THE EFFECT OF THE SCANNING PATHWAY IN HIGH-INTENSITY FOCUSED ULTRASOUND THERAPY ON LESION PRODUCTION

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Abstract—Because tumors are much larger in size compared with the beam width of high-intensity focused ultrasound (HIFU), raster scanning throughout the entire target is conventionally performed for HIFU thermal ablation. Thermal diffusion affects the temperature elevation and the consequent lesion formation. As a result, the lesion will grow continuously over the course of HIFU therapy. The purpose of this study was to investigate the influence of scanning pathways on the overall thermal lesion. Two new scanning pathways, spiral scanning from the center to the outside and spiral scanning from the outside to the center, were proposed with the same HIFU parameters (power and exposure time) for each treatment spot. The lesions produced in the gel phantom and bovine liver were compared with those using raster scanning. Although more uniform lesions can be achieved using the new scanning pathways, the produced lesion areas (27.5 ± 12.3 mm² and 65.2 ± 9.6 mm², respectively) in the gel phantom are significantly smaller (p < 0.05) than those using raster scanning (92.9 ± 11.8 mm²). Furthermore, the lesion patterns in the gel phantom and bovine liver were similar to the simulations using temperature and thermal dose-threshold models, respectively. Thermal diffusion, the scanning pathway and the biophysical aspects of the target all play important roles in HIFU lesion production. By selecting the appropriate scanning pathway and varying the parameters as ablation progresses, HIFU therapy can achieve uniform lesions while minimizing the total delivered energy and treatment time. (E-mail: yfzhou@ntu.edu.sg) © 2011 World Federation for Ultrasound in Medicine & Biology.

Key Words: High-intensity focused ultrasound, Thermal ablation, Lesion production, Scanning pathway, Thermal diffusion.

INTRODUCTION

High-intensity focused ultrasound (HIFU) is emerging as a new modality for ablating solid tumors, such as uterine fibroids and cancers of the prostate, kidney, liver, breast, and pancreas (Meaney et al. 2000; ter Haar 2001; Wu et al. 2001, 2004; Dubinsky et al. 2008). In China and Europe, more than 100,000 cases have already been treated using HIFU in clinics, with promising results. The principle of HIFU therapy is focusing a high-intensity ultrasound beam into a small region where a tumor is located under the guidance of either magnetic resonance imaging (MRI) or ultrasound imaging (Bailey et al. 2003). The acoustic intensity at the focus is several 1000 W/cm² so that the temperature can exceed 65°C within seconds to induce irreversible coagulation necrosis in the tissue. In comparison to traditional cancer treatment methods (i.e., open surgery, radiotherapy or chemotherapy) and other physical methods for tissue ablation (i.e., laser, microwave or radio-frequency [RF]), HIFU ablation has the advantages of noninvasiveness, precise focusing and deeper penetration without exposing patients to ionizing radiation. Substantial evidence suggests that the risk of metastasis is not increased after HIFU treatment (Oosterhof et al. 1997; Wu et al. 2003; Kenney 2005), and fewer treatment related complications have been observed (Thuroff and Chaussy 2000; Aus 2006).

Despite its uniqueness and encouraging preliminary clinical results, HIFU remains a therapeutic modality in development, with several technical problems limiting it from becoming a widely adopted procedure for both patients and physicians (Aus 2006; Rewcastle 2006; Zhou 2011). Engineers and scientists are devoting
themselves to the goals of achieving accurate focusing, developing appropriate treatment planning methods and providing real-time monitoring of the thermal field and lesion formation. Because tumors are typically several centimeters in diameter, much larger than the size of the focus of the HIFU transducer (on the order of millimeters in diameter and approximately 1 cm in length), ablation of the entire volume of tumors requires multiple treatment spots. Individual treatment spots are conventionally administered in a raster pattern over a treatment layer by either mechanical movement or electrical steering. In the acoustic field, the tissue absorbs the acoustic energy and converts it into thermal energy. Between 60°C and 100°C, the almost instantaneous induction of protein coagulation that irreversibly damages key cytosolic and mitochondrial enzymes and nucleic acid histone complexes occurs (Thomsen 1991). Meanwhile, the thermal energy spreads in a temperature gradient, known as the thermal diffusion effect. Because of thermal diffusion from the nearby treated region, the lesion size of each treatment spot will gradually become larger as the HIFU therapy progresses (Curiel et al. 2004), which may cause insufficient treatment of the initial spots and over-treatment of those later ones. A scanning path optimization method was developed to treat the tumor volume as fast as possible while keeping the temperature in the healthy tissue within a safe threshold (42°C) based on the minimum time formulation from optimal control theory (Malinen et al. 2005). Large numbers of phased array elements (530) and foci in the target (300 for a sphere with radius of 1.9 cm) are required in the theoretical simulation, but these are unattainable for most commercially available HIFU systems.

In this study, two new scanning pathways, spiral scanning from the center to the outside and spiral scanning from the outside to the center, are proposed and compared with the conventional raster scanning method using the same HIFU parameters (acoustic power and exposure duration) in both gel phantom and ex vivo bovine liver samples. The scanning pathway affects lesion production, with more uniform lesion patterns but smaller volumes obtained using the new approaches. The produced lesion pattern in the gel phantom is similar to the theoretical simulation using a temperature-threshold model and the lesion pattern in the ex vivo experiment agrees with the calculations, assuming a thermal dose-threshold. Therefore, thermal diffusion, the scanning pathway and the biophysical properties of the tissue are important in HIFU lesion formation. By selecting the appropriate scanning pathway and varying the output parameters as ablation progresses, HIFU therapy can achieve uniform lesions while minimizing the total delivered energy and treatment time.

**MATERIALS AND METHODS**

**Scanning pathway**

Raster scanning is a conventional scanning approach used in clinical HIFU therapy (Fig. 1a). For simplicity, only one treatment layer is considered here. In addition to raster scanning, two new scanning pathways, spiral scanning from the center of the treatment area to the outside (Fig. 1b) and spiral scanning from the outside to the center (Fig. 1c), were proposed and evaluated. In this study, 25 treatment spots were arranged in the shape of a diamond with a grid spacing of 4 mm. The treatment parameters for each spot are the same as those used in the clinical treatment: 60 pulses per spot with duty cycle of 50% and a pulse repetition frequency of 3.3 Hz (150 ms of HIFU on followed by 150 ms of HIFU off in each pulse), a 6-s interval time between treatment spots (including mechanical movement time) and 1000 J of absorbed acoustic energy at the target. The electrical output power of the HIFU transducer was calculated to be about 290 and 366 W for the gel and bovine liver samples, respectively, using our proposed method (Hwang et al. 2009). The pressure waveforms at the focus were measured with a fiber optic probe hydrophone (FOPH) (Zhou et al. 2006), from which the acoustic intensities were calculated to be about 3850 and 5250 W/cm², respectively, for the gel and bovine liver samples.

**Theoretical simulation**

A theoretical model was established to simulate the acoustical and thermal fields at the HIFU focal region and the subsequent lesions produced with different scanning pathways. The Khokhlov-Zabolotskaya-Kuznetsov (KZK) nonlinear evolution equation has been used widely to model high-intensity acoustic beams numerically (Bailey et al. 2003) and was applied to simulate the acoustic field generated by the HIFU transducer,

\[
\frac{\partial p}{\partial z} + \frac{p}{c_0 \rho_0} \frac{\partial p}{\partial \tau} - \frac{b}{2c_0} \frac{\partial^2 p}{\partial \tau^2} = \frac{C_0}{\rho_0 c_0} \int_{-\infty}^{\tau} \Delta \Delta p(\tau')d\tau',
\]

where \(p\) is the acoustic pressure, \(z\) is the coordinate along the beam axis, \(c_0\) is the small-signal sound speed, \(\rho_0\) is the ambient density, \(\tau=t-z/c_0\) is the retarded time, \(b\) is the coefficient of nonlinearity, \(c_0\) is the dissipative parameter and \(\Delta \Delta\) is the Laplacian operator with transverse coordinates \(r=(x,y)\). In the frequency-domain schemes, the solution of eqn (1) is represented in the form of a Fourier series expansion,

\[
p(z,r,t) = \sum_{n=-\infty}^{\infty} C_n(z,r) \exp(-i\omega_0 t),
\]

where \(\omega_0\) is the fundamental frequency of the HIFU pulses and \(C_n\) is the complex amplitude of the \(n\)th
The mathematical model for temperature elevation in the tissue is based on the bioheat transfer equation (BHTE) (Bailey et al. 2003),

$$\frac{\partial T}{\partial t} = k \Delta T - \frac{T - T_0}{t_p} + \frac{Q}{c_v};$$  \hspace{1cm} (3)

where $t$ is the time, $t_p$ is the perfusion time (inverse of the perfusion rate), $T(r, t)$ is the tissue temperature, $T_0$ is the equilibrium temperature (25°C in both the gel phantom and bovine liver experiments), $k = K/c_v$ is the local tissue temperature conductivity, $K$ is the heat conductivity, $c_v$ is the heat capacity of a unit volume and $\Delta$ is the Laplacian operator. The absorbed ultrasound energy, $Q$, is calculated from the KZK equation,

$$Q = 4 \sum_{a=0}^{100} \alpha_a |C_n|^2/c_0 \rho_0,$$  \hspace{1cm} (4)

where $\alpha_a = (n\omega_0)^2 b/2c_0^2 \rho_0$ is the attenuation coefficient, which exhibits quadratic frequency dependence according to eqn (1). One hundred harmonics were used in our calculation as a compromise between accuracy in the solution and computational burden. The thermal dose (TD) was calculated using

$$TD_{43°C}(t) = \int_0^t R_{43°C}^{3°C}(t')dt',$$  \hspace{1cm} (5)

with $R = 0.25$ if $T(t) < 43°C$ and 0.5 otherwise (Sapareto and Dewey 1984). The thermal dose was then logarithmically normalized by the value required to create thermally irreversible damage in most tissue types, which is equivalent to the thermal dose of a 240-min exposure at 43°C (Lele 1967; Sapareto and Dewey 1984; Damanion and Hynynen 1994) for easy comparison.

$$\log_{14400} \left( \frac{TD_{43°C}(t)}{TD_{43°C}(240)} \right) = 0.$$

**Experiment set-up**

The HIFU system used in this study (FEP-BY02; Yuande Bio-Engineering Ltd., Beijing, China) consists of 251 individual lead zirconate titanate (PZT) elements, with all driven in phase and arranged in a concave spherical holder. Each PZT element has a center frequency of ~1 MHz and a diameter of 16 mm. The HIFU transducer has an outer diameter of 33.5 cm and an inner diameter of 12 cm with an integrated ultrasound imaging probe (S3, Logiq 5; GE, Seongnam, Korea) mounted in the central
hole coaxial to the HIFU beam. The optically transparent gel phantom ($L \times W \times H = 5.5 \times 5.5 \times 5 \text{ cm}$) was composed of polyacrylamide hydrogel and bovine serum albumin (BSA) and became optically opaque when thermally denatured (Lafon et al. 2005). The gel was surrounded by a tissue-mimicking phantom that contains 6.5% Alginate impression material (Jeltrate; Dentsply International, York, PA, USA) and was placed into a sample holder. The holder was immersed in degassed water at room temperature ($\sim 25^\circ\text{C}$) and connected to the treatment table. The center of the transparent gel phantom was aligned to the HIFU focus under the guidance of B-mode ultrasound imaging. A LabVIEW (National Instruments, Austin, TX, USA) program was written and run on a PC to send commands to the micro control unit (MCU) of the FEP-BY02 system via a RS-232 port to control the motion of the treatment table and the delivery of HIFU pulses (Fig. 2). After the treatment, the HIFU phantom was removed and the lesions were photographed for comparison. Furthermore, the projected lesion areas and maximum lesion lengths were calculated by processing the images in Photoshop (Adobe Systems Inc., San Jose, CA, USA) and MatLab (Mathworks, Natick, MA, USA). At least five gel samples from each scanning pathway were used for the statistical analysis.

**Ex vivo study**

*Ex vivo* studies were performed using freshly excised bovine liver obtained from a local slaughterhouse on the day of the experiment. The samples were cut to a size of $4 \times 4 \times 4.5 \text{ cm}$, immersed in phosphate buffered saline (PBS) solution and then degassed in a vacuum chamber for at least 30 min until visible bubbles were no longer emerging. The degassed tissue samples were inserted into a tissue-mimicking phantom ($L \times W \times H = \sim 16 \times 16 \times 7.5 \text{ cm}$) made of alginate impression material with a hole ($L \times W \times H = \sim 4 \times 4 \times 4.5 \text{ cm}$) at the bottom, where an alginate stand-off was added to simulate the abdominal wall (Hwang et al. 2009). The attenuation of the alginate stand-off was measured before each treatment using a standard technique with a broadband transmission ultrasound system (Bloch 1998). The phantom combo was connected to the treatment table and its sandwiched structure could be clearly seen during ultrasound imaging (Fig. 3). The center of the tissue sample was then aligned to the focal point of the HIFU system. Immediately after the HIFU treatment, the tissue samples were placed in a slider box, stored in a vacuum-sealed plastic bag, and frozen at $-10^\circ\text{C}$ for 1 h to ensure that sufficient stiffness was achieved to facilitate optimal slicing while
minimizing the amount of tissue expansion. The tissue was then sectioned and lesion image capture was carried out using our custom-built system and established protocol (Andrew et al. 2002). The tissue sample was advanced until the tissue face was even with the plane of the slicer blade. The tissue was advanced by rotating a pushrod and the distance was displayed in a digital caliper. The excess tissue was cut away and the newly exposed face was photographed with a digital camera. The process was repeated until no lesions were observed for at least three consecutive slices. The image files were then downloaded to a computer for further processing. At least six bovine liver samples were treated using each scanning pathway.

RESULTS

Simulation

The simulated pressure distribution, both along and transverse to the transducer axis, using the KZK model in the focal region is similar to our measurement using a polyvinylidene fluoride (PVDF) needle hydrophone and the fiber optic probe hydrophone (FOPH) (data not shown). The simulated thermal fields from the theoretical model are shown in Figure 4. Using the raster scanning method, the thermal field, either temperature elevation or thermal dose, was asymmetric. In contrast, with the new spiral scanning pathways, the thermal fields were more symmetric. Two models were used to calculate lesion generation: temperature and thermal dose threshold models. In the temperature threshold model, the lesion formation is assumed to begin when the absolute temperature reaches 65°C or a temperature elevation of 40°C in our study (Fig. 4b) while the thermal dose is assumed to determine the lesion formation in the thermal dose-threshold model (Fig. 4d).

By using the raster scanning method and the temperature-threshold lesion formation model, the lesion can only be seen beginning from the 3rd one (Fig. 4b). In addition, two others on the boundary of the therapy region, the 5th and 10th lesions, were invisible. Over the course of the HIFU treatment, the lesion size became larger because of thermal diffusion from nearby lesions. However, the lesion size does not change monotonically. For example, the 16th lesion is relatively small and the largest lesion is not the last treatment spot but the 23rd one. When using the spiral scanning pathway from the center to the outside, the generated lesions were smaller in comparison to those generated by raster scanning. The lesion pattern using spiral scanning from the outside to the center had different characteristics (Fig. 4b) with all of the lesions on the boundary (the first 12 lesions) being invisible. Because the thermal energy is concentrated toward the center of the treatment area, the last lesion was the largest one.

The temperature elevations at each treatment spot were compared (Fig. 5). The relationship of the temperature elevation pattern is complicated by the progress of the HIFU treatment and depends on the specific scanning pathway. The spots with the highest temperature elevation using these three scanning pathways are the 23rd, 10th and 25th, and the corresponding temperature elevations are 51.3°C, 45.5°C and 57.1°C, respectively. Moreover, their temperature profiles are compared in Figure 6 and they are characterized by a sharp temperature rise that is followed by a slow decay. The temperature rise time was the same as the HIFU exposure time (18 s in this study) and the elevation amplitude was determined by the absorbed acoustic energy, heat capacity and conductivity of the target. The exponential decay rate mainly depended on the perfusion time, \( t_p \). The thermal diffusion effect from nearby lesions, playing an important role in the thermal field, had a similar temperature profile as the source but with amplitude inversely proportional to \( r^2 \), where \( r \) is the distance from the thermal source. Thus, the temperature profile of a spot includes the HIFU-induced temperature elevation and the combined contributions from the other lesions. For example, in the temperature profile of the 10th lesion using the spiral scanning pathway from the center to the outside, the first peak at the retarded time of \(-110 \) s was mainly due to diffusion from the 3rd and 4th lesions, while the last peak at the retarded time of 298 s was mainly contributions of the 20th and 21st lesions. If a lesion is surrounded by recently treated ones, as with the 25th lesion in the spiral scanning pathway from the outside to the center, then the thermal contributions from these “neighboring” lesions will not be determined easily because of the small differences in the exposure starting time in comparison to the perfusion time (on the order of hundreds of seconds). As a result, the temperature baseline was enhanced significantly (i.e., 22.6°C) and higher temperature elevation and larger lesions were achieved (Fig. 6).

In comparison, the simulated lesions using the thermal dose-threshold model (170.9, 117.0 and 130.8 mm², respectively) are much larger than those using the temperature-threshold model (40.7, 18.9 and 25.2 mm², respectively) but they have similar lesion characteristics (Fig. 4d). The corresponding logarithmically normalized maximum thermal doses of these three scanning pathways were 6.4, 4.6 and 8.2, respectively (Fig. 4c). In addition, lesion coalescence occurred using this model, such as with the 22nd ~ 24th lesions in raster scanning and the 21st ~ 25th lesions in spiral scanning from the outside to the center.

Lesions in the gel phantom

The lesions generated in the gel phantom were found to have similar patterns and characteristics as predicted by...
the temperature-threshold model when observed from both the top view and lateral directions (Fig. 7). However, merging of lesions at the end of the treatment using raster scanning or spiral scanning from the outside to the center was found. The total lesion areas of 25 spots for each of the three scanning pathways (raster scan, spiral scanning from the outside to the center and spiral scanning from the center to the outside) were calculated to be
The differences in the areas are statistically significant ($p < 0.05$, Fig. 8a). Although the coalescence of large HIFU-generated lesions prevents accurate determination of the lengths of individual lesions in the gel phantom, some observations can be made. First, the lesion length increases with the temperature elevation of each lesion. The maximum lesion lengths using raster scanning, spiral scanning from the center to the outside and spiral scanning from the outside to the center were $10.1 \pm 0.65$ mm, $6.8 \pm 0.92$ mm and $12.3 \pm 0.54$ mm, respectively ($p < 0.05$, Fig. 8b). Second, “tadpole-shaped” lesions could be seen at locations with corresponding high-temperature elevations, while the symmetric “cigar-shaped” lesions correlate well with low temperature rises, which is obvious when using raster scanning and spiral scanning from the outside to the center. Third, the lesions produced using spiral scanning from the center to the outside are symmetric.

**Lesions in the tissue**

The frozen treated tissue samples were sliced, and the lesions produced at the focal plane using the three scanning pathways are shown in Figure 9. The influence of the diffusion effect on lesion production is apparent, which confirms the validity of this phenomenon in the clinical environment. However, the lesion sizes were larger than those in the gel phantom and their patterns were similar to the simulation using the thermal dose-threshold model (Fig. 4d), which suggests that lesion formation in the tissue may be different from that in the BSA-embedded gel phantom. Because the lesion boundaries were not visually clear and the vessel lumen frequently showed up in the cut bovine liver, accurate determination of a lesion should be carried out via a histologic technique using a microtome on the whole tissue and a three-dimensional (3-D) reconstruction method. Due to facility limitations, the histologic capability was only for a small volume ($1 \, \text{cm} \times 1 \, \text{cm} \times 5 \, \text{cm}$), and further *ex vivo* investigation will be performed later.

**DISCUSSION**

HIFU has been used in the clinical treatment of solid tumors and cancers in China and Europe with promising results but remains a developing technology. Currently, the HIFU focus is scanned throughout the target in either discrete points/spots, as with the FEP-BY02, Ablatherm (EDAP-TMS, Vaulx-en-Velin, France), Sonablate-500 (Focus Surgery Inc., Indianapolis, IN, USA), and ExAblate systems (InSightec Ltd., Tirat Carmel, Israel) or predetermined scanning trajectories, as with the model IC system (Chongqing Haifu Technology Ltd., Chongqing, China). The treatment parameters are typically kept the same during the treatment unless the exposure is beyond the patient’s tolerance. Because of thermal accumulation and diffusion effects, the lesion size will increase as the HIFU therapy progresses. Therefore, the lesions produced at the beginning of the HIFU therapy may be insufficient to cause tissue necrosis, while those at the end of the therapy may be overexposed, increasing the potential of unintended collateral thermal injury. Such an asymmetric lesion production pattern was observed both in our gel phantom and *ex vivo* studies. A similar progressively enlarged lesion formation pattern was also found using raster scanning (Curiel et al. 2004) or the constant scanning rate method (Kaczkowski et al. 2002) *ex vivo*. In the study by Kaczkowski et al.,
the thermal accumulation that occurred within an interior region in the bovine liver sample was found as circular tracks that were placed in a sequence of decreasing radii. Although no in vivo study has been performed to confirm this phenomenon, extrapolating this lesion production pattern to the clinical environment is reasonable no matter whether the HIFU focus is scanned in discrete spots or trajectories. Some clinical devices, such as the Sonalleve (Philips, Andover, MA, USA), have a long waiting interval time between treatment spots to allow the target cool to body temperature to avoid temperature elevations in the surrounding healthy tissue (Damaniou and Hynynen 1994). Using this strategy, the heat accumulation effect described in this study will not be present but the treatment duration for the whole target will be much longer.

Several studies have been performed to understand the mechanisms of HIFU lesion production (ter Haar 2001; Vaezy et al. 2001; Rabkin et al. 2005; Khokhlova et al. 2006). In those experiments, a single lesion was usually studied. However, clinical HIFU treatment of tumors requires multiple lesions for effective ablation, which is more complex than the simple summation of multiple single lesions. Owing to the thermal diffusion effect, the thermal energy at the focal region will spread and the temperature of the surrounding or neighboring tissues will increase. Larger lesions are formed at a higher temperature baseline with the same delivered energy. Therefore, the lesion size will gradually increase as the HIFU therapy progresses. If the lesion size is larger than the interval distance between spots, then lesions may coalesce. Altogether, these results illustrate that thermal accumulation and the diffusion effects are critical in multi-lesion treatments. In this study, two new pathways, spiral scanning from the center to the outside and spiral scanning from the outside to the center, were evaluated and compared with conventional...
raster scanning. More uniform lesions are produced with the new spiral pathways, although they result in different lesion patterns. Therefore, the scanning pathway has a large impact on lesion production. The in vivo or clinical outcomes of these three scanning pathways are under investigation.

The biophysical aspects of the tumor-heat interaction, such as perfusion time and heat capacity, must be taken into account when performing thermal ablation. A hypervascular tumor, such as hepatocellular carcinoma, has a short perfusion time. Substantial evidence suggests that vascular flow might be responsible for perfusion-mediated tissue cooling, which is referred to as the “heat-sink” effect. Vascular flow prevents achieving the cytotoxic temperature necessary to induce coagulation in the highly vascular regions of a tumor (i.e., the peripheral tumor-parenchyma interface) and this subsequently limits the extent of coagulation necrosis (Goldberg et al. 2000). A decreased volume of coagulation has been observed when comparing in vivo liver with ex vivo and nonperfused liver. Coagulation necrosis in vivo is often shaped by the hepatic vasculature. As a result, the progressively increased lesion pattern using raster scanning may not be as apparent as presented in this article. In comparison, the thermal perfusion effects are significant in hypovascular tissues, such as pancreatic cancer, so that thermal accumulation and diffusion might be comparable to those in ex vivo. Therefore, tissue type and biophysical properties need to be considered in HIFU therapy planning.

From the viewpoint of the physician, the three basic requirements for the HIFU ablation of solid tumors are (1) the ability to generate a predictable lesion for every treatment spot, (2) the uniformity of all of the generated lesions and (3) the ability to achieve complete coverage of the entire treated volume. The commercial HIFU products, both extracorporeal and endocavitary types, provide information on the treatment location and the number of spots, but cannot predict lesion shape and size. MRI guidance can monitor the temperature and detect the lesion during HIFU therapy to control the HIFU exposure energy for safety and efficacy; however, due to its low temporal resolution, temperature underestimation may occur (Khokhlova et al. 2009). Furthermore, although conventional B-mode ultrasound imaging has been widely used to visualize the progress of thermal therapy (Lele 1967), the coagulated tissue is difficult to identify because the tissue echogenicity does not change significantly (Hynynen 1997) except when hyperechoes occur due to boiling or cavitation (Vaezy et al. 1997; Kenney 2005). Some technologies have been developed to estimate the temperature by tracking the echo arrival time shifts in the ultrasound backscatter caused by changes in the speed of sound and tissue thermal expansion (Qian et al. 2006; Anand et al. 2007) or with amplitude-modulated harmonic-motion imaging (HMI) (Maleke and Konofagou 2008; Curiel et al. 2009). Lesion production can be monitored using the radiation-force technique (Lizzi et al. 2003), echo-strain imaging (Souchon et al. 2005) and elastography (Righetti et al. 1999). Until recently, only MRI has been accepted by the US Food and Drug Administration (FDA) for monitoring HIFU ablation. Therefore, appropriate HIFU ablation monitoring is necessary. To generate uniform lesions, the delivered acoustic energies should be adjusted at each treatment spot. In our gel phantom study, the first lesion was never visible no matter which pathway was used. A rational approach would be setting the highest acoustic energy for the first lesion and gradually decreasing the output for the subsequent ones. How to dynamically

![Fig. 8. The statistical comparison of (a) the lesion area detected from the top view and (b) the maximum lesion length detected from the lateral view generated using different scanning pathways. Five gel samples were used in each group. Scanning protocol #1: raster scan; #2: spiral scanning from the center to the outside; #3: spiral scanning from the outside to the center.](image-url)
adjust the HIFU treatment parameters depends on the specific scanning pathway used. In this article, only three scanning pathways were compared. Although raster scanning achieves the largest lesion volume, it may not be the optimal mode. The optimization of the scanning pathway and HIFU parameters will be emphasized in the future.

Two lesion formation models, the temperature and thermal dose-threshold models, were used to simulate the lesion sizes and shapes in this study. Thermal denaturation of BSA or egg-white protein (Divkovic and Jenne 2004) creates coagulation effects in the polyacrylamide tissue phantom, and the coagulation process was found to be more sensitive to the temperature than to the thermal dose (Nandlall et al. 2008). The 7% BSA gel phantom began to denature at temperatures in excess of 58°C (Bouchard and Bronskill 2000) and the gel opacity increased with the temperature increase in the gel (Lafon et al. 2005). Although the gel opacity increased quickly and significantly during the first 200 s when immersing the phantom in the water bath, the value continued to increase slowly over a long duration at the elevated temperature (Lafon et al. 2005). A hybrid (both temperature and thermal dose threshold) model may be able to predict lesion formation in the gel phantom accurately and explain the discrepancies between the simulation and experimental observations. The thermal dose concept was defined by Sapareto and Dewey to find the relevance between hyperthermia and its induced biological effects (Sapareto and Dewey 1984). A 240-min exposure at 43°C can generate irreversible damage to tissue, including tumors and cancers (Damianiou and Hynynen 1994). Although this definition originated from the hyperthermia protocol (heating to a temperature of 43–45°C for several hours), this model gave good estimations of the thermal lesion at the higher temperatures caused by HIFU in muscle and liver samples (Damianiou and Hynynen 1994; Curiel et al. 2004). The intensity at the focal point of HIFU, greater than 1000 W/cm², is beyond the cavitation threshold and inertial cavitation usually occurs during thermal ablation.

Fig. 9. Representative photos of lesions in the bovine liver using different scanning pathways in the ex vivo experiment: (a) raster scanning, (b) spiral scanning from the center to the outside and (c) spiral scanning from the outside to the center.
The violent bubble collapse of inertial cavitation, producing shock waves of very high pressure (20～30,000 bar) and high temperature (2000～5000 K) in the microenvironment (Mason 1998), can cause damage to biologic cells, such as apoptosis. In apoptotic cells, the nucleus of the cell self-destructs with rapid degradation of DNA by endonucleases. Apoptosis may be an important delayed bioeffect in tissue exposed to HIFU (Luo et al. 2007; Poff et al. 2008), especially in cell types that regenerate poorly, such as neurons. In addition, numerous studies have illustrated that the HIFU-induced cavitation effect causes a local increase in the attenuation around the bubble, which then absorbs the subsequent acoustic pulses, and prevents the deposition of heat beyond the focal area (Hynynen 1991; Holt and Roy 2001). Subsequently, this effect leads to a large temperature increase and enhanced lesion generation (growing broader, moving closer to the transducer and becoming tadpole-shaped) (Khokhlova et al. 2006).

Although the occurrence of cavitation or boiling bubbles produces hyperechoes in the B-mode ultrasound images for HIFU therapy monitoring, in practice it inhibits the generation of precisely sized and positioned lesions planned to completely necrose a tumor volume. These tadpole-shaped lesions are larger in dimension but are less controllable, which has a considerable impact on intervening vital structures (i.e., arteries and nerves) and when ablating proximal tumor layers. Therefore, feedback control from the lesion detection technique in real-time would enhance the efficacy and efficiency of HIFU therapy. Overall, considering the presence of HIFU-induced bubbles is important to simulate both the acoustic and thermal fields at the focal region to calculate the thermal dose for lesion estimation (Chavrier et al. 2000; Curiel et al. 2004) and to monitor the ablation progress in clinics as well.

In summary, the lesion production pattern using conventional raster scanning was studied in this article. Because of thermal diffusion from nearby lesions, the size of subsequent ones will gradually become larger as the HIFU therapy progresses, which may cause insufficient treatment of the initial lesions and over-treatment of the later ones unless parameters are varied. In addition, two new scanning pathways, spiral scanning from the center to the outside and from the outside to the center, were proposed and the produced lesions were compared with raster scanning. Theoretical simulation, gel phantom, and ex vivo bovine liver experiments demonstrate that the new scanning pathways produce more uniform lesions than conventional raster scanning, although with smaller lesion volumes. Thermal diffusion, the scanning pathway and the biophysical aspects of the target are important in lesion production during HIFU ablation. Optimizing the scanning pathway and dynamically adjusting the HIFU parameters seem advantageous for producing uniform and complete lesions with higher efficacy and safety but without significantly increasing the treatment time.

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