the ROI, with the expectation that ablation may extend to a region beyond the ROI in all directions. The control ROI shape was chosen to approximate an upside-down isosceles trapezoid, matching the observed typical shape of bulk US thermal lesions in these preliminary experiments, as shown in Fig. 2(a). For simplicity, the ROI was formed from three rectangles with fixed widths and lateral edges separated by 1 mm on each side, as shown in Fig. 1(b). ROI width (i.e., width of the topmost rectangle) was varied between 10-24 mm in increments of 2 mm, while ROI height (i.e., height of the three combined rectangles) was 9, 12, or 15 mm. Each ROI was placed parallel to the transducer aperture,

centered at the midline of the US image (white dashed line in Fig. 1(b)), with its top boundary 2 mm below the tissue surface, to reduce influence of the bright reflection from the tissue surface on echo decorrelation within the ROI.

For a number of candidate ROIs of this type, all preliminary trials were classified into ablated-ROI (ROI fully within the ablated region, as shown in Fig. 2(a)) and unablated-ROI (ROI not fully within the ablated region, as shown in Fig. 2(b)) groups. The minimum of the spatial-average, cumulative echo decorrelation inside the ROI under investigation was computed for each group. In order to determine an ROI suitable for meaningful testing of control efficacy, optimum control ROI dimensions were chosen as those providing a large difference in mean $\min$ between ablated-ROI and unablated-ROI groups, while also providing a sufficiently large fraction of ablated-ROI trials. The result was selection of a 16 mm $\times$ 12 mm (width $\times$ height) ROI, which was fully ablated in 23.3% of the preliminary trials.

An optimum control threshold was then sought, with the goal of achieving high prediction specificity and reasonable sensitivity for complete ROI ablation. Rates of true-positive (sensitivity) and true-negative (specificity) predictions of complete ROI ablation were computed as a function of $\min$, as shown in Fig. 2(c). The control threshold was selected as $\text{th} = -3.20$ ($\log_{10}$ -scaled echo decorrelation per ms), corresponding to 91.3% specificity and 57.1% sensitivity for prediction of complete ROI ablation.

To assess this first control approach, a series of controlled and uncontrolled ablation experiments were conducted using the same experimental setup shown in Fig. 1(a). In controlled trials ($N=15$), the control ROI was placed 2 mm below the tissue surface, azimuthally centered on the B-mode image as shown in Fig. 1(b). The maximum number of sonication cycles for all controlled trials was set to $M=18$ [36], twice the maximum number of sonication cycles used by Fosnight et al. [8] for *in vivo* bulk ultrasound ablation. For the controlled treatments, sonication sequences (73.1% duty cycle, 5.0 MHz frequency) began with 9 sham cycles, followed by constant-intensity sonication cycles (I_{STP} range of 38–49 W/cm²), with treatments ending when the minimum cumulative echo decorrelation $\min$ within the ROI exceeded th or when the sonication cycle index m exceeded M . During the rest period of each cycle (2.2 s), echo decorrelation maps were computed and overlaid on the B-mode images. Controlled trials were compared with uncontrolled trials employing 9 ($N=15$) or 18 ($N=14$) cycles of the same sonication sequence, as described in section II.E.

D. Experiments Using Average-Decorrelation Criterion

To test the sensitivity of the closed-loop control algorithm and the proposed optimization method to choice of echo decorrelation feedback predictors, a second series of controlled ablation experiments was performed using the average cumulative echo decorrelation as a stopping criterion, similar to the approach used in another study of HIFU ablation control by echo decorrelation imaging [35].

These experiments also employed variable-intensity sonication (lower-power sonication cycles followed by higher-power cycles) in an attempt to increase the depth of thermal lesioning. The variable sequence started with a series of lower-intensity sonication cycles,

followed by a series of higher-intensity sonication cycles, to reduce shadowing effects associated with overtreatment at shallow tissue depths [4]. In these controlled ablation experiments, treatments were terminated once the average echo decorrelation within the control ROI exceeded a predefined threshold.

To optimize the control ROI dimensions and ablation threshold, the approach described in section II.C was applied. The preliminary experiments analyzed here comprised the previous preliminary experiments ($N=30$), controlled trials ($N=15$), and uncontrolled trials ($N=29$) trials described in section II.C, as well as additional preliminary experiments ($N=12$, 9-18 therapy cycles, 73.1% duty, $I_{\text{STP}}=36.1 \text{ W/cm}^2$, 5.0 MHz). For all 86 preliminary trials analyzed here, nine sham cycles were followed by 7-18 (average 12.3) sonication cycles.

Similar to the optimization approach described in section II.C, *post hoc* analysis was employed to specify control ROI dimensions, based on successful ablation of the entire ROI and echo decorrelation contrast between ablated-ROI and unablated-ROI groups. ROI widths considered ranged from 12-18 mm with a 2 mm increment, while ROI heights considered were 9 mm and 10.5 mm. The spatially averaged cumulative echo decorrelation inside the ROI under investigation was computed for each group. The optimum ROI dimensions were chosen as 12 mm $\times$ 9 mm, corresponding to complete ROI ablation in 67.4% of the preliminary trials. The control threshold was selected as -1.576 ($\log_{10}$ -scaled echo decorrelation per ms), corresponding to 78.6% specificity and 60.3% sensitivity for prediction of complete ROI ablation, as shown in Fig. 2(d).

To assess the ability of average decorrelation feedback approach for controlling bulk US thermal ablation using the optimized control ROI and threshold, a series of controlled and uncontrolled ablation experiments ($N=33$) was conducted using the same approach and experimental setup (Fig. 1(a)). In the controlled trials ($N=13$), the control ROI was placed as described in the previous section. For controlled bulk US treatments ($N=13$), the variable sonication sequence (73.1% duty cycle, 5.4 MHz frequency) began with 9 sham cycles, followed by 9 sonication cycles at 38.3 W/cm^2 I_{STP} and up to 9 cycles at 43.1 W/cm^2 . This initial lower intensity approximately equals the lowest intensity employed in the constant-intensity sonication sequences described in section II.C, while the higher intensity approximately equals the average of all constant intensities employed. Treatments ended when the average cumulative echo decorrelation $_{\text{avg}}$ within the ROI exceeded $_{\text{th}}$ or when the sonication cycle index m exceeded M . Controlled trials were compared with uncontrolled trials employing 9 ($N=10$) or 18 ($N=10$) cycles of the same sonication sequence.

During treatments, the occurrence of audible popping sounds [43] associated with tissue vaporization was noted by the operator, together with the corresponding therapy cycle index, to study the relationship between the popping-sound phenomenon and the average decorrelation $_{\text{avg}}$ inside the control ROI. For statistical analysis, trials were classified into audible sound ($N=17$) and no audible sound ($N=16$) groups for comparison of $_{\text{avg}}$ levels in each group.

E. Data Analysis

After treatments, tissue handling and processing followed the procedures described in section II.B. Segmented TTC-stained tissue sections were used to characterize bulk thermal lesions by their depth, width, and area [36]. Lesion depth was defined as the distance between the most proximal and distal ablated points along the vertical line at zero azimuth of the transducer (white dashed line in Fig. 1(b)). Lesion width was defined as the horizontal distance between the left and right edges of the ablated region, measured at the midpoint of the lesion depth. Lesion area was computed as the total area of all pixels in the ablated region. Ablation rate (cm^2/min) was defined as the ablated area divided by the treatment time.

Statistical analysis was done using R software (R Foundation, Vienna, Austria). Means and standard errors of the lesion width, depth, area, treatment time and ablation rate were calculated for all groups. Normality of the data was tested using the Shapiro-Wilk test [44]. For non-normally distributed groups, a Kruskal-Wallis rank sum test [45] (significance criterion $p < 0.05$) was conducted to test the hypothesis of no median difference, followed by Dunn's test [46] for multiple pairwise comparisons with Bonferroni adjustment [47]. Homogeneity of variances was tested statistically for the normally and non-normally distributed groups using the Bartlett test [48] and Levene test [49], respectively. For normally distributed groups, analysis of variance (ANOVA) was applied to test the hypothesis of equal means. If significant, ANOVA was followed by a *post hoc* Tukey's honest significance difference (HSD) test for multiple comparison of means.

To assess the ablation prediction capability of echo decorrelation imaging for each group, receiver operating characteristic (ROC) curves and areas under the ROC curve (AUC) values were computed for each group [8], [24], [25]. Cumulative echo decorrelation maps were corrected for motion and noise artifacts using a method described previously [8], [26]. ROC curves were computed by comparing the corrected cumulative echo decorrelation map to the TTC-segmented tissue binary mask point-by-point, plotting rates of true positive predictions ($\text{Sensitivity} = \text{TP}/(\text{TP} + \text{FN})$) and false positive predictions ($1 - \text{Specificity} = \text{FP}/(\text{FP} + \text{TN})$) over all image pixels for all echo decorrelation thresholds. AUC was calculated by integrating ROC curves using the trapezoidal rule. Statistical significance of AUC values was determined vs. the null hypothesis ($\text{AUC} = 0.5$) and each other (controlled vs. uncontrolled) using a general model for AUC standard error [50] (one-tailed) and DeLong's method [51] (two-tailed) respectively. AUC statistical tests were adjusted for their effective sample size, based on the maximum packing density of circular windows separated by 2.35 mm for independent predictions [8], [25].

The average lesion width of each group for both approaches was tested against the transducer aperture using one-sample *t*-tests (two-tailed, significance criterion $p < 0.05$). The average treatment time of each controlled group was tested against the corresponding fixed treatment times of the 9-cycle and 18-cycle uncontrolled groups using one-sample *t*-tests (two-tailed, significance criterion $p < 0.025$ including Bonferroni correction).

To compare between the minimum-decorrelation and average-decorrelation feedback approaches, lesion dimensions (width and depth), ablation rates, and treatment times of the

successfully controlled trials for each criterion were statistically compared using two-sample t -tests (two-tailed, significance criterion $p < 0.05$). In addition, relative differences between outcomes of controlled and matching uncontrolled trials were compared between the two experimental series.

To assess the ability of echo decorrelation imaging to predict tissue ablation area, an optimal decorrelation cutoff for ablation prediction was determined, such that the estimated ablated area was equal to the area of all pixels exceeding the cutoff. RMS errors between measured and estimated ablated areas were calculated for a range of echo decorrelation cutoffs from -4 to -1 ($\log_{10}$ -scaled echo decorrelation/ms) using the echo decorrelation maps for all groups of both approaches ($N=70$). The echo decorrelation cutoff corresponding to the minimum overall RMS ablated area error was considered the optimum for ablated area prediction. Using this cutoff, absolute RMS errors, defined as the root-mean-square difference between predicted and measured ablated areas, were computed for each group. Normalized RMS error was defined as the ratio between absolute RMS error and the RMS value of the measured ablated area.

A retrospective study was also performed to compare performance of the two control criteria investigated. For trials using the minimum-decorrelation feedback approach, the $12 \text{ mm} \times 9 \text{ mm}$ control ROI from the average-decorrelation experiments, together with its associated control threshold ($\epsilon_{th} = -1.576$), were applied to archived echo data from all controlled experiments. For each of these experiments, control using the average-decorrelation feedback criterion was simulated by computing ϵ_{avg} within the control ROI for each cycle. The *post hoc* threshold-crossing time for each trial (i.e., the treatment time if the average-decorrelation feedback criterion had been employed) was defined as the number of therapy cycles required to exceed the alternative control threshold, multiplied by the therapy cycle duration (8.2 s). Similarly, controlled trials employing the average-decorrelation feedback criterion were retrospectively analyzed by applying the $16 \text{ mm} \times 12 \text{ mm}$ control ROI from the minimum-decorrelation experiments with its selected control threshold ($\epsilon_{th} = -3.20$). Means and standard errors of the *post hoc* threshold-crossing time for all controlled trials of each feedback criterion were computed and statistically compared using two-sample t -tests (two-tailed, significance criterion $p < 0.05$). In addition, all successfully controlled trials using the minimum-decorrelation approach were assessed for complete ablation of the smaller control ROI employed in the average-decorrelation approach. Similarly, all successfully controlled trials using the average-decorrelation approach were assessed for complete ablation of the larger control ROI employed in the minimum-decorrelation approach.

III. Results

A. Experiments Using Minimum-Decorrelation Criterion

In the first series of experiments, employing constant-intensity sonication and the minimum-decorrelation stopping criterion, successful control (ϵ_{min} exceeding ϵ_{th}) was achieved in 11 of the 15 controlled trials (73.3%), with the threshold reached in an average of 9.7 cycles or 79.8 s (maximum 14 cycles or 114.8 s; minimum 7 cycles or 57.4 s). The $16 \text{ mm} \times 12 \text{ mm}$

control ROI was fully ablated in 3 of 11 successfully controlled trials, 0 of 4 unsuccessfully controlled trials, 3 of 15 9-cycle uncontrolled trials, and 3 of 14 18-cycle uncontrolled trials.

Fig. 3 shows final B-mode image frames, overlaid by final cumulative echo decorrelation maps, together with corresponding registered and segmented TTC-stained tissue sections for representative trials from the 9-cycle, successfully controlled, and 18-cycle groups. The white line and dashed green lines indicate the segmented tissue and predicted ablation region boundaries in the hybrid echo decorrelation/B-mode images. In the TTC-stained sections, red and green lines indicate segmented tissue boundaries and ablated regions respectively. Lesion depths for the trials shown in column (a), (b), and (c) approximately match the minimum, average, and maximum values for each group, respectively.

Fig. 4(a) shows ROC curves and AUC values for prediction of local ablation in the successfully controlled (AUC=0.862), 9-cycle uncontrolled (AUC=0.668), and 18-cycle uncontrolled (AUC=0.842) groups. AUC for all three groups was significantly greater than chance ($p < 10^{-16}$), and were significantly larger for the controlled and 18-cycle groups, compared to the 9-cycle group ($p < 10^{-16}$). The optimum cumulative echo decorrelation threshold for local ablation prediction, based on point-by-point ROC curve computation [8] for the successfully controlled trials, was -2.2 ($\log_{10}$ -decorrelation/ms), corresponding to 79.6% sensitivity and 78.5% specificity.

Fig. 4(b-d) shows statistics of lesion dimensions and ablation rate for successfully controlled trials and uncontrolled trials employing the minimum-decorrelation, constant-intensity approach. Ablated lesion widths, depths and rates passed the Shapiro-Wilk test ($p > 0.05$), indicating normal data distribution. ANOVA tests showed significant differences between lesion widths and ablation rates ($p = 3.2 \cdot 10^{-3}$, $p = 9.4 \cdot 10^{-8}$, respectively), but no significant differences between ablation depths ($p = 0.23$). Based on Tukey's HSD test, average ablation rate for the 18-cycle group was found to be significantly smaller than for the successfully controlled and 9-cycle groups ($p < 10^{-4}$). Average lesion width for the 9-cycle group was found to be significantly smaller than for the 18-cycle group ($p = 2.2 \cdot 10^{-3}$) and the transducer aperture ($p = 6.3 \cdot 10^{-5}$). The Bartlett test indicated no significant difference among the variances of ablation widths, depths, or rates. Ablation areas were non-normally distributed according to the Shapiro-Wilk test and were significantly different according to the Kruskal-Wallis test ($p = 0.031$), with the 9-cycle group ($2.74 \pm 0.12 \text{ cm}^2$) significantly smaller than the 18-cycle group ($3.48 \pm 0.19 \text{ cm}^2$; $p = 0.0137$), but with the successfully controlled group ($3.14 \pm 0.28 \text{ cm}^2$) not significantly different from either uncontrolled group, and with no significant differences in variance. Mean $\pm$ standard error of the treatment time was $79.8 \pm 5.9 \text{ s}$ for successfully controlled trials, statistically equivalent to the fixed 73.8 s treatment duration for the 9-cycle group, but significantly smaller than the fixed duration of 147.6 s for the 18-cycle group ($p = 4.1 \cdot 10^{-7}$). For unsuccessfully controlled trials ($N=4$), means $\pm$ standard errors for the ablation width ($23.5 \pm 0.9 \text{ mm}$), depth ($14.9 \pm 0.94 \text{ mm}$), area ($3.20 \pm 0.20 \text{ cm}^2$), and rate ($1.30 \pm 0.09 \text{ cm}^2/\text{min}$) were close to the 18-cycle uncontrolled group.

B. Experiments Using Average-Decorrelation Criterion

In the second series of experiments, employing variable-intensity sonication and average-decorrelation as the stopping criterion, successful control (ρ_{avg} exceeding ρ_{th}) was achieved in 10 of the 13 controlled trials (77%), with the threshold reached in an average of 13.9 cycles or 114.0 s (maximum 16 cycles or 131.2 s; minimum 12 cycles or 98.4 s). The ROI was fully ablated in 8 of 10 successfully controlled trials, 3 of 3 unsuccessfully controlled trials, 1 of 10 9-cycle uncontrolled trials, and 8 of 10 18-cycle uncontrolled trials.

Fig. 5 shows final B-mode frames, overlaid by final cumulative echo decorrelation maps, with corresponding registered and segmented TTC-stained tissue sections for representative trials from the 9-cycle, controlled, and 18-cycle groups, with formatting matching Fig. 3. Lesion depths for the trials shown in column (a), (b), and (c) approximately match the minimum, average, and maximum values for each group, respectively.

Fig. 6(a) shows ROC curves and AUC values for prediction of local ablation in the successfully controlled (AUC=0.871), 9-cycle uncontrolled (AUC=0.327), and 18-cycle (AUC=0.722) uncontrolled groups. AUC values for the successfully controlled and 18-cycle groups were significantly greater than 0.5 ($p < 10^{-16}$) and were significantly higher for controlled than 18-cycle uncontrolled trials ($p < 10^{-8}$). For successfully controlled trials, the optimum ρ_{cum} for local ablation prediction was found to be -2.3 ($\log_{10}$ -scaled decorrelation/ms), corresponding to 77.3% sensitivity and 82.8% specificity.

Fig. 6(b-d) shows statistics of lesion dimensions and ablation rate for successfully controlled trials and uncontrolled trials employing the average-decorrelation, variable-intensity approach. Shapiro-Wilk test results indicated all ablation lesion dimensions and rates were normally distributed ($p > 0.05$). ANOVA tests showed significant differences between depths ($p = 1.9 \cdot 10^{-5}$) and areas ($p = 8.2 \cdot 10^{-6}$), but no significant differences between ablation rates or lesion widths. Successfully controlled trials and 18-cycle uncontrolled trials had statistically equivalent lesion depths and areas, both significantly larger than the 9-cycle uncontrolled group ($p < 10^{-3}$). The Bartlett test indicated no significant difference among the variances of ablated lesion depths, widths, or rates for all groups. However, the lesion area of the 9-cycle group ($2.13 \pm 0.10 \text{ cm}^2$) had smaller mean ($p < 10^{-3}$) and variance ($p < 0.04$) compared to the successfully controlled ($3.66 \pm 0.22 \text{ cm}^2$) and 18-cycle ($4.06 \pm 0.32 \text{ cm}^2$) groups. Average lesion width for the successfully controlled 18-cycle uncontrolled group was significantly larger than the transducer aperture ($p = 0.016$, $p = 3.1 \cdot 10^{-3}$, respectively). Mean $\pm$ standard error for the duration of successfully controlled treatments was $114.0 \pm 4.1 \text{ s}$ for successfully controlled trials, significantly larger than the fixed 73.8 s duration of 9-cycle uncontrolled treatments ($p = 4.6 \cdot 10^{-6}$) but significantly smaller than the fixed duration of 147.6 s for 18-cycle uncontrolled treatments ($p = 2.0 \cdot 10^{-5}$). As in the minimum feedback control approach, means $\pm$ standard error values for unsuccessfully controlled trials ($N=3$) were close to the 18-cycle uncontrolled trials for lesion width ($26.1 \pm 0.29 \text{ mm}$), depth ($17.0 \pm 0.7 \text{ mm}$), area ($4.32 \pm 0.25 \text{ cm}^2$), and rate ($1.75 \pm 0.08 \text{ cm}^2/\text{min}$).

Fig. 6(e) shows statistics of final ρ_{avg} values within the control ROI for the group with audible popping sounds ($N=17$) and the group with no audible sound ($N=16$). Based on the Shapiro-Wilk test, values of ρ_{avg} were non-normally distributed ($p < 0.05$). The median of

$\bar{\Delta}_{\text{avg}}$ for the audible-sound group was significantly greater than the no-sound group ($p = 8.4 \cdot 10^{-6}$). Maximum values of the ensemble-averaged decorrelation $\bar{\Delta}(y, z, m)$ for cycles with observed popping sounds ranged from -1.91 to -0.82 , with mean $\pm$ standard deviation -1.23 ± 0.31 ($\log_{10}$ -scaled decorrelation per ms). The audible popping sound synchronized with the treatment end point for 60% of the successfully controlled trials using the average-decorrelation criterion.

C. Comparison of Control Approaches

Ablation outcomes differed somewhat between the two control approaches, as illustrated in Figs. (7, 8, and 9). Successfully controlled trials employing the average-decorrelation criterion and variable-intensity sonication (section II.D) showed significantly greater lesion width ($p = 0.020$, Fig. 7(a)), statistically equivalent lesion depth ($p = 0.97$, Fig. 7(b)), significantly greater treatment time ($p = 1.63 \cdot 10^{-4}$, Fig. 7(c)), and significantly smaller ablation rate ($p = 0.011$, Fig. 7(d)) compared to successfully controlled trials employing the minimum-decorrelation criterion with constant-intensity sonication (section II.C).

For prediction of ablated area by echo decorrelation, the cutoff for minimum RMS error (1.42 cm^2) between predicted and measured areas over all trials ($N=70$) was found to be -2.6 ($\log_{10}$ -scaled decorrelation/ms). Fig. 8 shows scatter plots of ablated areas predicted by this optimum echo decorrelation cutoff for all treatment groups using both the minimum-decorrelation and average-decorrelation approaches. In the series of experiments employing the minimum-decorrelation criterion with constant-intensity sonication, absolute and normalized RMS errors for predicted areas were 0.94 cm^2 (30.3%) for successfully controlled trials, 1.69 cm^2 (62.0%) for 9-cycle uncontrolled trials, and 0.78 cm^2 (23.6%) for 18-cycle uncontrolled trials. In the series of experiments employing the average-decorrelation criterion with variable-intensity sonication, corresponding absolute and normalized RMS errors were 0.74 cm^2 (21.6%) for successfully controlled trials, 1.87 cm^2 (90.0%) for 9-cycle uncontrolled trials and 1.99 cm^2 (52.6%) for 18-cycle uncontrolled trials.

Post hoc analysis results for both series of controlled ablation experiments are shown in Fig. 9. For all trials controlled using the minimum-decorrelation criterion ($N=15$), Fig. 9(a) shows final $\min$ values from each experiment together with final avg values from *post hoc* analysis using the average-decorrelation feedback parameter and the corresponding $12 \text{ mm} \times 9 \text{ mm}$ control ROI. In the *post hoc* analysis, the average-decorrelation threshold of -1.576 was crossed in 11 of these 15 trials with average threshold-crossing time $81.3 \pm 6.7 \text{ s}$. Notably, the average threshold-crossing time for trials from the minimum-controlled group, subjected *post hoc* to the average-decorrelation criterion, was statistically equivalent to the treatment time for trials successfully controlled using the average-decorrelation criterion.

For all trials controlled using the average-decorrelation criterion ($N=13$), Fig. 9(b) shows final avg values from each experiment together with final $\min$ values from *post hoc* analysis using the minimum-decorrelation criterion and its corresponding $16 \text{ mm} \times 12 \text{ mm}$ control ROI. In the *post hoc* analysis, the minimum-decorrelation threshold of -3.20 was crossed in 8 of these 13 trials with average threshold-crossing time $111.7 \pm 4.6 \text{ s}$. Similar to

the minimum-decorrelation controlled trials, the average threshold-crossing time for trials from the average-decorrelation controlled group, subjected *post hoc* to the minimum-decorrelation criterion, was statistically equivalent to the treatment time for trials successfully controlled using the minimum-decorrelation criterion.

Both control approaches showed similar success in ablation of equivalent control ROIs. Successfully controlled trials using the minimum-decorrelation criterion achieved complete ablation of the 12 mm $\times$ 9 mm average-decorrelation control ROI in 7 of 11 cases, compared to 8 of 10 cases for trials successfully controlled using the average-decorrelation approach. Similarly, successfully controlled trials using the average-decorrelation criterion achieved complete ablation of the 16 mm $\times$ 12 mm minimum-decorrelation control ROI in 3 of 10 cases, compared to 3 of 11 cases for trials successfully controlled using the minimum-decorrelation approach.

IV. Discussion

In this study, the concept of controlling bulk thermal ablation using US echo decorrelation imaging feedback was demonstrated in *ex vivo* bovine liver using two feedback approaches. Successful control, defined as meeting the prespecified echo decorrelation feedback threshold, was achieved in $> 70\%$ of trials for either approach. Successfully controlled trials using either feedback approach resulted in higher ablation rates and better capability to predict local ablation, as judged by area under the ROC curve, than matching 9-cycle or 18-cycle uncontrolled groups. However, successfully controlled trials using either feedback approach did not provide improved consistency for the ablated tissue area; for either approach, ablated area variance for the controlled group was not significantly smaller than for either matching uncontrolled group. In either group, results of controlled ablation trials were similar to those for the matching 18-cycle group, both in terms of thermal lesion dimensions and capability to predict ablation; however, controlled ablation trials required significantly less treatment time, which could be considered an advantage of this control approach.

The proposed optimization method resulted in different ROI sizes and decorrelation thresholds for the two echo decorrelation feedback predictors. The optimum ROI selected for the minimum-decorrelation criterion was larger than that for the ROI-average criterion experiments (16 mm $\times$ 12 mm vs. 12 mm $\times$ 9 mm), while the corresponding decorrelation threshold was smaller (-3.20 vs. $-1.576 \log_{10}$ -decorrelation/ms). Nonetheless, retrospective comparison of the two control approaches showed that their control performance was very similar. For either series of controlled ablation experiments, the average treatment time for successfully controlled ablation nearly matched the threshold-crossing time for the other series when subjected *post hoc* to the same feedback approach used experimentally. Similarly, when assessing complete ablation of the same ROI, successful control by either approach resulted in nearly equal success rates. These results imply that the proposed optimization successfully set appropriate control criteria for both feedback approaches, such that meeting either stopping criterion had a nearly equivalent effect on ablation outcomes. In general, control thresholds optimized using this approach will increase with smaller control

ROI sizes, and will be larger when based on the average echo decorrelation, compared to the minimum echo decorrelation.

Successfully controlled trials for both feedback approaches showed better prediction capability for local ablation than 9-cycle or 18-cycle uncontrolled trials of the same ablation sequence reported here, as well as the uncontrolled *in vivo* bulk US ablation experiments ($N=10$, AUC=0.620 in liver, AUC=0.675 in VX2 tumor) reported by Fosnight et al. [8] using a constant-intensity sonication scheme (7-9 therapy cycles, 60-70.5% duty cycle, 50-63 W/cm² I_{SPT} , 5.0-5.4 MHz frequency). Successfully controlled trials using the average-decorrelation criterion showed ability to predict local ablation (AUC=0.871) statistically equivalent to trials controlled by the minimum-decorrelation criterion (AUC=0.862), consistent with the observation that either approach provided equivalent feedback on ablation progress.

Echo decorrelation imaging showed anomalous prediction performance for the 9-cycle uncontrolled group (AUC=0.327) using the average-decorrelation criterion with variable-intensity sonication. AUC values less than 0.5 correspond to negative prediction outcomes, i.e., for these experiments, higher echo decorrelation tended to predict the absence of thermal ablation. The probable reason for this anomalous result is that 9 cycles of sonication at 38.3 W/cm² caused heating insufficient to cause high decorrelation. previous analyses have shown that high decorrelation occurs most consistently for temperatures exceeding 80 °C [27]. In addition, prediction performance for this group was adversely affected by false-positive predictions due to substantial echo decorrelation out-side the treated region (Fig.5 (I-a,b)), believed to be associated with air-filled cavities in the *ex vivo* tissue [36].

Comparing ablation outcomes of the two control approaches, successfully controlled trials using the average-decorrelation criterion with variable-intensity sonication showed larger and more consistent coagulation area but also significantly longer treatment time, compared to successfully controlled trials using the minimum-decorrelation criterion with constant-intensity sonication (Fig. 7). Results of the retrospective study comparing *post hoc*-applied feedback criteria indicate that the different feedback approaches did not cause these differences in ablation outcomes. Therefore, the likely reason is the different sonication scheme used for each control approach. The larger observed ablation area for controlled ablation using the variable-intensity sonication scheme was primarily due to a significant increase in lesion width (along the azimuthal direction, parallel to the transducer surface), rather than in lesion depth as originally anticipated for the variable-intensity sonication sequence, possibly because the overall tissue heating rate was lower. Similarly, the shorter treatment time for controlled trials using the constant-intensity sonication scheme is likely due to the faster heating rate early in these trials, leading to earlier occurrence of high echo decorrelation.

Several studies [43], [52], [53] have investigated the relation between complications (e.g., bleeding, dissemination and tumor metastasis) arising from RFA treatment and the occurrence of audible popping sounds due to tissue vaporization, believed to cause significant mechanical damage to tissue. Methods employed to delay this vaporization have included monitoring tissue impedance [43], applying lower RF power (i.e., maximum 70 W)

[53] and injecting Sonazoid® microbubbles [52]. In the experiments reported here, audible popping sounds always coincided with large echo decorrelation values (maximum ensemble-averaged decorrelation $> 10^{-2}$ per ms) at the same cycle. These results suggest that control by echo decorrelation, e.g. using a lower threshold, could be useful to reduce or prevent tissue vaporization and the concomitant undesirable mechanical tissue damage.

Clinical translation of the proposed control approach requires further investigation. The control methods investigated were optimized here for bulk ultrasound ablation, but could also be optimized for controlling clinical thermal ablation techniques (e.g. RFA and MWA) with minor changes. Since bulk thermal ablation using RFA or MWA is inherently a 3D problem, 3D imaging and controlling methods are needed for better ablation assessment and control [13], [54]. The feasibility of 3D echo decorrelation imaging has been shown previously [26]. For ablation control using 3D echo decorrelation imaging, the target volume could be subdivided into multiple control ROIs, accounting for likely spatial variations in ablation rates caused by differences in local anatomy (e.g., local tissue type, large blood vessels, and tissue boundaries). Treatments would then continue until the average or minimum echo decorrelation within all control ROIs exceeds a prespecified control threshold. The optimum size, geometry, and number of ROIs as well as optimal control thresholds could be selected similarly to the approach employed here for unfocused ultrasound ablation, based on 3D echo decorrelation volumes acquired and archived during clinical RFA and MWA procedures. The same process could then be repeated for different thermal ablation techniques and tumor types. Treatment near vulnerable structures could potentially be performed safely by confining vulnerable areas to a safety ROI, ceasing treatment after a lower decorrelation threshold has been met within that ROI [36].

Compensation for motion and noise artifacts is also important for successful clinical translation of the control approach investigated here. Recently in offline processing, echo decorrelation artifacts due to tissue motion and electronic noise were successfully compensated by the method described in Hooi et al. [26] in the *in vivo* bulk US thermal ablation experiments [8] and have also been compensated using motion gating for *in vivo* RFA experiments [25]. For better control performance during future *in vivo* ablation experiments, motion and noise correction to echo decorrelation imaging [26] could be implemented in real time. In this approach, the cumulative ensemble-averaged echo decorrelation map from initial sham sonication cycles is utilized to compensate echo decorrelation maps computed during therapy cycles using a previously derived formula [8], [26]. For *in vivo* bulk US ablation, higher acoustic intensities will be needed to overcome the heat-sink effect due to blood perfusion. Further improved performance in the presence of tissue motion may be achievable by combining echo decorrelation imaging with real-time image fusion approaches employing automatic tracking of the ultrasound imaging probe position [23].

V. Conclusion

Two optimized echo decorrelation imaging feedback approaches were investigated for control of bulk US thermal ablation in *ex vivo* bovine liver. Feedback using either the minimum-decorrelation or average-decorrelation criteria, with constant-or variable-intensity

sonication respectively, resulted in greater ablation rate compared to matching uncontrolled trials. Either feedback criterion, when employing control thresholds and ROIs optimized by the same approach, provided equivalent information on ablation progress. Successfully controlled ablation trials using either approach also provided better prediction of local ablation than uncontrolled trials. These results indicate that echo decorrelation imaging feedback, using either minimum-decorrelation or average-decorrelation criteria, is feasible for control of bulk thermal ablation.

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Biography

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T. Douglas Mast (M'98) was born in St. Louis, MO, USA, in 1965. He received the B.A. degree in Physics and Mathematics from Goshen College, Goshen, IN, USA, in 1987, and the Ph.D. degree in Acoustics from Pennsylvania State University, State College, PA, USA, in 1993. He was a Postdoctoral Fellow with the Ultrasound Research Laboratory of the University of Rochester, NY, USA, until 1996. From 1996 to 2001, he was with the Applied Research Laboratory, Pennsylvania State University as a Research Associate and Assistant Professor of Acoustics. He was a Senior Electrical and Computer Engineer with Ethicon Endo-Surgery, Cincinnati, OH, USA, from 2001 to 2004. In 2004, he joined the University of Cincinnati, where he is currently Professor of Biomedical Engineering and leads the Biomedical Acoustics Laboratory. His research interests include ultrasound image guidance for minimally invasive therapy, cavitation detection and imaging, therapeutic ultrasound for cancer treatment and drug delivery, the simulation of ultrasound-tissue interaction, image-based biomechanics measurements, and inverse scattering. Dr. Mast is a Senior Member of the American Institute of Ultrasound in Medicine and a Fellow of the Acoustical Society of America.

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Fig. 1:

Experimental setup. (a) 64-element image-treat array aligned with top surface of *ex vivo* bovine liver. (b) Control geometry for bulk US thermal ablation. The control ROI, bounded by a yellow line, is superimposed on a hybrid echo decorrelation/B-mode image. (c) Feedback control algorithm flow chart. (d) Treatment timing diagram.

Fig. 2:

Optimization approach for control criteria. Segmented TTC-stained tissue sections of preliminary ablation trials were classified into (a) ablated-ROI and (b) unablated-ROI groups for ROI size selection. Sensitivity and specificity curves for the chosen ROIs were used to optimize Δ_{th} for (c) minimum-decorrelation ($N=30$) and (d) average-decorrelation ($N=86$) prediction of complete ROI ablation. The blue line represents the selected ablation control threshold for each approach.

Fig 3:

Representative histologic and US images for controlled and uncontrolled trails using the minimum-decorrelation feedback approach. Rows (I-III) represent 9-cycle uncontrolled, successfully controlled, and 18-cycle uncontrolled trails with segmentation of tissue boundaries and ablated regions. Red and green lines represent segmented tissue and ablation region boundaries, while white and dashed green lines indicate the segmented tissue and predicted ablation region boundaries in the hybrid echo decorrelation/B-mode images. Columns (a-c) represent trails with approximately minimum, average, and maximum measured lesion depth for each group.

Fig. 4: Statistical analysis of ablation results using the minimum-decorrelation feedback approach. (a) ROC curves for successfully controlled, 9-cycle uncontrolled, and 18-cycle uncontrolled groups (AUC: area under ROC curve). Means and standard errors are shown for (b) lesion width, (c) lesion depth, and (d) ablation rate. (** $p < 10^{-2}$ and *** $p < 10^{-3}$)

Fig. 5:

Representative histologic and US images for controlled and uncontrolled trials using the average-decorrelation feedback approach. Rows (I-III) represent 9-cycle, controlled, and 18-cycle trials with segmentation of tissue boundaries and ablated regions. Red and green lines represent segmented tissue and ablation region boundaries, while white and dashed green lines indicate the segmented tissue and predicted ablation region boundaries in the hybrid echo decorrelation/B-mode images. Columns (a-c) represent trials with approximately minimum, average, and maximum measured lesion depth of each group.

Fig. 6: Statistical analysis of results from ablation trials using the average-decorrelation feedback approach. (a) ROC curves for successfully controlled, 9-cycle uncontrolled, and 18-cycle uncontrolled groups. Means and standard errors are shown for (b) lesion width, (c) lesion depth, and (d) ablation rate. (e) Box plot of average echo decorrelation value inside the control ROI for trials with observed audible sound ($N=17$) and with no audible sound ($N=16$). (***) $p < 10^{-3}$

Fig. 7: Statistical comparison of ablation results for successfully controlled trials using the minimum-decorrelation and average-decorrelation feedback criteria. Means and standard errors are shown for (a) lesion width, (b) lesion depth, (c) treatment time and (d) ablation rate. (* $p < 0.05$ and *** $p < 10^{-3}$)

Fig. 8:

Comparison of predicted vs. measured ablation areas. Scatter plots are shown for (a) 9-cycle, (b) successfully controlled, and (c) 18-cycle groups using (I) minimum-decorrelation and (II) average-decorrelation control approaches.

Fig. 9:

Experimental and *post hoc* results for trials controlled by (a) minimum- decorrelation and (b) average-decorrelation criteria. Red, black and blue lines represent the experimental, *post hoc*, and threshold echo decorrelation values inside the region of interest, respectively.