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**Detection of Gaps between High-Intensity Focused Ultrasound (HIFU)-
Induced Lesions using Transient Axial Shear Strain Elastograms**

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Purpose: High-intensity focused ultrasound (HIFU) is becoming an effective and noninvasive treatment modality for cancer and solid tumors. In order to avoid the cancer relapse and guarantee the success of ablation, there should be no gaps left among all HIFU-generated lesions. However, there are few imaging approaches available for detecting the HIFU lesion gaps in real time during ablation.

Methods: Transient axial shear strain elastograms (ASSEs) were proposed and evaluated both numerically and experimentally to detect the lesion gaps immediately after the cessation of therapeutic HIFU exposure. Acoustic intensity and subsequent acoustic radiation force were first calculated by solving the nonlinear Khokhlov–Zabolotskaya–Kuznetsov (KZK) equation. Motion of being- and already-treated lesions during and after HIFU exposure was simulated using the transient dynamic analysis module of finite element method (FEM). The corresponding B-mode sonography of tissue-mimicking phantom with two HIFU lesions inside was simulated by FIELD II, and then axial strain elastograms (ASEs) under static compression and transient ASSEs were reconstructed. An ultrasound imaging probe was integrated with the HIFU transducer and used to obtain radio-frequency (RF) echo signals at high frame rate using plane wave imaging (PWI). The resulting strains were mapped using the correlation-based method and block search strategy.

Results: Acoustic radiation force from the therapeutic HIFU burst is sufficiently strong to produce significant displacement. As a result, large and highly localized axial shear strain appears in the gap zone between two HIFU-generated lesions and then disappears after sufficient HIFU ablation (no gap between them). Such capability of detecting the lesion gap is validated at the varied acoustic radiation force density, gap width, and the size of the lesion. In contrast, conventional ASEs using the static compression cannot distinguish whether a gap exists between

1 lesions. Static ASEs and transient ASSEs reconstructed using both high-speed photography and
2 sonography in the gel phantom show the same conclusion as that in the simulation. *Ex vivo* tissue
3 experiments further confirmed that the presence of large axial shear strain in the gap zone. The
4 ratios of axial shear strain in the porcine kidney and liver samples had statistical differences for
5 two HIFU-generated lesions without and with a gap ($p < 0.05$).

6 **Conclusions:** Large axial shear strain induced by the acoustic radiation force from therapeutic
7 HIFU burst only appears between two HIFU-generated lesions with a gap between them.
8 Transient ASSEs reconstructed immediately after the cession of HIFU exposure can easily,
9 reliably, and sensitively detect the gap between produced lesions, which would provide real-time
10 feedback to enhance the success of HIFU ablation.

11
12 **Key words** high-intensity focused ultrasound (HIFU), lesion gap, acoustic radiation force,
13 transient axial-shear strain elastograms (ASSEs), static axial strain elastograms
14 (ASEs), real-time monitoring, plane wave imaging

1. INTRODUCTION

Thermal ablation by high-intensity focused ultrasound (HIFU) shows great promise as a noninvasive cancer therapy. The tumors treated by HIFU in clinics include primary and metastatic liver cancer, malignant bone tumors, benign breast cancer, soft tissue sarcomas, kidney cancer, pancreatic cancer, abdominal and pelvic malignant tumors, uterine myoma, hepatic hemangioma and other solid tumors.¹ The treated tumor becomes coagulated at 1 month, partially fibrotic at 3 months and completely fibrotic at 6 months. The fibrous structure is gradually resorbed. In the early clinical trials of HIFU ablation in 10 Chinese hospitals, the survival rates of 6 months and 1 year of a total of 474 patients with liver cancer (including hepatocellular carcinoma and metastatic liver cancer) were 82.6% and 53.4%, respectively.² The survival rate of 153 patients with primary and metastatic malignant neoplasms was 85%.² Despite promising results in the survival rate and improved quality of life, local tumor recurrence after the ablation was also observed.³ In 7 of 9 patients with biopsy-proven localized prostate carcinoma (cT₁₋₂N₀M₀), a vital bilateral tumor was found at the dorsal side of the treated HIFU area.⁴ In the other studies of HIFU treatment on prostate cancer, biochemical relapses in 4 patients out of 25;⁵ 56% of 71 patients had evidence of prostate cancer progression at the 3-month follow-up;⁶ the actuarial disease recurrence rates of 140 patients at 5 and 7 yr were 33% and 41%, respectively.⁷ One of the reasons for cancer relapse may be the untreated gaps within the planned treatment area.² Ideally, all HIFU-induced lesions should cover the whole volume of cancer with certain margin (usually 1-2 cm from the diagnosed boundary) without any gaps or untreated regions. Therefore, accurate monitoring of volume and location of HIFU produced lesions in real time is a critical and preferable issue of improving the efficacy and success of

HIFU ablation as well as minimizing the complications. However, HIFU operators usually perform the ablation empirically despite great variations among patients and diseases.

Currently, there are several approaches applied to monitor HIFU treatment. Magnetic resonance imaging (MRI) can provide thermometry of the target during HIFU ablation as well as high spatial resolution, good soft tissue differentiation, and excellent correlation with pathologic results especially after the injection of contrast agent (e.g., the extent of tumor infiltration and stage as well as the critical surrounding structures) in the evaluation of ablation outcome. However, the exclusion of patients with metal implants, pregnant women, children or large patients, low temporal resolution for the anatomic images, extensive labor, non-portability, and high operation cost may limit its application in real-time monitoring and efficacy evaluation.⁸

Integration of ultrasound (US) imaging probe with the HIFU transducer could assess the acoustic condition in the propagation pathway of HIFU burst and monitor the soft tissue in real time. Radio frequency (RF) data of sonography could be analyzed for real-time monitoring of HIFU ablation, such as by using the manifold learning method and entropy of RF time series of backscattered signals.⁹⁻¹¹

Because of the much lower acoustic impedance of the bubbles in comparison to that of soft tissue, a hyperechoic area will appear in the HIFU focal region in the B-mode sonography. However, the presence of bubble may not relate well with the shape and location of HIFU lesions, and lesions can even be formed without the hyperechoes.¹² The change in blood flow patterns in the three-dimensional contrast-enhanced power Doppler ultrasound (3D-CE-PDU) after therapy can be used to locate and quantify the extent of affected tissue in a good correlation with the histopathology of the specimen (Pearson correlation $r = 0.94$).⁴ However, the outer ring of the macroscopic hemorrhagic necrosis was found 1-2 mm beyond the

border of actually dead tissue, and continuous injection of contrast agent (microbubbles) during HIFU therapy is unfeasible.

Protein denaturation and coagulation of soft tissue result in a significant increase of its stiffness so that elastography was used to visualize and characterize the formed lesions. Magnetic resonance elastography (MRE) could quantitatively assess the mechanical stiffness of tissue by examining the propagation of mechanical waves through it.¹³ In HIFU ablation of prostate cancer *in vivo*, uniform compression was applied using a balloon while a sector image was acquired using a transrectal US probe. Axial strain elastograms (ASEs) was constructed from the gradient of the displacements obtained from the ultrasonic RF signals using the cross-correlation technique. But it suffers the decorrelation effects because of low signal-to-noise ratio (SNR) and out-of-plane motion induced by respiration.¹⁴ Another type of elastography in the investigation is axial-shear strain elastograms (ASSE) where the axial-shear strain caused by quasi-static compression as for ASE is determined and constructed. It has been introduced to visualize the boundaries of breast tumor and HIFU lesions.¹⁵⁻¹⁸ Although the iso-intensity contour of both the ASE and ASSE can evaluate the area of the enclosed single lesion in canine livers cast in a gelatin block, ASSE is less sensitive to iso-intensity threshold selection (from -2 dB to -6 dB). In addition, ASSE enables high-contrast visualization of a small gap between HIFU lesions.¹⁷ The feasibility of real-time monitoring during HIFU treatment was also explored. ASSEs can not only improve lesion visualization and size measurement of a single lesion but also identify untreated gaps between adjacent lesions with high contrast at certain conditions.¹⁹ However, the opposite polarity axial-shear strain at the boundary of the stiff regions will cancel with each other when two HIFU lesions are aligned exactly vertically with an untreated region between them. A gap as thin as 0.1 mm is detectable in the simulation when the axial-shear strain with the same

polarity reinforces each other from two lesions vertically offset in an appropriate distance or the gap between two adjacent lesions should be at a non-normal orientation with respect to the axis of compression.^{16, 17} Realization of this requisite condition in practice is a problem, and the effect of the orientation angle of a gap on the contrast is under the investigation. Furthermore, quasi-static compression of ultrasound imaging probe requires a different acoustic window from that for HIFU exposure in order to avoid damage to the probe and influence to the propagation of HIFU bursts. However, the available acoustic window may not always be available and sufficient in clinical HIFU therapy.

The compression of soft tissue is also possible in a remote way. The generation of acoustic radiation force (ARF) by the momentum transferred to the tissue due to the acoustic absorption could cause the tissue displacement.²⁰ Acoustic radiation force impulse (ARFI) imaging can monitor lesion formation and the resulting tissue stiffening in *ex vivo* samples that correspond to discolored regions in gross pathology.²¹ The acoustic intensity of HIFU burst itself is much higher than that of ARFI from the imaging probe. Such a single HIFU burst as long as only 5 ms can produce detectable motion for relative stiffness changes of HIFU lesion but well below the thermal dose of lesion formation.²² Its use for transient strain imaging, the instantaneous strain immediately following the cessation of ARF, shows a superior contrast-transfer-efficiency and permits the sensing of variations in tissue elastic properties at depth within homogeneous gels and within stiff inclusions that is difficult with conventional static elastography, due to greater independence from boundary conditions.²³ Amplitude-modulated (AM) harmonic motion imaging (HMI) for the focused ultrasound (HMIFU), utilizing an oscillatory ARF, could detect the mechanical response of tissue during thermal ablation based on the variation of the HMI displacements.²⁴⁻²⁶ The disturbance created by ARF also induces the

1 propagation of a shear wave, travelling sideways through the tissue. Both shear modulus and
2 viscosity of soft tissues can be quantitatively mapped by shear wave elastography (SWE).²⁷⁻²⁹
3 However, a very high frame rate of RF data acquisition ($> 10,000$ frames/s) is required **in order**
4 **to accurately measure the speed of a** shear wave. Overall, there are few reports of detecting the
5 gap between HIFU lesions **using these lesion monitoring modalities**.

6 In this study, a novel transient ASSE was developed using the remote palpation from the
7 therapeutic HIFU burst itself **instead of quasi-static compression in the conventional ASSE**. The
8 focusing capability of HIFU beams causes the localized motion of currently being produced
9 lesion, but much less for the adjacent lesion, from which the instantaneous axial-shear strain can
10 be determined to visualize the gap between HIFU lesions. Both numerical and experimental
11 **investigations were** carried out to evaluate **the** feasibility of this approach. The distribution of
12 ARF generated by the HIFU burst was calculated, and B-mode sonography, static ASEs, and
13 transient ASSEs of two lesions with and without a gap between two HIFU-generated lesions
14 were simulated. The effects of gap width, lesion size, and the magnitude of ARF density on the
15 gap detection ability were investigated. Experiment in the gel phantom and *ex vivo* tissue
16 samples confirmed that the reconstructed transient ASSEs immediately after the cessation of
17 HIFU exposure could sensitively and reliably detect the presence of a gap between two HIFU-
18 generated lesions, which may provide an easy, reliable, and sensitive guidance for HIFU ablation
19 in order to enhance its efficacy and success.

2. MATERIALS AND METHODS

2.A. Numerical simulation

Figure 1. (a) Schematic diagram of the acoustic radiation force applied to the lesion inside the phantom in the dimension of 4 cm x 4 cm, (b) the distribution of meshes used in the finite

element method (FEM) simulation, and (c) the distribution of calculated acoustic radiation force density in kN/m^3 from the HIFU transducer at the acoustic power of 56 W.

The model of lesion motion inside the phantom ($4 \text{ cm} \times 4 \text{ cm}$ in size) is shown in Fig. 1a. Two elliptical lesions in the size from $9 \text{ mm} \times 3 \text{ mm}$ to $15 \text{ mm} \times 5 \text{ mm}$ adjacent to each other are aligned exactly vertical with the gap width from 1.5 mm to 0 mm (no lesion gap); the right one is already-treated while the left one is being-treated by HIFU exposure. There are two types of forces applied to the sample in the simulation. The first is the uniform static compression applied to the top of the sample while the other is the ARF produced by HIFU burst during ablation. The acoustic field of an annular single-element concave HIFU transducer (H-172, outer diameter = 100 mm , inner diameter = 78 mm , $F = 125 \text{ mm}$, Sonic Concept, Bothell, WA) at the excitation frequency of 2.2 MHz was calculated using HIFU simulator (Food and Drug Administration, Silver Spring, MD) in the Matlab (Mathworks, Natick, MA) by solving the nonlinear Khokhlov–Zabolotskaya–Kuznetsov (KZK) equation in the frequency-domain schemes.³⁰ The solution of KZK equation is represented in the form of a Fourier series expansion,

$$p(z, r, t) = \sum_{n=0}^N C_n(z, r) \exp(-in\omega_0 t) \quad (1)$$

where $\omega_0 = 2\pi f_0$ is the fundamental frequency of the HIFU pulses, C_n is the complex amplitude of the n th harmonic, and N is the maximum number of harmonics included and set as 50 for the following calculation. The acoustic intensity is derived as

$$I(z, r) = \frac{1}{Z} \int_0^T p^2(z, r, t) dt = \frac{1}{2Z} \sum_{n=0}^N C_n^2(z, r) \quad (2)$$

The magnitude of ARF in the sample is given by²⁰

$$F_z = \frac{2\alpha I}{c} = \frac{1}{Zc} \sum_{n=0}^N C_n^2(z, r) \cdot \alpha_0 n f_0 \quad (3)$$

where $\alpha(f) = \alpha_0 f$, $\alpha_0 = 0.5$ dB/cm/MHz is the acoustic attenuation coefficient, Z is the acoustic impedance, and $c = 1550$ m/s is the speed of sound in the medium. The major axis of the elliptical lesion is parallel to the vertical axis and the HIFU transducer axis. Both the phantom and lesion are considered as homogeneous and elastic media. The tissue-mimicking phantom is placed 6 cm away from the transducer in the degassed water. The Young's modulus of lesions is 6 kPa which is 5 times as that of surrounding medium.³¹

The dynamic vibration of lesions and phantom during and after HIFU exposure was simulated using the transient dynamic analysis module of finite element method (FEM) software (ANSYS, Canonsburg, PA). The phantom is assumed linear, incompressible medium with the Poisson's ratio of 0.495. The Rayleigh model was used to describe the dynamic process,

$$[M] \frac{d^2\{u\}}{dt^2} + [C] \frac{d\{u\}}{dt} + [K]\{u\} = \{R\} \quad (4)$$

where $\{u\}$ is the displacement vector, $[M]$ is the mass matrix, $[C]$ is the damping matrix, $[K]$ is the elasticity matrix, and $\{R\}$ is the residual force vector. $[C]$ is expressed as

$$[C] = \alpha[M] + \beta[K] \quad (5)$$

where α and β are Rayleigh damping parameters and set as 6.22 and 0.01, respectively.³²

Triangular meshes were adapted to discretize the computational zone, and there are 23,000 elements and 12,000 nodes in total with much smaller elements inside the lesion (see Fig. 1b).

The boundary conditions of the bottom and other sides of the phantom are set as fixed and slip boundaries, respectively.

2.B. ASE and ASSE reconstruction

Sonography of tissue-mimicking phantom with 2 HIFU lesions inside was simulated by FIELD II (<http://field-ii.dk/>). 10,000 scatterers were assumed within the phantom with a Gaussian distribution of the reflecting ability of acoustic waves along the path. A diagnostic ultrasound transducer with 192 elements in total (width of 5 mm and kerf of 0.05 mm) and 64 active elements was used in the simulation, and the apodization method was applied to eliminate the side lobes. The excitation burst was 2-cycle sinusoidal wave at the driving frequency of 5 MHz. The sampling frequency of sonography was 40 MHz. The total received response in the pulse-echo mode for reconstructing the sonography is determined by convolving the transducer excitation function with the spatial impulse response of the emitting aperture and the receiving aperture.

The speckle motion under small static compression was calculated by FEM.³³ A coarse-to-fine 2D block matching method was adapted to determine the displacement.³⁴ Every rectangular kernel selected from pre-compression RF data was compared with those within the searching region in the post-compression frame. The kernel size was set as 11 axial samples by 9 RF lines, and the sum-squared difference (SSD) calculation equation is as follows,

$$SSD = \sum_{i=-4}^4 \sum_{j=-5}^5 [r_1(I+i, J+j) - r_2(I+i+u, J+j+v)]^2 \quad (5)$$

where r_1 and r_2 are pre- and post-compression RF data; I and J are axial and lateral coordinate; u and v are axial and lateral searching length. In order to reduce the estimation errors and increase the computational efficiency, a certain strategy of error detection and correction was applied every a certain number of rows.³⁵ Briefly, a segmentation method was used to the estimated displacement for each row from left to right if the displacement difference between adjacent

positions is larger than 2 samples. Then **two** non-adjacent groups were merged if the difference between the nearest end points of them is smaller than a certain threshold (e.g., 3 samples). Finally, the group with the largest number of displacement estimates was assumed to be the correct one. The remaining displacement values of the wrong groups were estimated using those of the correct group by linear interpolation. So the size of the searching region could be reduced, but is enough to cover the exact corresponding block based on the previously estimated displacement.

The ASE was reconstructed by estimating the axial strain,

$$\varepsilon_{axial} = \left(\frac{\partial u_y}{\partial y} \right) \quad (7)$$

The ASSE was reconstructed by estimating the axial shear strain based on the staggered-strain algorithm,¹⁶

$$\varepsilon_{axial-shear} = \left(\frac{\partial u_y}{\partial x} \right) \quad (8)$$

where u_x and u_y are the lateral and axial displacement, respectively, and x is the lateral direction. Axial-shear strains are usually generated at the boundaries of a firmly bonded inclusion, thus producing high contrast to visualize the boundary directly.³⁴

2.C. Experimental setup

1

(b)

2

3 Figure 2. (a) Schematic diagram and (b) photo of the experimental setup.

The HIFU transducer was driven by the electrical signal generated by a function generator (AF3021B, Tektronics, Beaverton, OR) and amplified by a power amplifier (BT1000-AlphaA, Tomco Technologies, Adelaide, Australia). An imaging probe (L14-5/60W, the central frequency of 14 MHz with a bandwidth of 60%, BK Ultrasound, Peabody, MA) was integrated with the HIFU transducer and aligned coaxially and confocally. Both the HIFU transducer and the phantom were immersed in the degassed and deionized water ($O_2 < 4$ mg/L, $T = 25^\circ\text{C}$, measured by DO700, Extech Instrument, Waltham, MA) in a Lucite tank ($L \times W \times H = 50 \text{ cm} \times 35 \text{ cm} \times 25 \text{ cm}$). The integrated transducers were mounted on a 3-D stepper motor system (BiSlide, Bloomfield, Velmex, NY). An acoustic absorber was put at the bottom of testing samples to minimize the ultrasound reflection. The experimental setup is shown in Fig. 2. In order to generate uniform static compression on the testing samples, the imaging probe was connected to the 3D stepper motor system and applied to the top of samples. Ultrasonic RF data were acquired with an ultrasound research platform (Sonix-500 RP, BK Ultrasound) at the sampling frequency of about 40 MHz. A LabView program (National Instruments, Austin, TX) was written to control the HIFU pulse delivery, signal synchronization, and RF data acquisition.

2.D. Gel phantom and *ex vivo* sample

The optically transparent polyacrylamide gel with 10% of bovine serum albumin (BSA) which becomes denatured and opaque at temperatures over $60\text{-}65^\circ\text{C}$ was prepared to evaluate the HIFU-induced lesion.³¹ Briefly, the liquid mixture of polyacrylamide, BSA, and the 5% Tris-Buffer was degassed for about 1 h in a desiccant chamber (420100000, Scienceware, Pequannock, NJ) by a vacuum pump (VTE8, Thomas, Sheboygan, WI) at a pressure of 150 mbars, then the degassed mixture was poured into a custom mold ($L \times W \times H = 5 \text{ cm} \times 5 \text{ cm} \times 4 \text{ cm}$) made of clear acrylic sheet (Ying Kwang Acrylics Trading, Singapore). The polymerization

was then finalized by the addition of 10% (w/v) ammonium persulfate solution (APS, Sigma-Aldrich, Singapore) and N,N,N',N'-tetra-methylethylenediamine (TEMED, Sigma-Aldrich) in 5 min. The concentrations of tris-buffer and polyacrylamide are a little lower than the protocol used in most HIFU phantom³¹ while the concentration of BSA is higher in order to increase the stiffness ratio of the lesion to the surrounding medium. The polyacrylamide gel phantom was embedded in another semi-transparent gelatin phantom (powder to water ratio of 1:10 for solution) which did not produce many speckles in the sonography.

Fresh porcine kidney and liver samples were purchased from a local slaughterhouse (Primary Industries Pte Ltd, Singapore) with the approval of Agri-Food & Veterinary Authority, Singapore. Samples were immersed in phosphate-buffered saline (PBS) solution and degassed in a vacuum oven for at least 30 min and used for the experiment within 4 h of harvest. Tissue samples were fixed in the gelatin phantom and put into a custom-designed holder. After the experiment, the samples were cut to record the lesions using a digital camera (PowerShot SX230 HS, Canon, Tokyo, Japan). The boundary of the produced lesions was determined by the edge detection in digital image processing software (ImageJ, National Institute of Health, Bethesda, MD), and the gap between lesions was determined quantitatively after calibration using a ruler.

2.E. Tracking particle motion

The motion of an array of markers in the gel phantom was recorded using a high-speed camera (S-PRI plus, AOS Technologies AG, Dättwil, Switzerland) working at 1,000 frames per second in a resolution of 640×480 pixels. An optical lens (focal length of 12.5 – 53 mm, *f*/1.8D, Nikon, Tokyo, Japan) and a set of the close-up lens (Nikon) were mounted on the camera to achieve an appropriately magnified view. The camera was triggered by a transistor-transistor

logic (TTL) pulse from a digital delay generator (DG535, Stanford Research Systems, Sunnyvale, CA) to synchronize the photography with HIFU exposure, and the recording started 10 ms before the delivery of HIFU pulses. Because of the limited memory of the camera, only one second of HIFU exposure was recorded. A 1000 W white light (Model H10, Hi-Tech Electronics, Singapore) was used as the illumination for the photography. The individual frame could be extracted from the captured videos using software (AOS imaging Studio V3, AOS Technologies AG) companioned with the high-speed camera.

Plane wave imaging (PWI), where a plane wave is formed and excited from all the elements of imaging probe,³⁶ was used to monitor the transient response of speckles at a high frame rate (theoretically up to 15,000 Hz for a 5-cm imaging depth³⁷). Diffraction hyperbola that presents the inhomogeneous point spread function for PWI is produced from scatterer as the receiving RF data by all the elements simultaneously. In the reconstruction of sonography, all the hyperbolas should be migrated back for coalescence into their apexes. In the beamforming of plane wave echo RFs in a high image quality, the Stolt migration method in the frequency-wavenumber (f - k) domain based on the exploding reflector model³⁸ was carried out because of its better contrast-noise ratio and lateral resolution than conventional delay-and-sum (DAS) and Fourier-based methods.³⁹⁻⁴¹ Compound f - k migration images with a small number of steering angles (0° , 0.98° , 1.88° , and 2.87°) are of quality similar to those obtained with a state-of-art dynamic focusing mode.

2.F. Data processing

All ultrasonic RF data were acquired and saved as binary files. Then they were transferred to a PC (AMD QC-4000 1.3-GHz CPU, 4 GB RAM, Windows 8.1) to process and generate static ASEs and transient ASSEs offline. B-mode sonography was first produced by the

1 Hilbert transform and log-compression of the RF echo frame in the Matlab. The ASEs were
2 reconstructed using the corresponding sonograms before and after the static compression. To
3 minimize the computation load, the transient ASSEs were computed and shown only over the
4 restricted regions of interest (ROI) containing the HIFU-induced lesions in the size of 1.2 cm ×
5 1.2 cm in the gel phantom and 1-1.5 cm × 1.5 cm in the tissue, respectively. In static ASEs
6 overlaid with transient ASSEs, the axial shear strain was only retained if its absolute value is
7 higher than 0.015 and 0.15 in the simulation and experiment, respectively.

8
9

1 **3. RESULTS**

2 **3.A. Dynamic motion of lesion**

3

Figure 3. (a) Dynamic distribution of axial shear strain in the phantom produced by 0.1 s-HIFU exposure (see animation file of Dynamic Lesions Motion.gif in the supplementary material) and (b) the temporal change of the displacement of 4 reference points around two lesions in the simulation.

The distribution of simulated ARF from the single-element concave HIFU transducer with the initial acoustic pressure of 0.165 MPa at the surface of the transducer or at the acoustic power output of 56 W is shown in Fig. 1c. Its -6 dB size is 1.8 mm × 13.4 mm (lateral×axial) similar to that of acoustic pressure. HIFU focus was applied to an elliptic HIFU lesion (being-treated) in the size of 15 mm × 5 mm adjacent to another identical lesion (already-treated) aligned exactly vertical with the gap width of 1 mm. Simulated transient ASSEs during and after the termination of 0.1 s-HIFU exposure are shown in Fig. 3a. As the ARF is proportional to the HIFU exposure time, the displacement of 4 reference points initially in the same vertical position (center of being-treated lesion, right boundary of being-treated lesion, left boundary of already-treated lesion, and center of already-treated lesion) increases almost linearly to the exposure time

1 (see Fig. 3b). Afterward, the displacement decreases exponentially. It is found that the center of
2 the currently being-treated lesion (point 1) has much larger displacement than the other 3
3 reference points. As a result, the localized and significant axial shear strain could be produced in
4 the gap region during HIFU exposure.

Figure 4. The (a) B-mode sonography, (b) axial strain elastogram (ASE) of two lesions in the gel phantom under static compression, transient axial shear strain elastogram (ASSE) of two lesions in the gel phantom (c) with and (d) without a 1-mm gap between them, and corresponding ASE (in gray) overlaid with ASSE (in color) in (e) and (f).

The simulated sonography, static ASE, and transient ASSE of the gel phantom are shown in Fig. 4. Because of little difference of acoustic impedances and backscattering ability between lesions and surrounding soft medium and irrelevance of the stiffness to the amplitude of ultrasonic echoes, it's hard to distinguish the presence of lesions in the B-mode sonography.¹⁹ Although the boundary of two elliptic HIFU lesions can be clearly figured out in the ASE in a high contrast by static compression of 2 mm, it is challenging to determine the presence of a gap between lesions because the lesions can support most of the static compression in the vertical direction and the gap region has relatively small axial strain. In comparison, the reconstructed transient ASSE using the remote palpation of 0.1 s-HIFU exposure could clearly illustrate the very high axial shear strain (in red) in the gap region and significantly decreased value if there is no lesion gap, which suggests the high possibility of the gap detection by such remote ARF palpation using therapeutic HIFU pulses.

1 3.B. Numerical evaluation of gap detection

2 Figure 5. Comparison of axial shear strain distribution with the ongoing of HIFU exposure
 3 to gradually increase the size of the being-treated lesion (left one) from 6 mm $\times$ 2 mm to 15 mm

× 5 mm and decrease the gap width (GW) with respect to the already-treated lesion (right one in the size of 15 mm × 5 mm) (a-e) from 1.5 mm to 0 mm, and (f) comparison of the axial shear strain across the lesion centers.

Performance of gap detection by the remote ARF palpation and transient ASSE was further evaluated numerically. With the ongoing of HIFU exposure, the produced lesion is assumed to gradually grow from the size of 6 mm × 2 mm to 15 mm × 5 mm with the corresponding decrease of lesion gap width from 1.5 mm to 0 mm with respect to the already-treated lesion in the size of 15 mm × 5 mm. The distribution of axial shear strain through the centers of these two lesions is shown in Fig. 5. It is found that although the axial shear strain on the right of already-treated lesion slightly decreases by 7% from 0.014 to 0.013 with the decrease of lesion gap width, those in the gap region and on the left of being-treated lesion have much more significant changes, decrease in 1.9 fold from 0.025 to 0.013 and in 1.4 fold from -0.024 to -0.018, respectively. It is noted that the axial shear strain at the lateral position of 0 mm (center of being-treated lesion) is almost constant.

Figure. 6 The axial shear strain across the lesion centers (a) at the acoustic radiation force density from 290.4 kN/m^3 to 203.3 kN/m^3 for two lesions in the size of $12 \text{ mm} \times 4 \text{ mm}$ with and without a gap of 0.5 mm , (c) at the acoustic radiation force density of 290.4 kN/m^3 for two lesions in the size of $12 \text{ mm} \times 4 \text{ mm}$ with the gap width (GW) from 1.2 mm to 0 mm , (e) at the acoustic radiation force density of 290.4 kN/m^3 for two lesions in the size from $15 \text{ mm} \times 5 \text{ mm}$ to $9 \text{ mm} \times 3 \text{ mm}$ with and without a gap of 0.8 mm , and comparison of axial shear strain ratio (b) at the acoustic radiation force density from 290.4 kN/m^3 to 203.3 kN/m^3 for two lesions in the size of $15 \text{ mm} \times 5 \text{ mm}$ with and without a gap of 1.5 mm and in the size of $12 \text{ mm} \times 4 \text{ mm}$ with and without a gap of 0.5 mm , (d) at the acoustic radiation force density of 290.4 kN/m^3 for two lesions in the size of $15 \text{ mm} \times 5 \text{ mm}$ and $12 \text{ mm} \times 4 \text{ mm}$ with the gap width from 1.2 mm to 0

mm, (f) at the acoustic radiation force density of 290.4 kN/m^3 for two lesions in the size from $15 \text{ mm} \times 5 \text{ mm}$ to $9 \text{ mm} \times 3 \text{ mm}$ with and without a gap of 1.1 mm and 0.8 mm .

Furthermore, the dependence of the ability and sensitivity of lesion gap detection on the HIFU operation parameters and lesion characteristics was investigated (see Fig. 6). Here the ratio of axial shear strain at the middle of these two lesions (ASS_B) to that at the left boundary of being-treated lesion (ASS_A see Fig. 4b) was used to discern the presence of the lesion gap at all testing conditions.

$$ASS \text{ ratio} = \left| \frac{ASS_B}{ASS_A} \right| \quad (9)$$

Firstly, the effect of the ARF density (from 203.3 kN/m^3 to 290.4 kN/m^3) on the gap detection was evaluated for two identical lesions in the size of $15 \text{ mm} \times 5 \text{ mm}$ and $12 \text{ mm} \times 4 \text{ mm}$. As expected, the axial shear strain in the lesion ROI with and without the gap increases with the ARF density. Secondly, two identical HIFU lesions (in the size of $15 \text{ mm} \times 5 \text{ mm}$ and $12 \text{ mm} \times 4 \text{ mm}$) with the various gap width between them from 1.2 mm to 0 mm (no gap) was calculated with response to the ARF density of 290.4 kN/m^3 . The axial shear strain in the gap region decreases with the gap width. Thirdly, the axial shear strain around two identical HIFU lesions in the size from $15 \text{ mm} \times 5 \text{ mm}$ to $9 \text{ mm} \times 3 \text{ mm}$ with the gap width of 1.1 mm , 0.8 mm , and 0 mm at the ARF density of 290.4 kN/m^3 was simulated. Axial shear strain ratio increases with the lesion size. Altogether, it is found that the threshold of 0.75 in axial shear strain ratio can be used to discern the lesion gap in all testing conditions. The proposed transient ASSE using the remote HIFU palpation can detect the lesion gap as small as 0.3 mm .

3.C. Phantom experiment

Figure 7. Photos of phantoms with two HIFU-produced lesions (a) without and (b) with a 2 mm-gap between them. The interval distance of an array of tiny markers is about 2 mm.

Because the phantom is transparent and homogeneous without trackable particles inside, array of small lesions (12×12) in the size of about 1 mm in diameter at the interval distance of about 2 mm were produced at the low HIFU energy (peak-to-peak voltage of 230 mV from the function generator for 0.3 s) as markers for photography. In comparison, high HIFU energy (peak-to-peak voltage of 260 mV from the function generator for 10 s) was used to produce two lesions in the size of about $2 \text{ mm} \times 6\text{--}8 \text{ mm}$ (lateral $\times$ axial) with and without a gap of about 2 mm (see Fig. 7). Then the motion of that array of markers in the transparent polyacrylamide gel phantom by 0.1s-HIFU exposure was recorded by high-speed photography, from which transient ASSE was reconstructed and then overlaid with ASE using the static compression (see Fig. 8). It is found that 2 adjacent HIFU lesions almost move together under HIFU exposure when there is no gap between them. In contrast, the being-treated lesion has a much larger displacement than the already-treated one when a 2 mm-gap exists between them. Therefore, a high axial shear stress region appears in the gap region. Although lesion boundaries in the static ASEs without

- 1 and with a gap seem a little different, it's difficult to determine whether there is a gap between
- 2 lesions.

Figure 9. Comparison of two HIFU-produced lesions shown by white arrow without (top row) and with a 2 mm-gap (bottom row) in the gel phantom in high-speed sonography (a) immediately after the cessation of HIFU exposure and (b) when lesions come back to their initial positions, scale presenting 2 mm (see the animation file of Motion by Photography-Phantom.gif in the supplementary material), (c) static ASE in grey, (d) transient ASSE in color, and (e) static ASE overlaid with transient ASSE, and (f) lateral distribution of axial shear strain across the center of two HIFU lesions.

The proposed approach was further evaluated using the sonographically reconstructed transient ASSEs (see Fig. 9). Although the boundary of lesions is not clear in the B-mode sonography using PWI, the lesion displacement after the termination of 0.1 s-HIFU exposure could be measured and its characteristics of motion seem similar to those in the high-speed photography: two lesions without a gap moving together while the being-treated lesion having larger displacement than the already-treated one with a gap between them. A significant axial shear strain presents in the gap region (0.26 vs. 0.01 for the case without a gap) although the

1 shape of transient ASSE derived sonographically is slightly different from that obtained
2 photographically, which is due to the discrepancies in the distribution of speckles for tracking
3 their displacement.

4 **3.D. *Ex vivo* experiment**

1 Figure 10. Comparison of two HIFU-produced lesion without (left column) and with a gap
2 (right column) (a) in the *ex vivo* porcine kidney samples, (b) static ASE in grey, (c) transient
3 ASSE in color, and (d) static ASE overlaid with transient ASSE and contour of lesion boundary
4 in the histology.

5

Figure 11. Comparison of two HIFU-produced lesion without (left column) and with a gap (right column) (a) in the *ex vivo* porcine liver samples, (b) static ASE in grey, (c) transient ASSE in color, and (d) static ASE overlaid with transient ASSE.

Two lesions in the size of about 2–3 mm × 9–14 mm (lateral×axial, larger lesion size than those in the gel phantom is due to the higher acoustic attenuation of tissue) with and without a gap of about 1.5 mm were produced in the porcine kidney and liver samples. Sonographically reconstructed transient ASSE by the remote ARF palpation using the 0.1 s-HIFU burst itself is similar to that in the gel phantom but without the use of an array of markers. Several observations are found here (see Figs. 10 and 11). Firstly, the boundaries of lesions in the histology do not fit well with that of high stiffness region in the static ASEs. Secondly, the low axial strain in the gap region is similar to that inside the HIFU-induced lesion region so that detecting the lesion gap in the ASE using the static compression may be impossible. Finally, large axial shear strain presents in the gap region between two HIFU lesions as in the gel phantom studies. Experiments using porcine liver samples demonstrated the similar performance as those porcine kidney samples (see Fig. 11) that only large axial shear strain exists in the gap zone between two HIFU-generated lesions by the ARF during therapeutic HIFU exposure.

However, the variations in the shapes and sizes of HIFU-generated lesions in the liver are larger, which may be due to the more inhomogeneities associated with its hypervascular structure. So a larger number of samples ($n = 9$) were used.

Figure 12. Comparison of axial shear strain (ASS) ratios of *ex vivo* porcine kidney and liver samples without and with a gap between two HIFU-produced lesions.

ASS ratios of all *ex vivo* experiments ($n = 4$ and 9 in each kidney and liver groups, respectively, without and with a gap) are summarized and shown in Fig. 12. It is found that there are significant differences in ASS ratios between them ($p < 0.05$). The sufficiently treated lesions (without a gap) usually have ASS ratios less than 0.5 whereas the insufficiently treated ones (with a gap) have large ASS ratio, > 0.75 , the threshold used in discerning the lesion gap in the simulation. The discrepancy may be due to the higher Young's modulus of soft tissues (tissue elasticity) than that of gel phantom. Although the small displacement is produced for the medium

- 1 with the high Young's modulus, high contrast in the axial shear strain will result in more easily
- 2 discerning the presence of a lesion gap.
- 3

4. DISCUSSION

The minimization of cancer relapse after HIFU treatment is highly dependent on the complete coverage of lesions throughout the tumor/cancer volume without the presence of an untreated region or lesion gap. The detection of lesion gap is critical in clinical HIFU ablation, but there are few effective and possible solutions. Although observable contrast appears in the ASSEs in the gap zone between two surrounding lesions disposed at an angle with respect to the axis of static compression, such realistic condition may not be always possible in practice. When two lesions are aligned exactly perpendicular to the compression, the gap region doesn't shear, which means no axial shear strain. Mechanical motion of the ultrasound diagnostic probe attached to the skin of the patient to perform static ASEs or ASSEs needs to interrupt HIFU ablation. Although the imaging probe may be aligned at the different orientation from the axis of the HIFU transducer, it is not often applicable due to the limited acoustic windows required for both HIFU and diagnostic bursts except for a few targets, such as the breast. However, static ASE usually over-estimates the size of a single lesion due to a strain gradient that manifests about the interface of the stiff lesion and surrounding soft tissue.^{42, 43} Using the acoustic radiation force from the therapeutic HIFU pulses themselves during the treatment rather than the conventionally mechanical compression provides the possibility of real-time monitoring without interrupting the ablation procedure and moving the imaging probe. This method can employ a spatially localized force impulse at the low driving frequencies, outside the frequency range of the ultrasound imaging probe desired for the high resolution. Although the quantitative evaluation of ROI using the remote palpation from the acoustic radiation force is challenging because the produced axial strain depends on both the stiffness of the medium and the distribution of stress which are both difficult to measure *in vivo* due to the tissue inhomogeneity,

1 qualitative information of axial shear strain is sufficient in **determining** the presence of gaps
2 between HIFU lesions. The high-contrast visualization of these gaps in our transient ASSEs,
3 both numerically and experimentally, may help in guiding clinical HIFU treatment by providing
4 real-time, easy, reliable, and sensitive feedback. The underlying mechanism is that the hard
5 lesions are too hard to distort and they block the continuity of the axial shear strain as that in the
6 normal soft tissue. Note that axial strain and axial shear strain can be reduced and enhanced by
7 the gap region between lesions, respectively, **as shown in Fig. 4. Because of the elevated**
8 **interstitial fluid pressure (IFP, 5-30 mmHg) in many malignant tumors, their tissue elasticities are**
9 **usually high.⁴⁴ However, the stiffer tumor may not affect the generation of high ASS in the lesion**
10 **gap because only a small window is required inside the tumor and our proposed transient ASSE**
11 **also works well in the *ex vivo* tissue samples which is stiffer than the gel phantom.**

12 This kind of transient elastography has the advantages of reduced operational complexity
13 and no requirement of changing the treatment plan because it does not need the use of pushing
14 pulse as in ARFI, HMIFU, and supersonic shear imaging through the ROI. During HIFU
15 ablation which is usually **delivered** in the pulsed mode, the inter-pulse delay between the HIFU
16 bursts could be utilized to detect the displacement and subsequently monitor the gap between
17 lesions. The experimental results show that 0.03–0.05 s in the relaxation, depending on the
18 magnitude of ARF and material properties of the medium in the ROI, is sufficient to restore the
19 tissue to its initial position and to derive the displacement map. Such a time is much shorter than
20 the total duration of HIFU ablation at a single location, which is usually on the order of ten
21 seconds. In addition, the temperature change due to the thermal diffusion in such a short time is
22 negligible so that the effect of the variations in the speed of sound at the different temperatures
23 on the displacement could be ignored.⁴⁵ The irreversible tissue thermal expansion occurring after

necrosis is the most significant factor influencing the echo-time shift.⁴⁶ In order to avoid imperfect strain estimation and reduced contrast resolution, accuracy, and precision, static ASEs was reconstructed several minutes after HIFU ablation for complete thermal diffusion at the ROI to the ambient temperature.⁴⁷ The influences of thermal expansion to transient ASSE and lesion gap detection need further investigation. In addition, the effect of the respiration motion, which is compensated for by acquisition in the longitudinal scans and estimating the axial and lateral displacements,⁴⁸ is also minimized because of such a short acquisition period.

The two most important criteria of elastogram quality are the strain contrast and strain noise. The image contrast in static compression-induced ASE is not very satisfactory, which is unrelated to the distribution of tissue stiffness.⁴⁹ With the increase of the size of the displacement estimation window, the strain noise becomes less, but as well as the strain contrast. Elastography using the remote palpation, such as ARFI, is less susceptible to artifacts associated with the boundary conditions and elastic modulus inhomogeneities compared with static compression on the surface.²³ Furthermore, it demonstrates a reduced decay rate of strain SNR with the depth and improved contrast-transfer efficiency, particularly for those with negative modulus contrast or a slip boundary to the surrounding medium. The variance of the strain estimate is found to decrease at the high central frequency.⁴⁹ Overall, the contrast and SNR in our transient ASSE were found similar to the other remote palpation-generated elastography, but better than static ASE. The resolution of conventional elastography is almost as good as the B-mode sonography in both axial and lateral directions. In the transient ASSEs using HIFU exposure, its resolution is similar to the static compression-induced ASEs (about 1 mm) but larger than the clinical elastography due to fewer speckles in the displacement estimation. Optimal kernel sizes used for the tracking algorithm and strain estimator could improve the resolution. The minimum

detectable gap width is affected by the element width of the ultrasound imaging probe or the distance between two consecutive RF lines, 0.44 mm for L14-5/60W used in this study. The smallest lesion gap detectable in our *ex vivo* studies by the proposed approach is about 0.5 mm in the recorded photos (without histological examination the lesion boundary cannot be determined accurately). The accuracy and computation cost of elastography reconstruction is mainly dependent on the calculation of particle displacement using the 2D block matching algorithm. Because of much higher acoustic radiation force from the therapeutic HIFU pulse than the push pulse in the ARFI, large and irregular deformation of tissue/phantom will be produced so that inherent decorrelation between RF data and periodic ambiguities (false-peaks) associated with large search regions may occur. When using predicted displacement to reduce the size of the searching region, another type of displacement estimation error occurs and accumulates if the search region cannot enclose the true displacement. Therefore, continuous improvement on the displacement estimation is required.

Bubble cavitation is an important phenomenon in the acoustic field, especially at the high acoustic intensity. The presence of ultrasound-induced bubbles could enhance the absorption of delivered acoustic energy and scatter the incoming acoustic pulses toward the transducer. As a result, the produced lesion becomes larger but changes its symmetric shape of a cigar to an asymmetric tadpole with the large head gradually growing and moving away from the focus.⁵⁰ ASEs and ASSEs using static compression provide the accurate size of the lesion produced at the low-power setting. However, the presence of these cavitation bubbles produced at the high power was found to affect the lesion appearance in the elastography and have more influence in ASEs than in ASSEs.¹⁹ The contrast in ASEs discerns the lesion from the surrounding tissue whereas that in ASSEs shows the lesion boundary. Thus, cavitation bubbles inside the lesion

may not have a strong influence on the ROI in ASSEs. However, if many bubbles distribute in a large region during HIFU ablation with the presence of multiple lesions, their effect on ASSEs is still unknown. Hyperechoes from the array of markers and HIFU-induced lesions in the homogeneous gel phantom are found in the B-mode sonography, which suggests the presence of cavitation bubbles. They would enhance the SNR of sonography because of effective and strong acoustic reflection and scattering and, therefore, are beneficial to track the displacement of speckles in order to reconstruct the ASSEs in a better quality. The transient ASSEs using the remote palpation from the therapeutic HIFU pulses seems to have little influence from those bubbles. In comparison, a large boiling bubble will be produced at the high temperature, such as in the boiling histotripsy, and will block the propagation of the acoustic wave and cause the shadowing in the sonography. However, high temperature $>80^{\circ}\text{C}$ is usually avoided during HIFU ablation to minimize the unintended injury to the intervening tissues.

Sonography is conventionally realized by sweeping the ROI using a series of focused or multi-focused beams and then stacking all scanlines. Thus, the reconstruction time is proportional to the number of scanlines and the maximal depth of ROI. Subsequently, the frame rate is limited to about 30-50 Hz, which is not fast enough for transient elastography. Ultrafast sonography from a single transmit using PWI provides new perspectives and opportunities in the diagnosis without compromising the contrast-noise ratio and lateral resolution.^{23, 51} Although limited sonography width was applied in this study due to the required frame rate, it is sufficient (larger than the width of two typical lesions) to detect the gap between being-treated lesion and those already-treated ones. If no gaps are found at all previously treatment spots, such a small window will not affect the reliability and sensitivity of monitoring. With the advances in the

parallel computing,⁵² high-performance data transfer,⁵³ and high-speed processor,⁵⁴ a wide monitoring window is technically possible.

The limitations of this study include: 1) Lesions were produced by HIFU ablation first in the gel phantom and *ex vivo* samples at least 5 min before applying the HIFU palpation pulse to reconstruct the transient ASSE. The thermal effect was ignored here, and its effect on the accuracy and reliability of lesion gap detection is unknown. *In vivo* animal experiment with the progressive HIFU ablation and the gradual decrease of lesion gap will be carried out to further evaluate the performance of proposed transient ASSE for the future clinical translation; 2) The effect of respiratory motion on the outcome is unknown, but could be minimized during the stable stage because of short relaxation time in the tissue; 3) Computation burden is still high so that improvement in the block matching is required; 4) The minimal acoustic radiation force (depending on the acoustic intensity, pulse duration, acoustic attenuation of tissue, penetration depth, tissue stiffness, etc.) required for reliable gap detection has not been determined; 5) Only 2D model was used here, and our approach will be extended to the realistic 3D model in the future.

5. CONCLUSIONS

Detecting the presence of a gap between HIFU-induced lesions is a critical but challenging issue for clinical cancer/tumor ablation. HIFU exposure could produce a significant displacement in the tissue, from which transient axial shear strain elastograms (ASSEs) could be reconstructed. Large and localized axial shear strain presents in the gap zone between two HIFU lesions which can be exactly vertical. Both gel phantom and *ex vivo* tissue experiment confirm the possibility and sensitivity of the gap detection using the proposed approach. In contrast, conventional axial strain elastograms (ASEs) using the static compression can only show the contour of lesions, but not the lesion gap between them. In the numerical simulation, a threshold of axial shear strain ratio of 0.75 could be used to determine the presence of the lesion gap at various conditions, such as acoustic radiation force density, gap width, and lesion size. However, such a threshold in *ex vivo* experiment seems to be lower (e.g., 0.5), suggesting easier and more reliable and sensitive in the monitoring. The proposed approach could be applied to sonography-guided HIFU systems without interruption of the ablation procedure. The future *in vivo* studies are required to further evaluate its performance.

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CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose.

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Figure 6.

Figure 7.

without a gap

with a gap

(a)

(b)

(d)

(e)

Figure 8.

Figure 9.

Figure 10.

Figure 11.

Figure 12.