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Minimally invasive therapeutic ultrasound: Ultrasound-guided ultrasound ablation in neuro-oncology

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ABSTRACT

Introduction: To improve patient outcomes (eg, reducing blood loss and infection), practitioners have gravitated toward noninvasive and minimally invasive surgeries (MIS), which demand specialized toolkits. Focused ultrasound, for example, facilitates thermal ablation from a distance, thereby reducing injury to surrounding tissue. Focused ultrasound can often be performed noninvasively; however, it is more difficult to carry out in neuro-oncological tumors, as ultrasound is dramatically attenuated while propagating through the skull. This shortcoming has prompted exploration of MIS options for intracranial placement of focused ultrasound probes, such as within the BrainPath™ (NICO Corporation, Indianapolis, IN). Herein, we present the design, development, and *in vitro* testing of an image-guided, focused ultrasound prototype designed for use in MIS procedures. This probe can ablate neuro-oncological lesions despite its small size.

Materials & Methods: Preliminary prototypes were iteratively designed, built, and tested. The final prototype consisted of three 8-mm-diameter therapeutic elements guided by an imaging probe. Probe functionality was validated on a series of tissue-mimicking phantoms.

Results: Lesions were created in tissue-mimicking phantoms with average dimensions of 2.5 × 1.2 × 6.5 mm and 3.4 × 3.25 × 9.36 mm after 10- and 30-second sonification, respectively. 30 s sonification with 118 W power at 50% duty cycle generated a peak temperature of 68 °C. Each ablation was visualized in real time by the built-in imaging probe.

Conclusion: We developed and validated an ultrasound-guided focused ultrasound probe for use in MIS procedures. The dimensional constraints of the prototype were designed to reflect those of BrainPath trocars, which are MIS tools used to create atraumatic access to deep-seated brain pathologies.

1. Introduction

Focused ultrasound is an appealing tool for use in both noninvasive and minimally invasive surgical (MIS) procedures, as it can ablate pathologic tissue from a distance [1–3]. This is particularly helpful in patients diagnosed with inoperable tumors [4,5]. In neurosurgery, noninvasive (transcranial) focused ultrasound systems have been successfully used to treat movement disorders, including Parkinson and essential tremor [6]. However, their use for ablation of neuro-oncological tumors faces certain drawbacks [3]; namely, significant attenuation of the ultrasonic wave during propagation in the skull, which requires high powers directed at the patient's head [7–9]. In response to these drawbacks, MIS focused ultrasound approaches have been contemplated, necessitating miniature probes to ablate intracranial lesions from within the cranium [10,11].

One such example is a minimally invasive, focused ultrasound probe capable of being placed within the BrainPath™ (NICO Corporation, Indianapolis, IN), a device that allows atraumatic access to brain

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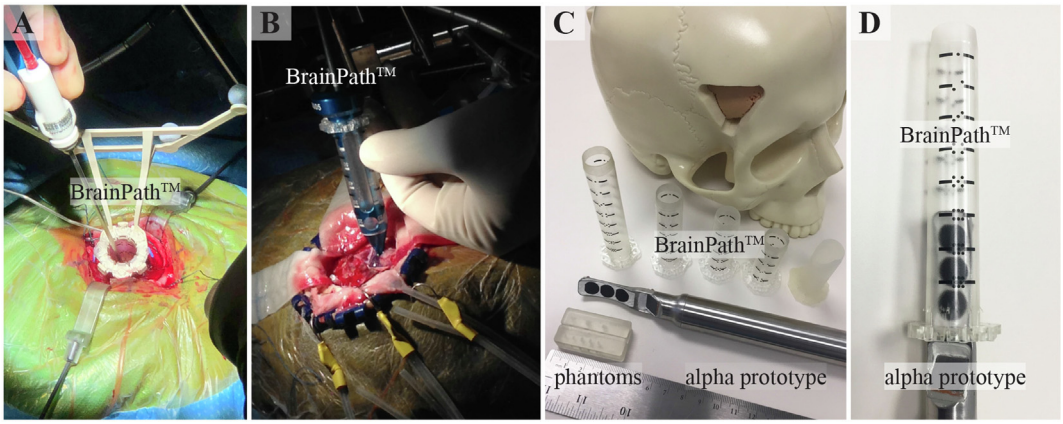

Fig. 1. The BrainPath™ is a minimally invasive neurosurgical toolkit that can accommodate neuroendoscopic devices. (A&B) The BrainPath™ trocar is inserted into brain tissue to create atraumatic surgical access to deep-seated lesions. (C&D) The ultrasound-guided focused ultrasound alpha prototype probe described in this study is shown in relation to the BrainPath™ dimensions. *A and B contain original images presented with permission from NICO Corporation.*

oncology (e.g., deep-seated tumors) in MIS settings (Fig. 1). The development of products like BrainPath™ represents a growing trend toward MIS options in healthcare, where surgical interventions are increasingly being performed with minimally invasive approaches or keyhole procedures to enhance patient outcomes and reduce blood loss or infection [12]. Of course, this trend requires development of novel, precise, miniature surgical instruments. Although larger transducer surface areas allow for better energy deposition, MIS encourages increasingly smaller probes to reduce incision sizes and dissection requirements—and this tradeoff demands better understanding of acoustic designs to balance both criteria [13–15]. In this study, we investigated preliminary focused ultrasound configurations for use in MIS settings, particularly for use in ablation of neuro-oncological lesions. Here, we report the development and *in vitro* testing of an initial series of probe designs small enough for use in MIS, yet with a large enough transducer surface area to generate the focal point ablations. With the placement of the probe within the BrainPath, all anatomies in the brain will be within 4–5 cm. As a result, such a focal length enables the treatment of brain lesions from within the BrainPath trocar.

2. Materials and methods

2.1. Therapeutic elements

Based on the dimensions of BrainPath™ and the guidelines for MIS and neuroendoscopy techniques (i.e., burr holes measuring 18 mm or smaller), the focused ultrasound transducer was designed to fit within a rectangular aperture of 9 × 32 mm (Figs. 1 and 2) [16–18]. In order to accommodate the anatomy of a typical adult brain, where a tumor may be 4–5 cm away from the probe placement within the BrainPath™, a transducer with a 45-mm radius of curvature (RoC) was designed to target a natural focal point lesion 4–5 cm away. Building upon our prior simulation studies that investigated the effects of variations in transducer frequency, RoC, and power on the thermal dose and energy deposition in tissue, we developed and manufactured 2 alpha prototype transducer designs with center frequency of 1.5 MHz (full width half maximum bandwidth: 1.20–1.80 MHz) for *in vitro* validation (Fig. 2) [19,20]. Design I was a 1-piece, 9 × 32 mm, cylindrically curved rectangular aperture with 45 mm RoC. Design II contained three 8-mm-diameter circular elements placed on the curved geometry described above. The therapeutic array had a width of 12 mm casing, which widened to 15 mm to accommodate a built-in imaging array, as described below.

2.2. Imaging elements

To reduce the need for intraoperative magnetic resonance imaging (MRI) guidance, a built-in ultrasound imaging probe was designed to demonstrate proof-of-concept for the ultrasound-guided focused ultrasound (USgFUS) approach studied here. An “off-the-shelf” IP-105 linear imaging probe from Sonic Concepts (Bothell, WA) was chosen. This 64-element, one-dimensional phased array (center frequency: 5.0 MHz) was placed within the device housing and was tilted 30° to provide real-time visualization of the ablation lesion. Customized software was developed to drive the probe and to store, study, and modify signals. This software was developed on MATLAB (MathWorks Inc, Natick, MA) and installed on a Vantage 64 LE system (Verasonics Inc, Kirkland, WA).

2.3. Experimental assessment

In vitro testing of the preliminary prototype was performed by submerging the device in a 4-gallon test tank filled with tap water. Water was degassed to reduce the amount of dissolved gasses within the tank. Water temperature throughout experimental testing was 23 °C, with less than 1 °C variation. An acoustic absorber was placed inside the tank to reduce acoustic reflections from the tank edges. A calibrated oscilloscope as well as voltage and current probes were used to measure the voltage, current, and subsequently the net power of the device under test conditions. Using a three-dimensional (3D) printed holder created on a commercial 3D printer (Objet260, Connex3, Stratasys Ltd., Eden Prairie, MN), blocks of solid water phantoms were positioned at the focal point. Solid water is a tissue-mimicking phantom, proprietary to Sonic Concepts, with acoustic properties (i.e., attenuation and propagation velocity) similar to those of water. The absorption coefficient at 1 MHz is ~0.01 dB/cm. Sound speed is 1500 m/s. The phantoms were used to create predictable lesions and correlate results with calibrated hydrophone measurements. Lesion generation was observed both visually and via the built-in imaging probe driven by a Vantage 64 LE system (Verasonics, Inc., Kirkland, WA). The experimental design is shown in Fig. 3.

A 1.620-MHz sonification waveform with a pulse period of 10 ms and 50% duty cycle was generated. The solid water sample was sonicated for 10 s. To test the built-in imaging probe of the device, brightness-mode (B mode) images were recorded using the imaging transducer described above.

The solid water sample was raised 5 mm parallel to the long shaft of the device and, using the aforementioned parameters, an additional lesion was created. This process was repeated to create 5 lesions (Fig. 4). During each ablation, ultrasound images were recorded from the built-in imaging probe of the device. A new solid water block was

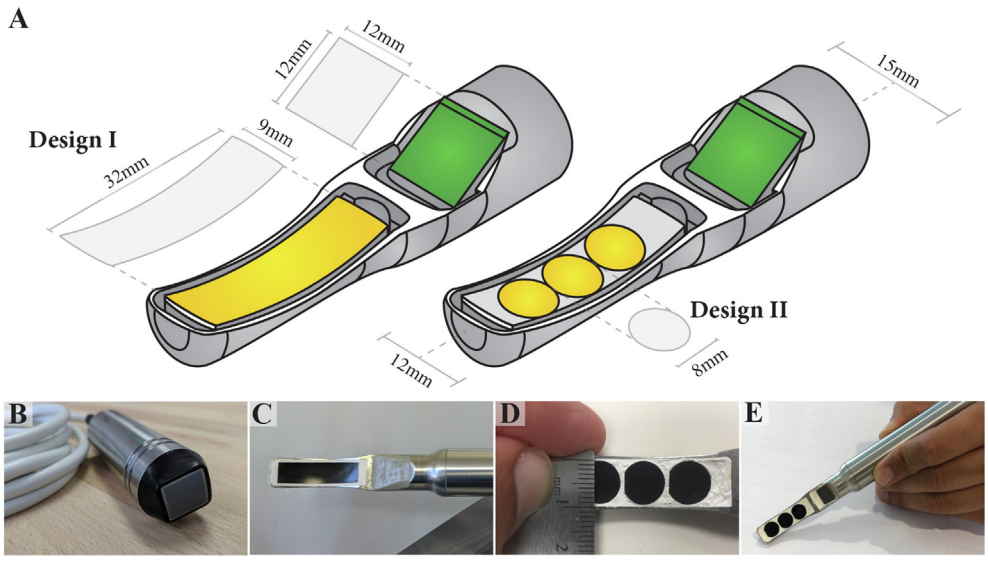

Fig. 2. Probe designs and prototyping details. (A) Two late-stage designs of the custom probe containing a 12 × 12-mm imaging transducer adjacent to a therapeutic component. Design I is a 1-piece, 9 × 32mm, cylindrically curved rectangular aperture with 45 mm RoC. Design II contains 3 circular therapeutic elements measuring 8 mm in diameter, arrayed along a 9 × 32mm, cylindrically curved rectangular aperture with 45 mm RoC. The therapeutic array fits within a casing 12 mm in diameter, which widened to 15 mm to accommodate the built-in imaging array. (B) A commercial imaging probe (Sonic Concepts IP-105, center frequency: 5 MHz) which was integrated into our custom ultrasound-guided probe; (C) functional prototype of the custom probe (Design I) housed in a stainless steel casing; (D) 8-mm-diameter circular therapeutic elements (Design II); (E) complete prototype of Design II, containing both the imaging and therapeutic components.

loaded, and the above-described procedure was repeated; however, a 30 s sonification was now performed for 3 trials. Axial, lateral, and elevation dimensions of the lesions were measured using a slide micrometer under microscope.

Subsequently, another block was placed in the water-filled tank at the acoustic maximum, as experimentally detected by a hydrophone (Y-Series High Intensity Hydrophones, Sonic Concepts Inc.). A thermocouple was assembled using a Type T thermocouple connector (SMPW-TM, OMEGA Engineering, Karvina, Czech Republic) and a 40-gauge Type T thermocouple wire with formvar enamel insulation (Pelican Wire, Naples, FL).

The thermocouple was inserted into the block at the acoustic maximum. Temperature measurements were acquired using a microprocessor thermometer (HH23, OMEGA Engineering). Per the aforementioned parameters, a 30 s sonification was performed with continuous temperature measurements. As mentioned previously, peak power was applied at 50% duty cycle.

3. Results

A prototype device based on Design I (Fig. 2) was built, but the design was abandoned due to lateral mode effects that resulted in multiple unwanted focal points and overheating during initial trials. A second prototype (Design II) was developed and underwent the same testing. At 118 W and 50% duty cycle, Design II generated lesions in the tissue-mimicking phantoms (Fig. 5 & Supplementary Video 1). Sonification of 10 s resulted in lesions with average dimensions of 2.5 × 1.2 × 6.5 mm (lateral, elevation, and axial alignments). 30 s sonification resulted in lesoins with average dimensions of 3.4 × 3.25 × 9.36 mm (Table 1).

Peak temperatures reached 42 °C at 10 s and 68 °C at 30 s of sonification. B-mode images acquired before, during, and after ablation resulted in lesion generation (Fig. 6 & Supplementary Video 2). Precise ablation was visualized by the built-in imaging probe during both 10 s and 30 s sonifications of the phantom blocks.

4. Discussion

Focused ultrasound devices facilitate targeted tissue ablation from a distance, providing a means to treat pathology previously considered inoperable due to inaccessibility. Noninvasive, transcranial focused ultrasound is limited by the acoustic properties of skull bone [2,3].

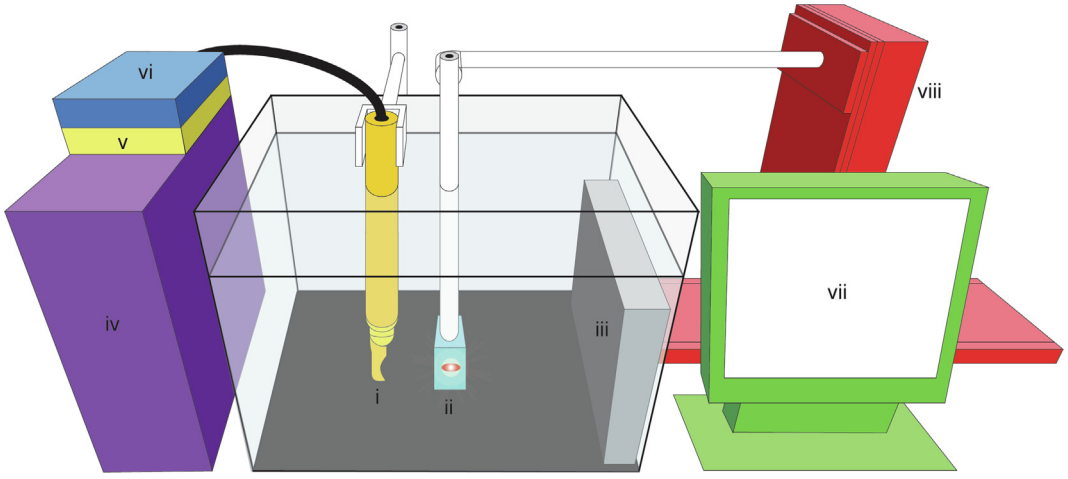

Fig. 3. Experimental setup. (i) ultrasound-guided focused ultrasound prototype, (ii) tissue-mimicking phantom, (iii) acoustic absorber, (iv) Vantage 64 LE system, (v) pre-amplifier, (vi) matching network, (vii) screen for real-time monitoring of ablation, and (viii) stepper motor to raise solid water tissue-mimicking phantoms with each sonification.

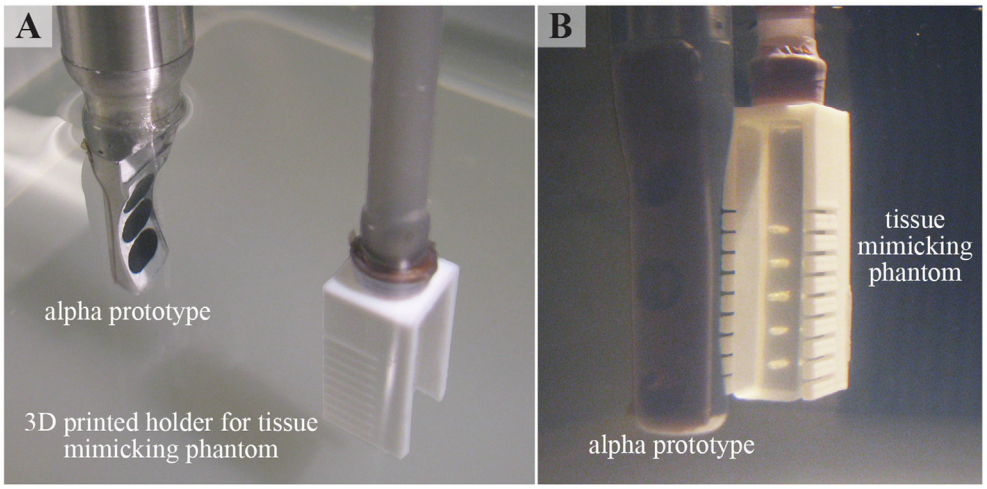

Fig. 4. Validation of the prototype. (A) Device aligned with the 3D-printed holder. (B) The prototype generated lesions in tissue-mimicking phantoms secured within the 3D-printed holder.

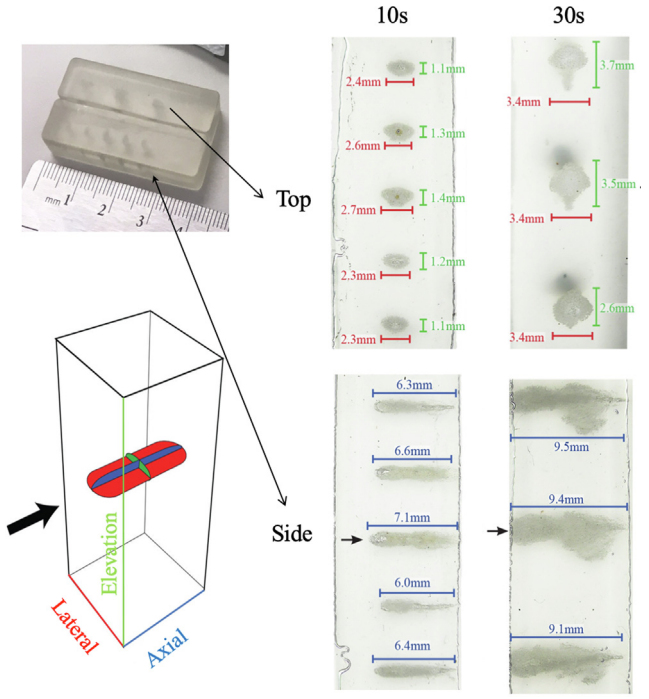

Fig. 5. Results of 10- and 30-second ablation of solid water samples. The maximum linear dimension of each lesion created was measured using a slide micrometer under microscope.

Table 1
Ablation measurements. *SD, standard deviation.

	10 s sonification			30 s sonification		
Axis	Z (mm)	Y (mm)	X (mm)	Z (mm)	Y (mm)	X (mm)
Trial						
1	2.29	1.09	6.45	3.39	3.71	9.53
2	2.33	1.19	6.01	3.42	3.50	9.43
3	2.71	1.43	7.11	3.40	2.56	9.15
4	2.60	1.29	6.63			
5	2.36	1.08	6.32			
Average	2.46	1.22	6.50	3.40	3.26	9.37
Min	2.29	1.08	6.01	3.39	2.56	9.15
Max	2.71	1.43	7.11	3.42	3.71	9.53
SD*	0.19	0.15	0.41	0.01	0.61	0.20

Minimally invasive, intracranial focused ultrasound circumvents these limitations, particularly in patients with excessively dense skulls [21]. However, developing focused ultrasound devices for use in MIS is challenging. Although acoustic physics favors larger transducer surface areas to achieve ablation, MIS demands tools with increasingly smaller dimensions [13,14,15]. The optimal geometry for functional, miniature focused ultrasound devices is not well studied [13]. This study summarizes a first step in the development of a focused ultrasound device small enough for use in MIS procedures such as neuro-oncological treatment performed with BrainPath™.

The novelty of the ultrasound transducer reported in this manuscript is two-fold:

(1) The **clinical novelty** of the present manuscript is concerned with a new surgical technique that allows remote treatment of inoperable tumors, primarily those in hard-to-reach regions of the brain that cannot be removed surgically because of their location. Currently, in most of these procedures, the BrainPath trocar tip is placed on the brain lesion, not outside the lesion. However, the new vision investigated in this study allows for BrainPath devices to be used in a manner that enables HIFU systems to be housed within them, to treat a lesion that is farther away. This may even apply to those tumors considered to be inoperable due to their locations or the sensitivity of the surrounding tissue. As a result, this new clinical application of BrainPath required design, development, and validation of a new HIFU device. This new device design and novel surgical approach can allow us to place BrainPath in a less sensitive region of the brain and remotely target tumor regions, even if there are sensitive areas in the intervening space.

(2) The **ultrasonic novelty** of the present manuscript is concerned with the development and validation of a transducer design (dimensions, geometry, frequency, number of elements, etc) that is small enough to fit into a BrainPath, yet capable of delivering sufficient energy deposition for tumor ablation. Specifically, the following design considerations were key:

According to the literature, a major consideration in transducer array design is the compromise between performance (favoring a large number of elements), and cost and complexity (favoring a small number of elements) [22,23]. Our study reports a thin (9-mm wide) array, consisting of three small, 8-mm diameter, piston transducers. This design allows for sufficient energy deposition, while fitting into BrainPath.

In addition to the above, typical frequencies applied by commercial neurosurgical systems (eg, Insightec's Exablate Neuro,

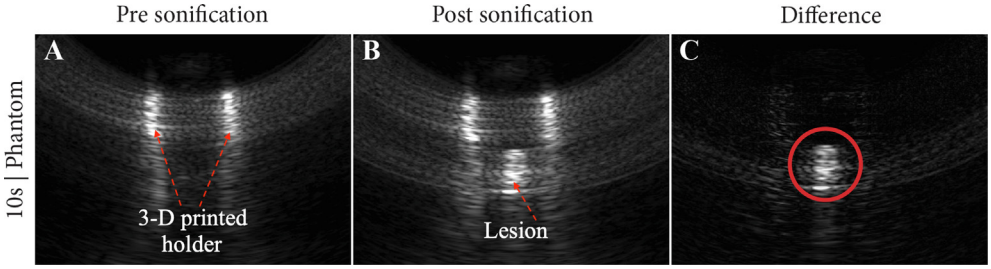

Fig. 6. 10 s sonification of solid water phantom as visualized by the built-in imaging probe: (A) pre ablation, (B) post ablation, and (C) the difference between. The red circle outlines the lesion. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Monteris Medical's NeuroBlate) are in the lower range compared to those for other organs (less than2 MHz) [24]. As the necessity for lower frequencies requires larger transducers, the design of a small (MIS), low-frequency, transducer proves even more challenging. For our ultrasound probe to fit within the BrainPath device, the diameter has to be smaller than 18 mm.

Over the past decade, other clinical applications have witnessed comparable designs and developments. An example includes a transesophageal probe reported in 26. Their device consists of eight concentric therapeutic annular rings and one imaging transducer in the middle (diameter of 14 mm). In this study, we have reported a new design with three therapeutic piston transducers (each 8 mm in diameter). Although these designs may look similar at a first glance, it is worth noting that they are quite dissimilar—for example, the circular transducers are therapeutic in our new design (see the circular yellow probes in Fig. 2**A**), whereas in the formerly reported transesophageal probe, the circular transducer is the imaging probe [26]. Finally, the lesions created in that paper were larger, while their probe was at 3 MHz in contrast to our 1.5 MHz, in this study.

Overall, the device presented in this study demonstrated a possible acoustic design, which with further iterations and miniaturizations, may catalyze the development of new minimally invasive USgFUS devices, particularly those designed for use in neuro-oncological settings.

5. Limitations and future directions

The device reported in this study was validated using tissue-mimicking phantoms within a controlled test tank, left in 23 °C water. However, the thermal dose needed to achieve ablation is known to vary by tissue type, and possessing 37 °C [25]. As a result, additional studies using fresh human brain tissue with histologic evaluation are needed to confirm successful focal point tissue necrosis and the effect on surrounding cells. Moreover, further *in vivo* testing is required to examine the effects of cerebrospinal fluid and perfusion on focal point and surrounding tissue heating. Future studies involving a larger number of array elements can investigate electronic delays as means to replace mechanical focusing of the probe to target lesions in 3D space.

Finally, although the built-in imaging probe of this device offered real-time visualization of the ablation, the image resolution resulting from a 5 MHz transducer was deemed by our clinical team as "*acceptable, yet in need of improvement*" for identification of lesions on the tissue-mimicking phantoms. Therefore, for real patients with vasculatures and other complex adjacent anatomies, the resolution and contrast of the image guidance will most likely need to be enhanced.

6. Conclusion

This study reports the development and validation of a USgFUS probe for use in MIS procedures. The dimensional constraints of the prototype were designed to reflect those of BrainPath™ trocars, which are MIS tools used to create atraumatic access to deep-seated brain pathologies. Laboratory testing demonstrated that the MIS USgFUS prototype successfully created lesions in tissue-mimicking phantoms and surpassed threshold temperatures for therapeutic applications. Real-time visualization was also achieved with a built-in imaging probe. Although this study demonstrates successful *in vitro* proof-of-principle, future studies should explore cadaveric validation and additional probe miniaturization for use in MIS procedures.

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Kyle Morrison, Francisco Chavez, and Kah Timothy Xiong are employees of Sonic Concepts, Inc. Dr. Brem is a consultant serving as Medical Advisory Board Chairman for InSightec. He is also on the board of directors for Galen Robotics. Dr. Nao J Gamo is the founder and CEO of Neurosonics Medical, Inc. Dr. Stephen Restaino is the Director of Engineering at Maryland Development Center, a startup studio supporting local medical device innovations.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kyle Morrison, Francisco Chavez, and Kah Timothy Xiong are employees of Sonic Concepts, Inc. They developed the reported customized transducer under contract from Johns Hopkins University. Dr. Henry Brem is a consultant serving as Medical Advisory Board Chairman for InSightec, a company active in the space of ultrasound for neurosurgical applications. He is also member of the board of directors for Galen Robotics. Dr. Nao J Gamo is the founder and CEO of Neurosonics Medical, Inc. Dr. Stephen Restaino is the Director of Engineering at Maryland Development Center, a startup studio supporting local medical device innovations.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ultras.2020.106210.

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