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TITLE:

Evaluating Targeting Accuracy in the Focal Plane of an Ultrasound-guided High-intensity Focused Ultrasound Phased-array System

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KEYWORDS:

Ultrasound-guided high-intensity focused ultrasound (USgHIFU), phased array, targeting accuracy, marker, phantom

SUMMARY:

This study describes a protocol to evaluate the targeting accuracy in the focal plane of an ultrasound-guided high-intensity focused ultrasound phased-array system.

ABSTRACT:

Phased arrays are increasingly used as high-intensity focused ultrasound (HIFU) transducers in the existing extracorporeal ultrasound-guided HIFU (USgHIFU) systems. The HIFU transducers in such systems are usually spherical in shape with a central hole where a US imaging probe is mounted and can be rotated. The image on the plane of treatment can be reconstructed through the image sequence acquired during the rotation of the probe. Therefore, the treatment plan can be made on the reconstructed images. In order to evaluate the targeting accuracy in the focal plane of such systems, the protocol of a method using a bovine muscle and marker-embedded phantom is described. In the phantom, four solid balls at the corners of a square resin model serve as the reference markers in the reconstructed image. The target should be moved so that both its center and the center of the square model can coincide according to their relative positions in the reconstructed image. Swine muscle with a thickness of about 30 mm is placed above the phantom to mimic the beam path in clinical settings. After sonication, the treatment plane in the phantom is scanned and the boundary of the associated lesion is extracted from the scanned image. The targeting accuracy can be evaluated by measuring the distance between the centers of target and lesion, as well as three derivative parameters. This method cannot only

evaluate the targeting accuracy of the target consisting of multiple focal spots rather than a single focal spot in a clinically relevant beam path of the USgHIFU phased-array system, but it can be also used in the preclinical evaluation or regular maintenance of USgHIFU systems configured with phased-array or self-focused HIFU transducer.

INTRODUCTION:

The phased array is increasingly designed and equipped in HIFU systems[1–7]. In USgHIFU phased-array systems, a US imaging probe is usually mounted in the central hole of the spherical HIFU transducer[1,2,8]. The probe is rotatable for targeting and image reconstruction in the three-dimensional space[9]. Precise targeting is required for the safety and efficacy of HIFU treatment. However, most of the studies for the evaluation of targeting accuracy have been performed for magnetic resonance-guided HIFU systems or USgHIFU systems configured with a self-focused HIFU transducer[10–16]. The purpose of the method described below is to evaluate the targeting accuracy in the focal plane for USgHIFU phased array systems.

A bovine muscle/marker-embedded phantom along the clinically relevant beam path is used in the evaluation of the targeting accuracy of a clinical USgHIFU phased-array system. A square model with four balls at the corners is fabricated and embedded, in combination with bovine muscle, into the transparent phantom. A regular hexagon is selected as the target based on the positions of the centers of four balls identified in the reconstructed US image on the treatment plane. After HIFU sonications, the treatment plane of the phantom is scanned, and the boundary of the lesion, as well as the positions of the four balls, can be determined in the scanned image. The targeting accuracy can be evaluated by measuring the distance between the centers of target and lesion, as well as three derivative parameters.

The method is simpler than the measurement of the targeting error using robotic movement with a specific reference object[11,17,18] and more clinically relevant in comparison to the method based on single focal spot ablation in a homogeneous phantom[10]. This method can be used in the evaluation of the targeting accuracy of USgHIFU phased array systems. It can be also used for other USgHIFU systems equipped with self-focused HIFU transducers.

PROTOCOL:

1. Marker design and fabrication

1.1. Design a square model using computer-aided design software. Set each side as sticks with lengths of 40 mm and thicknesses of 2 mm. Place a solid ball with a 10 mm diameter at each corner of the square model.

1.2. Use acrylonitrile butadiene styrene photosensitive resin as the material for printing.

1.3. Send the 3D model file to a manufacturer for fabrication.

2. Phantom preparation

2.1. Attach a plastic cylinder (with a diameter of 8 cm and a height of 3 cm) to an acrylic baseboard with silica gel to make a phantom holder at room temperature. Let it sit for 1 h.

2.2. Slice fresh bovine muscle into a square shape (30 mm x 30 mm, with a thickness of 10 mm) and ventilate it for 2 h to evaporate moisture.

2.3. Pour degassed and deionized water (115 mL) in a beaker, add in 13 g of acrylamide, and stir until dissolved. Add 0.24 g of bis-acrylamide and stir until dissolved. Then, add 0.2 mL of N,N,N',N'-tetramethylethylenediamine and stir uniformly.

NOTE: Put on a mask and rubber gloves.

2.4. Prepare 5 mL of degassed and deionized water in another beaker, add 0.3 g of ammonium persulfate, and stir to dissolve.

CAUTION: Acrylamide, bis-acrylamide, N,N,N',N'-tetramethylethylenediamine, and ammonium persulfate are toxic. Pay close attention and avoid physical contact.

2.5. Successively pour 40% of the solutions from steps 2.3 and 2.4 into the phantom holder, and stir for 5 s. Let the mixture sit for 20 min to solidify.

2.6. Place the 3D-printed square model on the surface of the solidified phantom, and put the sliced bovine muscle in the middle of the model. Pour the rest of the solution from step 2.3 into the phantom holder. Move the bovine muscle back and forth to remove the air between the interface of the phantom and the slice.

2.7. Pour the rest of the solution prepared in step 2.4 into the phantom holder, and stir for 5 s.

2.8. Fine-tune the location of the sliced bovine muscle to the center of the phantom along the transverse direction. Let it sit for 20 min to solidify the phantom.

2.9. Remove the silica gel between the cylindrical plastic and the acrylic baseboard, using a screwdriver.

2.10. Slowly detach the acrylic baseboard from the cylindrical plastic.

3. Setup of the USgHIFU system

3.1. Start the clinical USgHIFU system.

3.2. Turn on the water-processing module, and set the speed of water circulation at 80 rounds/min.

3.3. Fill an acrylic cylindrical water tank (with a diameter of 30 cm and a height of 13 cm) with degassed water at room temperature (22–25 °C).

3.4. Place the phantom holder into the degassed water and fix the holder tightly.

3.5. Move the cylindrical water tank onto the treatment bed. Lift the treatment bed and move it down the therapeutic unit into the degassed water.

4. US-guided targeting

4.1. Move the therapeutic unit slowly up and down to make sure that the depth of the treatment plane is located at the upper interface of the sliced bovine muscle and transparent phantom in the US image.

4.2. Rotate the US imaging probe to 0° and move the cylindrical water tank to make the rotating axis (also referred to as imaging axis) pass through the middle point of the two parallel sticks in the US image.

4.3. Rotate the imaging probe to 90° and move the cylindrical water tank to make the rotating axis pass through the middle point of the two parallel sticks in the US image.

4.4. Reconstruct the US image in the treatment plane at the depth of geometric focus.

4.5. Check if the four balls are clearly shown in the reconstructed US image and whether the target is located at the center of the square model.

NOTE: The center of the target is predetermined at the center of the reconstructed image. The ball is determined by a circle with a 10 mm diameter, the average gray value of which is highest in a 15 mm x 15 mm square. The center of the square model is determined by the diagonal of the four balls in the reconstructed image.

4.6. Move the water tank according to the relative positions between the target and the square model, and repeat steps 4.4 and 4.5.

4.7. Lift the therapeutic unit and put the swine muscle with a thickness of around 30 mm above the phantom. Then, move down the therapeutic unit until the depth of geometric focus is 3 mm beneath the upper surface of the sliced bovine muscle.

NOTE: The 3 mm focal correction along the beam path is estimated according to the thickness of the swine muscle based on the empirical formula from a previous study[19].

5. HIFU sonication

5.1. Select the following sonication parameters: pulse duration (400 ms), duty cycle (80%),

acoustic power (400 W), and cooling time between the sonication of successive focal spots (30 s).

5.2. Set the exposure time for the focal spots in the target.

5.2.1. Repeat the procedure for three concentric regular hexagonal targets with respective diagonals of 5.4 mm, 9 mm, and 12.6 mm. Set exposure times of 2.0 s, 2.5 s, and 3.0 s for the focal spots located at the inner, middle, and outer hexagon, respectively, and 2.0 s for the focal spot at the geometric center of the phased array.

5.3. Start the sonication and put one foot on the foot pedal for HIFU sonication.

5.4. Observe the change of echogenicity in the US image until the sonications are completed.

6. Evaluation of the targeting accuracy of the USgHIFU phased-array system

6.1. Fetch the phantom holder, and smoothly press the phantom to take it out.

6.2. Split the phantom along the treatment plane using a knife.

6.3. Scan the treatment plane of the phantom that contains the sliced bovine muscle.

6.4. Process the scanned image using mathematical software and extract the boundaries of the target and lesion.

6.5. Calculate the intercenter distance d_c and the maximal overshooting of the target boundary d_b.

NOTE: d_c is the distance between the centers of the target and its respective lesion. d_b is the maximum overshooting distance between the boundary of the lesion and its respective target.

6.6. Compute the ratio of the areas of lesion inside and outside the target to the target area as $\eta_I = (S_A \cap S_P) / S_P$ and $\eta_O = (S_A - S_A \cap S_P) / S_P$, respectively.

NOTE: S_P indicates the target area, S_A represents the lesion area.

REPRESENTATIVE RESULTS:

We made phantoms dedicated to evaluating the targeting accuracy of a clinical USgHIFU phased-array system with the targets of three different sizes. **Figure 1** displays the US image at angles of 0° and 90°. The interfaces are clear, and the sticks of the square model are bright in the US images. **Figure 2** demonstrates the reconstructed US image in the treatment plane and the focal spots of the largest target. The centers of the four balls were determined by the blue circles of the same size with the highest averaged grey value. **Figure 3** shows the scanned images of the treatment plane of the phantom and the extracted boundaries of the targets and lesions.

We were able to evaluate the targeting accuracy in the focal plane according to the parameters of d_c, d_b, η_l, and η_0 defined in section 6 of the protocol. The experiments were repeated three times for each target. The results are presented in **Table 1**.

FIGURE AND TABLE LEGENDS:

Figure 1: US images at angles of 0° and 90°. The thickness of the swine muscle was around 30 mm. The tissue-phantom-tissue interfaces along the beam path can be distinguished.

Figure 2: Reconstructed US image in the treatment plane. The blue circles (with the highest average grey value in red-dashed squares) determine the positions of four balls and the center of the square model, which is also the center of the targets (the red spot). The dark brown squares indicate the focal spots in the largest regular hexagonal target.

Figure 3: Scanned images and extracted boundaries of different targets after HIFU sonication. (**A**) Lesions of the three targets with diagonals of 5.4 mm, 9 mm, and 12.6 mm from left to right. (**B**) Extracted boundaries of the three targets (blue) and the corresponding lesions (black).

Table 1: Summary of parameters to evaluate the targeting accuracy. The values of d_c, d_b, η_l, and η_0 were expressed as mean ± standard deviation.

DISCUSSION:

Robotic components have been used for extracorporeal USgHIFU systems. To evaluate the targeting accuracy of such systems, reference markers[11,12,18], in vitro tissue[17], tumor-mimic models, and temperature-sensitive phantoms have been used alone or in combination[10,20]. Compared with the protocols in those studies, this method is more clinically relevant and makes it easy to quantify the targeting error in the focal plane. By combining the reference marker with the heterogeneous, transparent phantom, this method has been modified from another study for assessing the targeting accuracy of an USgHIFU system aimed at breast tumor ablation[21]. We have verified the efficacy of this method with our USgHIFU phased-array system used on uterine fibroids in the previous study[22]. We have performed tests without focal correction along the beam path, and only a small part (~2 mm in length) of the lesion was found in the sliced bovine muscle. After the focal correction based on the empirical formula[19], the lesion (~5 mm in length) was found in the sliced bovine muscle, which has confirmed the improvement in the targeting accuracy along the beam path. Moreover, the evaluation of targeting accuracy in the focal plane is of more practical value in comparison to the methods aimed at the accuracy of a single focal spot for solid tumor ablation.

The selection of bovine muscle makes the lesion clearly distinguishable from the surrounding tissue as compared with lesions created in porcine or chicken muscles by in vitro HIFU ablation. The making of the bovine muscle/marker-embedded transparent phantom is critical for the whole protocol of evaluating the targeting accuracy of the USgHIFU phased-array system. In addition, the determination of whether the centers of the target and the square model coincide

is essential in the evaluation procedure ; thus, the position of the phantom needs to be adjusted. The white intramuscular septum in the sliced bovine muscle makes the threshold segmentation insufficient to extract the lesion boundary from the scanned image; therefore, manual segmentation should be used when necessary.

There are still limitations to this protocol. This study aims for the evaluation of targeting accuracy in the focal plane only, and it is applicable to USgHIFU phased-array systems. However, for USgHIFU systems with a self-focused transducer, steps 4.2–4.4 of the protocol should be revised. The US image in the treatment plane can be reconstructed through the images acquired by translating the US imaging probe instead of by rotation, and the other steps in the protocol remain the same. The precise evaluation of targeting accuracy can be helpful when trying to reduce the safety margin and increase the ablation volume, which would improve the treatment efficacy. Moreover, this method can be used in the quality assurance of the HIFU driving system.

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DISCLOSURES:

Xiang Ji is a paid consultant for Zhonghui Medical Technology (Shanghai) Co., Ltd. The other authors have nothing to disclose.

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Figure 1

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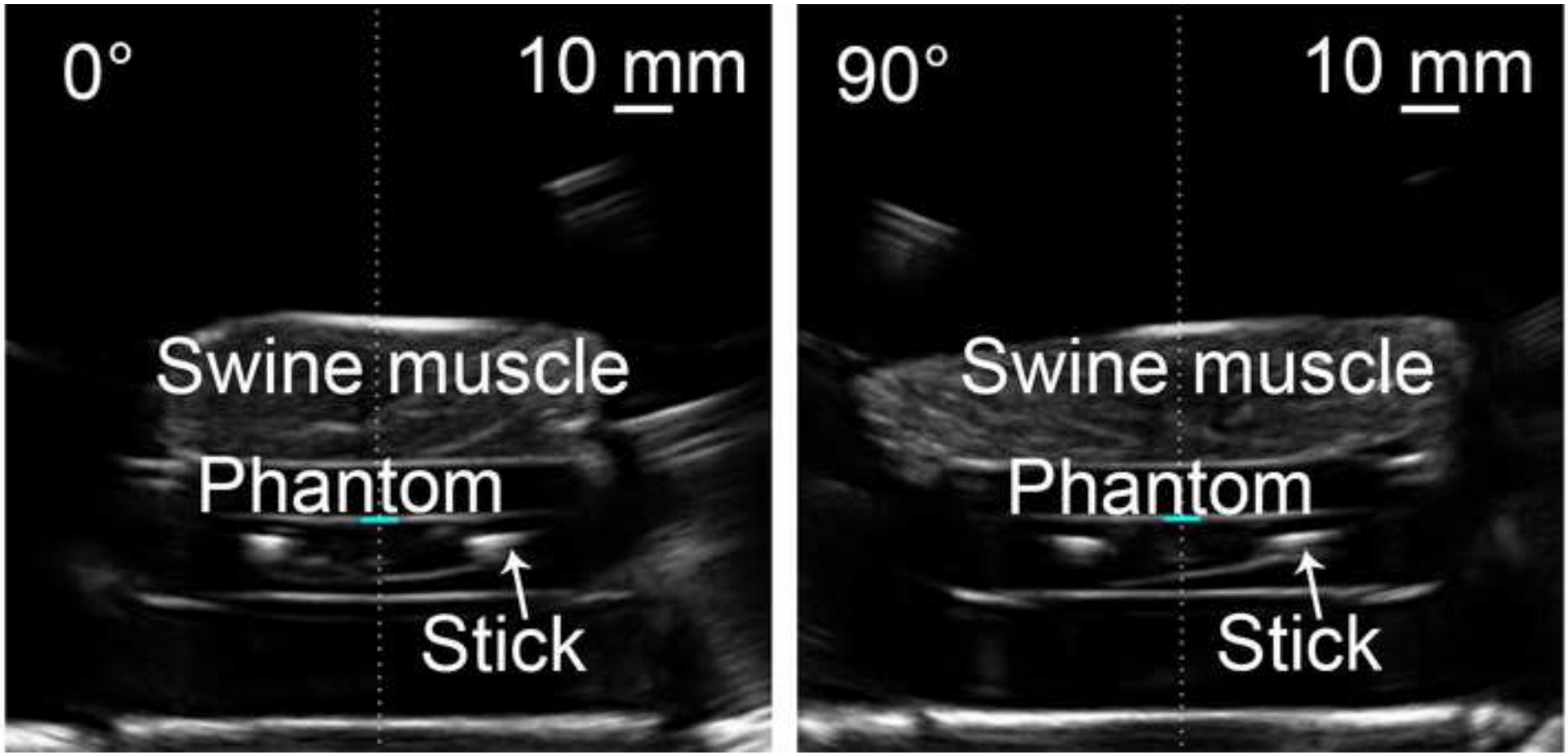

Figure 2

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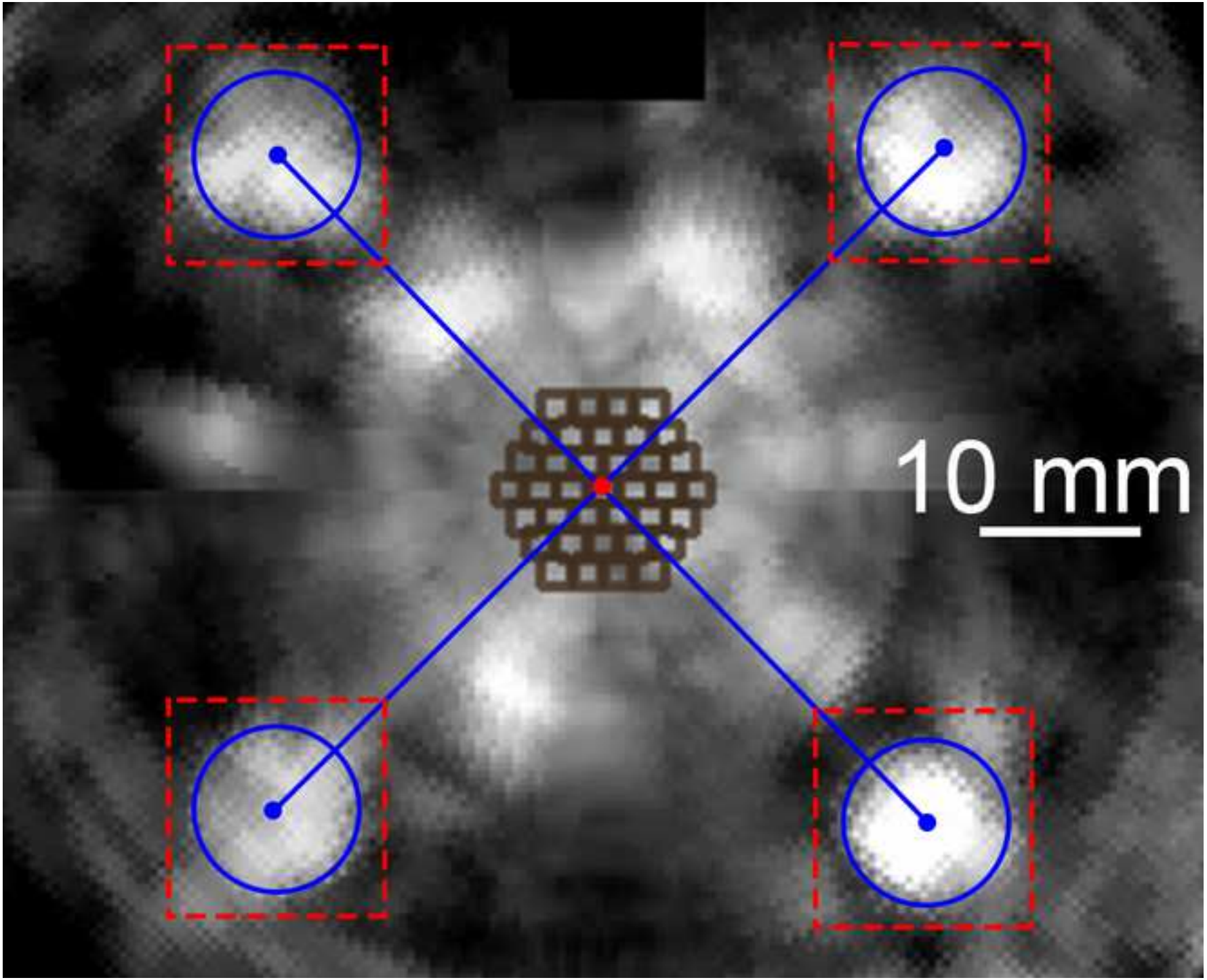

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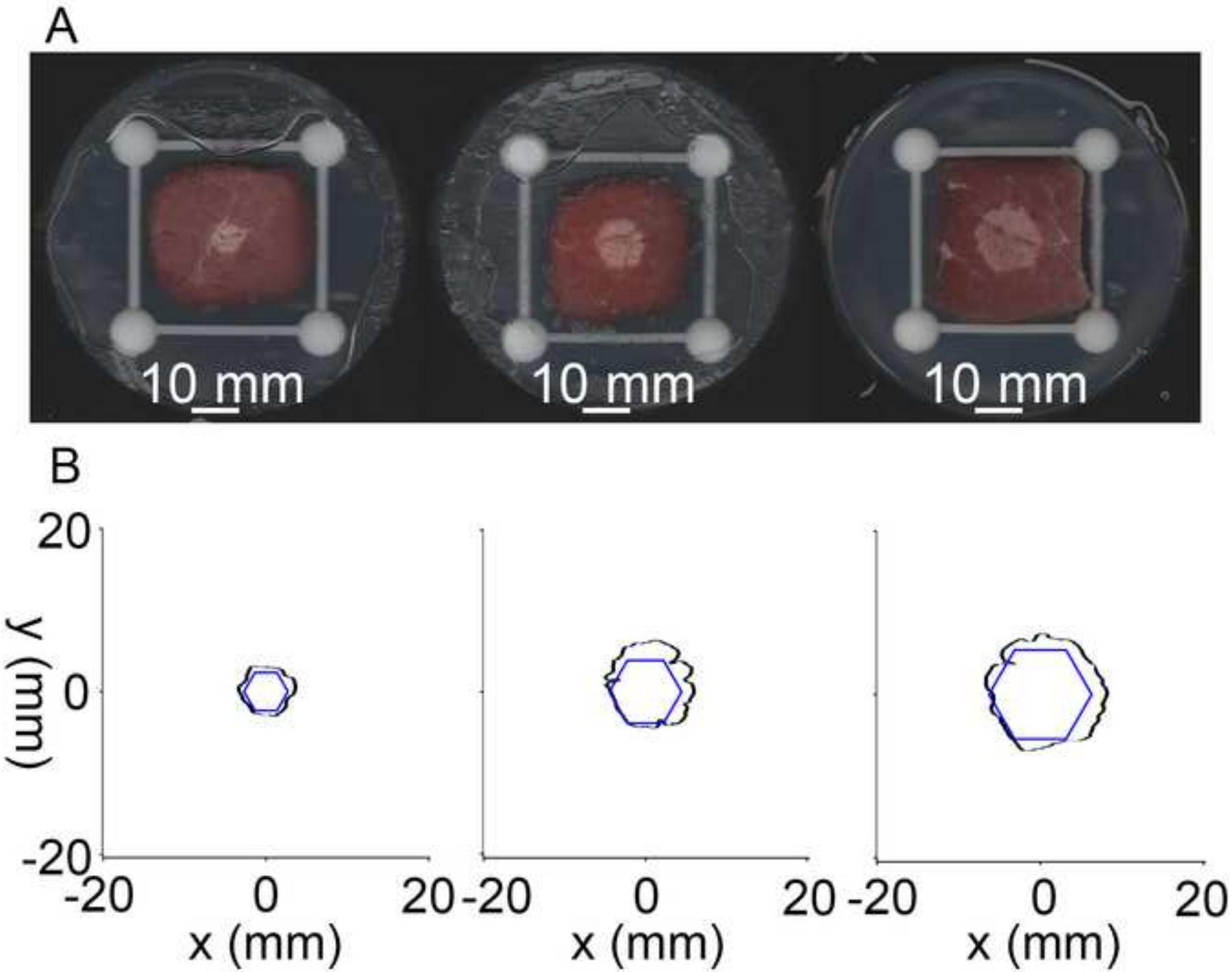

Table 1

Diagonal of regular hexagon (mm)	d_c(mm)	d_b(mm)	η_I	η_O
5.4	0.6 ± 0.3	1.6 ± 0.3	100 ± 0%	45 ± 11%
9.0	0.9 ± 0.3	1.7 ± 0.6	98 ± 1%	40 ± 6%
12.6	1.1 ± 0.4	1.7 ± 0.7	96 ± 3%	20 ± 6%

Name of Material/ Equipment	Company	Catalog Number	Comments/Description
Acrylamide	Amresco	D403-2	
Acrylic baseboard	LAO NIAO STORES	customized	
Acrylic cylindrical water tank	LAO NIAO STORES	customized	
Ammonium persulfate	Yatai United Chemical Co., Ltd (Wuxi, China)	2017-03-01	
Beaker	East China Chemical Reagent Instrument Store		
Bis-acrylamide	Amresco	M0172	
Bovine muscle	Market		
Chopping board	JIACHI	JC-ZB40	
Cylindrical plastic phantom holder	QIYINPAI	customized	
Degassed deionized water			made by the USgHIFU system
Electric balance	YINGHENG	11119453359	
Glass rod	East China Chemical Reagent Instrument Store		
Knife	SHIBAZI	SL1210-C	
Mask	Medicom	2498	
N,N,N’,N’–Tetramethylethylenediamine	Zhanyun Chemical Co., Ltd (Shanghai, China)		
Rubber glove	AMMEX	YZB/MAL 0587-2018	
Scanner	Fuji Xerox	DocuPrint M268dw	
Screwdriver	Stanley	T6	
Silica gel	GE	381	
Square model	QIYINPAI	customized	
Stainless steel spoons	East China Chemical Reagent Instrument Store		
Sucker	East China Chemical Reagent Instrument Store		
Swine muscle	Market		
USgHIFU system	Zhonghui Medical Technology (Shanghai) Co., Ltd	SUA-I	

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Article Title: A method to evaluate targeting accuracy in the focal plane for ultrasound-guided high-intensity focused ultrasound thrombolysis system

Signature: Xiang Ji Date: 2018.9.26

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Response to the Reviewers' Comments

Thanks for the editorial and reviewers' comments. According to the comments, the manuscript has been revised in the following aspects,

1. Swine muscle with a 30-mm thickness has been placed above the phantom to mimic the beam path in the clinical settings. And the evaluation of the targeting accuracy has been performed on the targets with three different sizes. In order to correct the focal shift caused by the tissue layer in the axial direction, the focal correction along the beam path has been employed based on the empirical formula[1]. Please see 4.7 and 5.2 in PROTOCOL.

2. The over goal of this study has been clearly stated in the section of INTRODUCTION. The sections of PROTOCOL and DISCUSSION have been rephrased, and spelling and grammar issues have been thoroughly addressed. In addition, the abstract in the manuscript has been rewritten.

3. The supplementary material has been added to provide the detailed description of our clinical USgHIFU phased array system. Besides, the drawing of the square model as well as the phantom holder has also been given.

We have considered the comments carefully and provided the response to the reviewers' comments as below.

Editorial comments:

Changes to be made by the author(s) regarding the manuscript:

1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.

Response: We have proofread the revised manuscript and addressed the spelling or grammar issues.

2. Please obtain explicit copyright permission to reuse any figures from a previous publication. Explicit permission can be expressed in the form of a letter from the editor or a link to the

editorial policy that allows re-prints. Please upload this information as a .doc or .docx file to your Editorial Manager account. The Figure must be cited appropriately in the Figure Legend, i.e. "This figure has been modified from [citation]."

Response: The method herein has been modified and the new results have been provided, therefore, the figures are different from our previous paper.

3. Please label/number the institutional affiliation of each author.

Response: The institutional affiliation of each author has been labeled in the manuscript.

4. Please rephrase the Introduction to include a clear statement of the overall goal of this method.

Response: The introduction has been rephrased to be more concise and the overall goal of this method is clear.

5. Please remove commercial language and use generic terms instead: SolidWorks, Matlab, etc.

Response: The commercial language has been replaced with generic terms in the manuscript.

6. 1.1 and 2.1: Schematics of the square model and phantom holder would be helpful.

Response: Schematic figures of the square model and the phantom holder have been provided in the supplementary material.

7. After you have made all the recommended changes to your protocol (listed above), please highlight 2.75 pages or less of the Protocol (including headings and spacing) that identifies the essential steps of the protocol for the video, i.e., the steps that should be visualized to tell the most cohesive story of the Protocol. Please note that design and calculation steps are not appropriate for filming.

Response: The essential steps of the protocol have been highlighted in red for the video.

8. References: Please do not abbreviate journal titles.

Response: The journal titles has been replaced with their full names.

9. Table of Equipment and Materials: Please sort the items in alphabetical order according to the

Name of Material/ Equipment.

Response: The items in the table of equipment and materials has been sorted in alphabetical order according to the Name of Material/ Equipment.

Reviewer #1:

HIFU is emerging as a safe and effective treatment modality in the cancer/solid tumor ablation. The calibration of the HIFU system is important for the consistent performance. The authors developed a method to evaluate the targeting accuracy in the focal plane. No significant scientific impact was found here despite a little practice trick. Targeting accuracy in the axial direction is more important. Defocusing through inhomogenous tissue is very critical issue in clinics using certain algorithm to elements for compensating the phase aberration.

Response: To mimic the beam path in the clinical settings, the protocol of our method has been modified by placing fresh swine muscle with a 30-mm thickness above the phantom. In order to take the focal shift along the axial direction caused by beam path into account, the empirical formula in our previous study[1] has been used, and the layer of the placed swine muscle could induce a focal shift of about 3 mm along the beam path according to equation (1).

$$|CO| = \frac{-|AO|}{\cos(\theta_i)} \cdot \frac{\sin(\theta_t - \theta_i)}{\sin(\theta_t) - 1.2} \tag{1}$$

where the focus shift is dependent on AO (tissue thickness), θ_i (determined by transducer F number), and θ_t (related with the tissue acoustic speed and transducer F number). And the result of the empirical formula is comparable to the numerical calculation.

To compensate the focal shift, the focal correction is performed by setting the depth of the focal plane at 3 mm beneath the upper surface of the bovine muscle tissue instead of phase correction. And the result without focal correction shows that only a small part (~2mm in length) of the lesion has been found in the sliced bovine muscle (see Figure 1(a)). However, after focal correction, the lesion (~5mm in length) has been found in the sliced bovine muscle (see Figure 1(b)), which has confirmed the improvement in the targeting accuracy along the beam path. Moreover, we have also used multi-layer inhomogenous tissue sample (skin, fat, muscle) along the beam path, and it shows that the focus shift can be also corrected. In our HIFU phased array, the incident angles of all the elements are less than 40° at the interface, and the incident angles of half elements are less than 30°. Therefore, beam distortion caused by refraction and reflection has less influence on HIFU treatment of soft tissue than transcranial application.

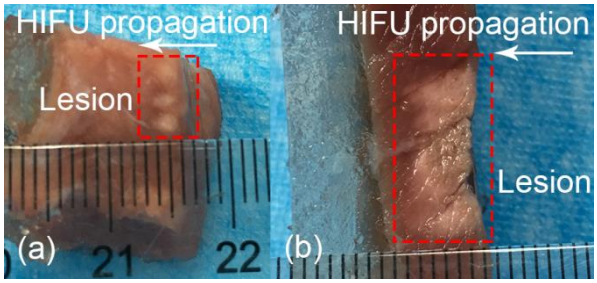

Figure 1. Lesion in the bovine muscle along axial axis after HIFU sonications without (a) and with (b) focal correction.

How to determine the center of the treated region that is critical issue in this paper is unclear. Production of a very small lesion is preferred to determine the location of focus.
High-intensity focused ultrasound (HIFU) phased arrays is becoming popular not only for ultrasound-guided system but also for MRI-guided one.

Response: The image in the focal plane was reconstructed, and the center of each solid balls was determined by searching the circle with the highest average gray value in the large square area (see Figure 2 in the manuscript). The target was set as regular hexagon and filled with focal spots on the focal plane. The center of the target was set at the intersection of the diagonals of the square model.

Line 40 change to "on the plane of"

Response: “on plane of” was changed to “on the plane of ”. See line 39.

Line 49 "picture" is not appropriate here

Response: The phantom was scanned instead of pictured and the sentence was changed to “After sonications, the treatment plane in the phantom is scanned and the boundary of the associated lesion is extracted from the scanned image”. See line 48-49.

Line 55 wrong use of "periodical" here

Response: “periodical” was changed to “regular”. See line 53.

Line 68 change "with" to "in"

Response: “with” was changed to “in”. See line 66.

Line 70-72 hard to understand this sentence

Response: This sentence means that the centers of the treatment cells in the focal plane coincided with the geometric focus of HIFU phased array. In the current manuscript, the evaluation of targeting accuracy was performed in the targets with three sizes (inner, middle and outer regular hexagons), and the number of focal spots in each target varied. See line 191.

Line 77 term of "targeting accuracy evaluation" is not good

Response: “targeting accuracy evaluation” was changed to “evaluation of targeting accuracy” in the manuscript. See line 81.

Line 79 change "in comparison with" to "in comparison to", thereafter

Response: “in comparison with” has been changed to “in comparison to” throughout the manuscript.

Line 99 this note could be deleted

Response: The note has been deleted.

Line 108 does slicing fresh beef require the lab coat and gloves?

Response: “Put on the mask and rubber gloves” is for phantom preparation and has been moved to another place. See line 110.

Line 147 Is another note of filling the cylindrical water tank with degassed water required here besides filling the water balloon

Response: This note has been deleted.

Line 163-169 B-mode sonographies at 0° and 90° are required

Response: The B-mode images at 0° and 90° have been provided. See line 239 or see Figure 1.

Line 182-183 what's the sonication time for each spot?

Response: The sonication time for each focal spot is the same on each regular hexagon. The sonication time of 2.0 s, 2.5 s, 3.0 s were set for the focal spots located at the inner, middle, and

outer hexagon, and 2.0 s for the focal spot at the geometric center of the phased array, respectively. See line 193-195.

Line 185-186 what are the diameters of inner, middle and out circles?

Response: The target has been changed from circles to regular hexagons. And the diagonals of the three regular hexagons are 5.4 mm, 9 mm, and 12.6 mm. See line 191-192.

Line 188-189 hard to understand this sentence

Response: It means that the sonication time for each focal spot on each circle is the same, and they are 2.0 s, 2.5 s, and 3.0 s for the focal spot on inner, middle and outer circles. In the current manuscript, the targets were replaced with regular hexagons of the same diameters, and the number of focal spots in each target varied. See line 193-195.

Line 208 the term of "ablation rate" is not defined appropriate here

Response: "ablation rate" has been replaced by "the ratio of the areas of lesion inside and outside the target to the target area", see line 217.

Line 238-239 how to determine the lesion sizes for each treatment cells?

Response: The "treatment cells" has been replaced with "targets". And the lesion sizes for each targets were determined by extracting the lesion boundaries from the scanned images through image segmentation.

Line 247-248 it is awful to have one table in two pages, and the term of η_I and η_O is not defined and clear in this manuscript

Response: The table has been put in one page, and the term of η_I *and* η_O is clearly defined in the manuscript. See line 217-218.

Line 264-270 usually muscle is not a good ex vivo tissue samples used in the evaluation of HIFU-induced lesion because the acoustic absorption is highly dependent on the fiber orientation. Liver and kidney are more homogenous, and the produced lesions have good contrast for image processing.

Response: We have tried using swine liver previously. However, the repetitive lesions were not obtained under the same parameters of sonication, so we did not choose the liver in the phantom.

On the contrary, the repetitive lesions were formed in the bovine muscle-embedded phantom, and the lesion boundary can easily extracted from the scanned image. See Figure 3 and Table 1.

Line 272 bad use of "induced by the buoyancy in water", maybe substitute it by "caused by"

Response: Initially, "induced by the buoyancy in water" was substituted by "caused by". But this sentence has been deleted in the revised manuscript.

Line 285 bad use of "over several centimeters"

Response: “over several centimeters” was replaced with “above several centimeters in diameter”. However, this sentence was deleted after consideration.

Reviewer #2:

Manuscript Summary:

This protocol suggests a method for a simple method to ensure targeting accuracy when using a clinical USgHIFU system with a steered phased array.

Major Concerns:

My main concern for this protocol is that it is very specific to the HIFU system used for this study, and would probably not be applicable to most other systems. This issue is further compounded by the fact that no information is given to the technical specifications of the system (i.e. how many elements, imaging frequency etc), making it even more difficult to relate to other systems..

Response: The technical specifications of the USgHIFU phased array system have been given in the supplementary material. This protocol can be used to evaluate the targeting accuracy for the systems like ALPIUS (Alpinion Medical Systems, Seoul, Korea). For USgHIFU systems with self-focused HIFU transducer, the steps in 4.2-4.4 in PROTOCOL in the manuscript should be revised. The US image in the treatment plane can be reconstructed through the images acquired by translating the US imaging probe instead of rotation, and the other steps in PROTOCOL are the same. Therefore, the modified protocol can be used in the assessment of targeting accuracy for most USgHIFU systems with self-focused HIFU transducer such as JC HIFU system (Chongqing Haifu Technology, Chongqing, China) and HIFUNIT9000 (Shanghai A&S Science and Technology, Shanghai, China).

Also it provided with a very simplistic approach to ensuring axial alignment, without

consideration for the beampath. I.e. if a tissue path had been used, rather than a water path, could the accuracy have been measured in this way? This is more relevant to clinical applications

Response: To mimic the beam path in the clinical settings, the protocol of our method has been modified by placing fresh swine muscle with a 30-mm thickness above the phantom. See 4.7 and 5.2 in PROTOCOL.

Minor Concerns:

Section 1) - could the stl files for this holder have been provided for those with the facilities to produce, also is there a specific need for a resin printer?

Response: The CAD drawing of the phantom holder has been provided in the supplementary material. Therefore is no need for a resin printer because the square model and the holder are rather simple. And both the square model and the holder can be used repeatedly.

Section 2) - Please specify what 'beef' means in this context, i.e. is it muscle, liver etc?

Response: ‘beef’ is muscle, and it has been replaced with ‘bovine muscle’ in the manuscript.

Section 4) - For a protocol that is for checking the alignment of USgHIFU, why are there no B-mode images in these results?

Response: The US images at the angles of 0°, 90° and the focal plane (reconstructed image) have been provided. See Figures 1 and 2 in the manuscript.

Reviewer #3:

Manuscript Summary:

The subject manuscript describes a method to evaluate the targeting accuracy in the focal plane for ultrasound-guided phased-array high-intensity focused ultrasound system. The manuscript is presented reasonably well, but can be greatly improved. I would suggest the authors to address few of the minor comments before this can be published.

Minor Concerns:

Line 91-97; Authors need to specify the fabrication parameters,? Perhaps authors can provide the CAD drawing as supplementary material

Response: The CAD drawing of the square model has been provided in the supplementary

material.

Line 106; Any temperature requirements?

Response: The procedure of sticking cylindrical plastic to acrylic baseboard was performed at room temperature. And it has been added in the manuscript. See line 100.

Line 110-112; This has to be done inside fumehood

Response: Yes. However, due to the restrictions, we prepare the phantom near the open window and put on mask and rubber gloves as well for substitution.

Line 117-118; Any specific reason for choosing polyacrylamide based phantoms? Why not agar or materials with substantially less safety hazards? Please specify this in the main text

Response: Polyacrylamide based phantom is robust, stable and can be exposed to successive doses, the stiffness is larger than that of human soft tissue while the attenuation is significantly smaller than that of soft tissues. Therefore, the phantom is easier to be fixed and denatured tissue on the focal plane in the phantom can be easily identified through the optically transparent gel. And the process to make such phantom is short, usually several hours. Also safeguard such as ventilating and wear mask and rubber gloves makes the procedure little safety hazards. However, agar based phantom needs longer time to fully gel (up to several weeks), and it is soft and not easy to be fastened.

Line 149-150; Needs to specify the temperature of water tank

Response: The temperature of the water tank is around 22°C ~25°C, and it has been added in the manuscript See line 144.

Line 160-161 Please specify whether the authors used an actuator, Manual or motorized?

Response: The movement of the water tank can be realized by moving the treatment bed which is motorized in three dimension and can be both coarsely and finely controlled with buttons. And the lifting of the treatment head can be controlled by both the buttons and the user interface.

Line 167- 169; Authors need to describe the reconstruction methodology in more detail.

Response: In this study, the B-mode US imaging probe was rotatable, and the image in the treatment plane can be reconstructed through the image sequence acquired during probe rotation.

Bilinear interpolation has been used for image reconstruction, and the detailed algorithm can be found in the previous study[2]. The reconstruction codes have been verified by phantom tests.

Reference

1 Li, D. H., Shen, G. F., Bai, J. F. & Chen, Y. Z. Focus shift and phase correction in soft tissues during focused ultrasound surgery. *IEEE Transactions on Biomedical Engineering.* **58** (6), 1621-1628, (2011).

2 Tong, S., Downey, D. B., Cardinal, H. N. & Fenster, A. A three-dimensional ultrasound prostate imaging system. *Ultrasound in Medicine and Biology.* **22** (6), 735-746, (1996).

Supplementary material

The clinical USgHIFU phased array system

A USgHIFU phased array system (SUA-I, Zhonghui Medical Technology (Shanghai) Co., Ltd., China) was used in the study. Figure S1 provides a full view of the system. In the system there are several components: therapeutic unit, HIFU driving unit, diagnostic ultrasound machine, user-interface (UI) console and HIFU driving console, water cycle unit, and treatment bed.

The therapeutic unit consists of a 144-element HIFU phased array transducer and a 3.5 MHz B-mode US imaging probe. The US imaging probe was placed into the 80-mm-wide central hole of the aluminum spherical shell, and the probe was connected to a commercial diagnostic ultrasound machine (OPENO580, Jiangsu Sinoways Medical Technology Co., Ltd., Yangzhou, Jiangsu). The therapeutic unit can be controlled by the UI console to move with three degrees of freedom: rotation (<= 15°) along both X-axis and Y-axis and translation (<= 400mm) along Z-axis. The aperture and radius of curvature of HIFU phased array were 18 cm and 14 cm. The elements were distributed annularly and each ring included 24 elements. A customized silicone-rubber water bag could be fastened to the therapeutic unit for skin contact.

The rotation axis of the US imaging probe was the axis of HIFU propagation so that the imaging plane could be switched to the plane where the focus was steered. The probe was able to rotate in a −90°-to-90° range at a step of 1° to cover the target volume where the energy of HIFU beams was delivered. Therefore, image guidance and monitoring could be implemented through the rotation of the probe. And the spots targeted in the images can be mapped to the focal spots generated by the HIFU phased array. With the US images acquired during probe rotation, the treatment plane can be reconstructed with bilinear interpolation.

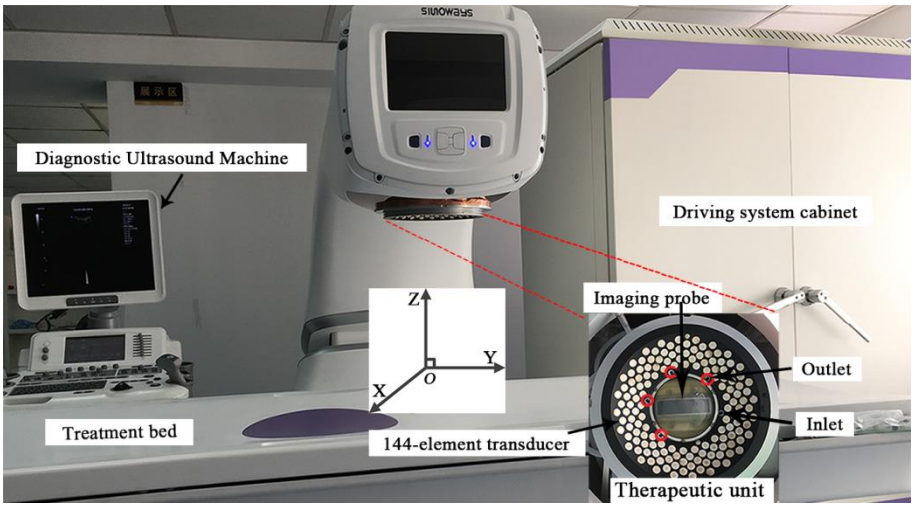

Figure S1. The USgHIFU phased array system.

The square model and the phantom holder

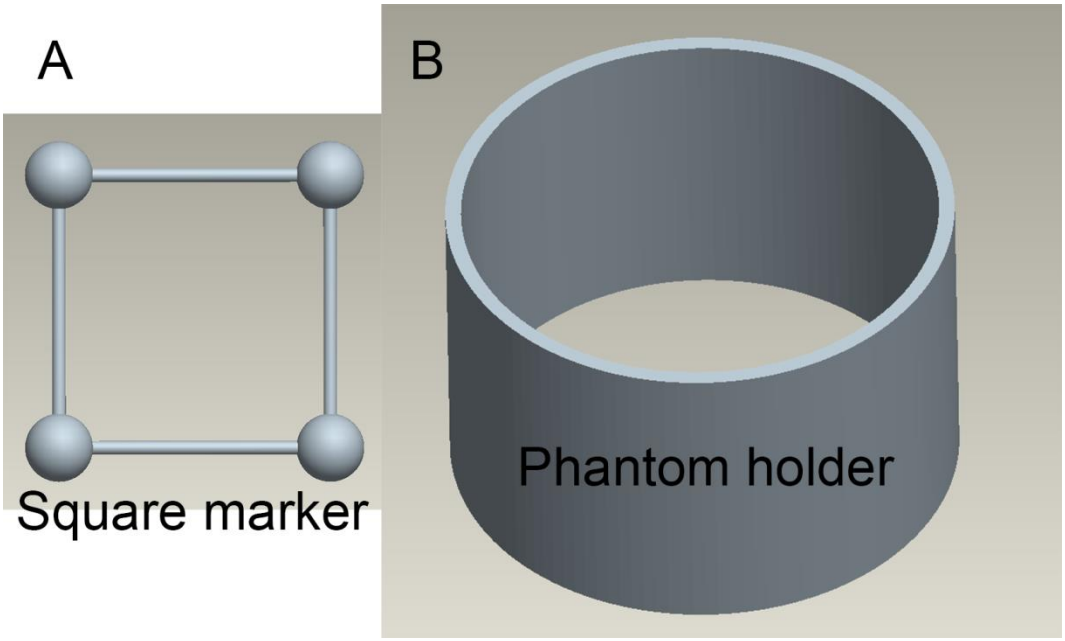

Figure S2. CAD drawing of the square model and the phantom holder.