Generation of uniform lesions in high intensity focused ultrasound ablation

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ABSTRACT
High intensity focused ultrasound (HIFU) is emerging as an effective oncology treatment modality according to the clinical experience in the last decade. The temperature at the focus can reach over 65 °C within seconds, denaturing cellular proteins and resulting in coagulative necrosis. HIFU parameters are usually kept the same for each treatment spot in tumor ablation. Because of the thermal diffusion from nearby spots, the lesion size will gradually increase as the HIFU therapy progresses, which leads to insufficient treatment of initial spots and over exposure of later ones. From the viewpoint of the physician, uniform lesions with the least energy exposure and the least energy are preferred in tumor ablation. In this study, an algorithm was developed to determine the number of HIFU pulses delivered to each spot in order to generate uniform lesions that fill the region-of-interest completely. The exposure energies required using different scanning pathways (raster scanning, spiral scanning from the center to the outside, and spiral scanning from the outside to the center), spot spacing (1 mm, 2 mm, 4 mm, and 6 mm) and motion time (from 0 s to 400 s) were compared with each other. It is found that spiral scanning from the outside to the center with spot spacing of 2 mm and motion time less than 10 s needs the least numbers of pulses or HIFU energy in uniform lesion production with the minimal temperature elevation. In addition, the effects of thermal properties of tissue (i.e., specific heat capacity, convective heat transfer coefficient, and thermal conductivity) on HIFU ablation were investigated in order to determine the HIFU treatment planning for various targets. Uniform lesion production in the transparent gel phantom and ex vivo bovine liver samples using the proposed algorithm proved effective and accord with the simulation for different scanning pathways by an extracorporeal clinical HIFU system. Therefore, dynamically adjusting ultrasound exposure energy can improve the efficacy and safety of HIFU ablation, and the treatment planning depends on the scanning protocol and thermal properties of the target.

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1. Introduction

High-intensity focused ultrasound (HIFU) is emerging as an effective oncology treatment modality according to more than 100,000 patients who have been involved in clinical trials in Asia and Europe [1–4]. Despite its technical advantages (i.e., noninvasiveness and nonionization) and encouraging preliminary clinical results for a variety of cancers and solid tumors (i.e., prostate, pancreatic, liver, breast, kidney cancers and uterine fibroids) with few complications and in-patient stays, HIFU is still a developing technology yet to be accepted widely by both patients and physicians. Because the detectable solid tumors and cancers are typically several centimeters in size, much larger than the focal zone of a HIFU transducer (i.e., 1–2 mm in diameter and approximately 1 cm in length), ablating the entire volume of tumor requires multiple treatment spots. Individual treatment spots are administered in a raster pattern in a treatment layer, and HIFU parameters (i.e., power output, pulse length, duty cycle, and total exposure duration) are kept the same, unless they are beyond the patient’s tolerance during the therapy. Subsequent layers are treated moving proximal to the HIFU source. Because of thermal diffusion from nearby treatment spots, the lesion size will gradually become large as the HIFU therapy progresses, which may cause insufficient treatment of the initial spots but over-exposure of the later ones. In addition, it is found that the scanning pathway affects the lesion production and spiral scanning, either from the outside to the center or from the center to the outside, will produce more uniform lesion patterns [5]. From the viewpoint of the physician, there are three basic requirements for the lesion production: (1) ability to generate a predictable lesion for every treatment spot; (2) all generated lesions need to be uniform in size; (3) complete coverage of the entire target volume. Furthermore, the efficacy and safety of HIFU are also of importance for its clinical application.

In the radiotherapy, treatment planning is a critical step made by a team consisting of radiation oncologists, radiation therapist, medical physicists, and dosimetrists. There are two types of planning methods: forward and inverse planning [6]. Forward planning...
is usually used in external-beam radiotherapy, and beams will be placed into a treatment plan to deliver sufficient radiation to a tumor while both sparing critical organs and minimizing the dose to the healthy tissue. However, this approach is only sufficiently adept at handling relatively simple cases, in which the tumor has an ordinary shape and is not near any vital organs. For more sophisticated situations, inverse planning, also known as “automated planning”, is used to create an intensity-modulated treatment plan. Given information of a patient’s tumor (i.e., shape, size, and location), critical organs, and radiation doses, an optimal treatment plan is determined to match all the input criteria. Inverse planning has already been applied successfully and widely in brachytherapy to deliver accurately a high dose of radiation to a target organ (i.e., breast and prostate)\[7\]. The optimal number, strength, and locations of small encapsulated radioactive seeds are determined prior to implantation, and this initial planning helps to ensure that “cold spots” (too little irradiation) and “hot spots” (too much irradiation) are avoided during treatment, as these can respectively result in treatment failure and side-effects. In order to generate uniform lesions in HIFU ablation, an algorithm was developed to determine the number of pulses delivered to each treatment spot while keeping the other parameters (i.e., power output, pulse length, and duty cycle) the same as inverse planning. The effects of scanning protocol (i.e., scanning pathway, spot spacing, and motion time) and thermal properties of target (i.e., specific thermal capacity, convective heat transfer coefficient, and thermal conductivity) on the lesion production were studied. Uniform lesion production in the transparent gel phantom and ex vivo bovine liver samples using the proposed algorithm proved effective for different scanning pathways by an extracorporeal clinical HIFU system. It is suggested that the HIFU energy need to be adjusted dynamically throughout the ablation procedure in order to generate uniform lesions and to enhance the subsequent therapeutic effect as well as safety. Treatment planning depends on the size and shape of target, scanning protocol, and physical characteristics of tumor (i.e., acoustic and thermal properties). Therefore, appropriate treatment planning is of importance in HIFU practice for a satisfactory outcome.

2. Methods

2.1. HIFU system

A clinical extracorporeal HIFU system (FEP-BY02, Yuande Bio-Engineering Ltd., Beijing, China), which has a center frequency of 1 MHz, an electrical-to-acoustic energy conversion efficiency of 42%, 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 co-axial to the HIFU beam, was used to generate uniform lesions in this study. A 7% bovine serum albumin (BSA) of polyacrylamide hydrogel phantom (\(L \times W \times H = 5.5 \text{ cm} \times 5.5 \text{ cm} \times 5 \text{ cm}\)), which becomes optically opaque when denatured by heat [8], was surrounded by a tissue mimicking phantom that contains 6.5% Alginate (Jeltrate, Dentsply International, York, PA). Ex vivo studies were performed using freshly excised bovine liver obtained from a local slaughterhouse on the day of the experiment using established protocol [5]. Briefly, the samples were immersed in phosphate-buffered saline (PBS) solution, degassed in a vacuum chamber for at least 30 min, and then inserted into the central hole of the tissue mimicking phantom. Center of the gel phantom or liver sample was picking phantom. Center of the gel phantom or liver sample was targeted. The corresponding acoustic pressures at the HIFU focus in the free field measured by a fiber optic probe hydrophone (FOPH-2000, RP Acoustics, Leutenbach, Germany) are 15.7/–8.4 MPa and 19.9/–9.1 MPa, respectively [10]. The –6 dB beam size is 1.4 × 9.6 mm (lateral × axial). The numbers of treatment spots that are arranged in a diamond shape with diagonals of 24 mm are 313, 85, 25 and 13 with a grid spacing of 1, 2, 4 and 6 mm, respectively (Fig. 1). In addition, the motion time between treatment spots varied from 0 s to 400 s.

2.2. Scanning protocol

Scanning protocol in HIFU ablation includes the scanning pathway (i.e., raster scanning, spiral scanning from the center of the treatment area to the outside, and spiral scanning from the outside to the center), spot spacing, and interval motion time between treatment spots [5]. Here, one treatment layer was considered for simplicity to calculate the thermal dose at the focal plane since no pre- or post-focal side effects (i.e., skin burns, perfusion of gastrointestinal tract, or pancreatic fistula) were found in clinics using FEP-BY02 [9]. The treatment parameters were the same for each spot as used in the clinics: the HIFU pulse is 300 ms in duration with a duty cycle of 50%, and the electrical power to the HIFU transducer is 290 and 366 W for the gel phantom and bovine liver samples, respectively [5]. The corresponding acoustic pressures at the HIFU focus in the free field measured by a fiber optic probe hydrophone (FOPH-2000, RP Acoustics, Leutenbach, Germany) are 15.7/–8.4 MPa and 19.9/–9.1 MPa, respectively [10]. The –6 dB beam size is 1.4 × 9.6 mm (lateral × axial). The numbers of treatment spots that are arranged in a diamond shape with diagonals of 24 mm are 313, 85, 25 and 13 with a grid spacing of 1, 2, 4 and 6 mm, respectively (Fig. 1). In addition, the motion time between treatment spots varied from 0 s to 400 s.

2.3. Treatment planning

BioHeat transfer equation (BHTE) was used to calculate temperature elevation in the tissue [11],

\[
\rho C_v \frac{\partial T}{\partial t} - h(T - T_0) + Q
\]

where \(\rho\) is the density, \(C_v\) is the heat capacity, \(T(t, \mathbf{r})\) is the tissue temperature, \(t\) is the time, \(h\) is the thermal conductivity, \(h\) is the convective heat transfer coefficient, \(T_0\) is the equilibrium temperature (37 °C in ex vivo study) and \(A\) is the Laplacian operator. The pressure waveforms through samples (bovine liver and BSA gel phantom) were measured using FOPH, from which the absorbed ultrasound energy as heat source, \(Q\), was calculated as

\[
Q = 4\pi \sum_{n=0}^{\infty} \frac{2n}{\pi} \frac{a_n^2}{c_n^2} \int_{0}^{\infty} R(t) \sin^{\alpha}(\omega t) dt
\]

where \(c_0\) is the sound speed, \(a_n\) and \(C_n\) are the attenuation coefficient and amplitude of the \(n\)-th harmonic in the measured pressure waveform, respectively. Twenty harmonics were used because of the signal-to-noise ratio of measured waveform and bandwidth of the digital oscilloscope. The thermal dose (TD) was calculated using:

\[
TD_{43, c}(t) = \int_{0}^{t} \frac{R(t) d\tau}{(1 + 3\tau)^{0.5}}
\]

with \(R = 0.25 \text{ if } T(t) < 43 \text{ °C} \text{ and } 0.5 \text{ otherwise}\ [12\]. A 240-min exposure at 43 °C could create thermally irreversible damage in most tissue types [12–14]. However, temperature-threshold model (lesion forming at a temperature higher than 65 °C) and the equilibrium temperature of 25 °C were used to predict lesions in the BSA gel phantom [5]. Properties of gel phantom and bovine liver were the same as the previous work [5]. A partial difference equation (PDE) toolbox in Matlab (N. Nortick, MA, USA) was used to solve the BHTE. An algorithm was proposed to determine the HIFU treatment planning (Fig. 2). Briefly, the thermal field and the corresponding lesion were calculated at the end of each pulse delivery by solving the BHTE. If the lesion size along any Cartesian coordinates (\(x\) and \(y\)) from the HIFU focus was smaller than half of the grid size or spacing between treatment spots, HIFU exposure would be continued. Otherwise, HIFU exposure would be terminated (\(Q = 0\) and
the transducer focus would be moved to the next location at the interval time pre-determined by the scanning protocol. The total number of delivered pulses and maximum temperature elevation in the target with varying scanning protocols and target properties were compared with each other.

3. Results

3.1. Production of uniform lesions

Using the proposed algorithm, the maximum temperature elevation and the consequent lesions in the three-dimensional space using the raster scanning in the simulation are shown in Fig. 3. In comparison to those applying the strategy of the same HIFU energy for each treatment spot [5], the thermal field is more uniform. Although the first side lobes on the axis with pressure of about –15 dB respect to that at the focus occur at $Z = -11.2 \, \text{mm}$ and $Z = 13 \, \text{mm}$, respectively, the corresponding temperature elevations are less than 10 °C, resulting in no unintentional “hot spots” or lesions in the out focal region of this HIFU transducer. Therefore, the focal plane, where has the maximum temperature elevation and the largest lesion production and is aligned to the solid tumor/cancer under the guidance of imaging (i.e., ultrasound or magnetic resonance imaging (MRI)), is of interest in this investigation. However, the post-focal lesion is a little smaller than that in the pre-focal region because of the accumulated attenuation in the acoustic wave propagation path.

3.2. Effect of scanning pathway

The numbers of pulses delivered to each treatment spot for uniform lesion production using different scanning pathways with a grid spacing of 4 mm and an interval motion time of 6 s between treatment spots, and the corresponding lesion patterns are shown in Fig. 4. As expected, all lesions covered the target region uniformly. However, these on the boundary (i.e., the 1st spot on the spiral scanning from the outside to the center and the 25th one on the spiral scanning from the center to the outside) were a little smaller. Using the spiral scanning from the outside to the center, the number of pulses required to generate a 4-mm lesion gradually decreased with the progress of HIFU ablation. Because of the thermal diffusion effect from nearby lesions towards the target center, lesion size instantly reached 4 mm after a single-pulse exposure at the last two spots. The total numbers of pulses delivered in generating uniform lesions using these three scanning pathways are 1910, 1834, and 2061, respectively, with the maximum temperature elevation in the target of 52.2 °C, 51.1 °C, and 51.7 °C, respectively. Therefore, the spiral scanning from the outside to the center seems the best pathway studied here, which will be investigated in vivo later. In addition, the thermal diffusion effect may lead to a continuous growth of lesion size after the termination of HIFU exposure. As a result, lesion coalescence occurred and there was no gap appearing in both diagonal directions, although the algorithm only determined the lesion size in the Cartesian coordinate directions. Using the iterative method, the lesion coalescence can be avoided for the minimal number of pulses in uniform lesion production [15]. However, the computation burden is too great to be applied prior to HIFU therapy.

The effect of grid spacing between treatment spots was investigated (Fig. 5). It is found that the maximum temperature elevation increased monotonically with the grid spacing from 26.9 °C to 61.9 °C. However, the number of total pulses needed in uniform lesion production reached its minimal value, 1492, at a grid spacing of 2 mm. The first treatment spot always needed more HIFU exposure energy than the others, which is due to no elevation of the equilibrium temperature by the thermal diffusion from nearby lesions [5], and the corresponding number of pulses increased significantly from 19 to 285 when the grid spacing changed from 1 mm to 6 mm. With the progress of HIFU ablation, the delivered energy decreased gradually in an oscillatory way. The amplitude of such an oscillation decreased with the grid spacing, 7.5 ± 1.3 vs. 188.5 ± 46.6 at a grid spacing of 1 mm and 6 mm, respectively. Furthermore, smaller grid spacing resulted in a smoother lesion boundary of the treatment region. Altogether, appropriate selection of grid spacing between treatment spots could reduce the total exposure energy to the target in the uniform lesion production.

The interval motion time between treatment spots is found to have a greater effect on the total energy delivered than the maximum temperature elevation in the target region (Fig. 6). Although the maximum temperature elevation decreased slightly from 52.9 °C to 50.2 °C when increasing the interval motion time from 0 s to 100 s, saturation was achieved quickly afterwards (i.e., 50 °C at interval motion time of 400 s). In comparison, the number of total pulses delivered to the target region increased exponentially with the motion time. At the interval motion time of 400 s, a total of 3061 pulses are needed in lesion production, which is 1.6 times as that at the interval motion time of 6 s. In addition, with the increase of interval motion time, the lesion coalescence, especially in the diagonal directions, became less significant. It is noticed that if there is no motion time between treatment spot, such as using electronic steering of a phased array HIFU transducer, the number of total pulses required in the thermal ablation is almost the same (1908 vs. 1910) as that of the default setting (interval motion time of 6 s and grid spacing of 4 mm).

3.3. Effect of thermal properties

There are great variations in the tissue’s properties [9], whose influences on the uniform lesion production were investigated (Fig. 7). It is found that increases of specific heat capacity, $C_v$, and...
connective heat transfer coefficient, $h$, led to a significant increase in the number of total pulses delivered (or total HIFU exposure energy), but a slight decrease of the maximum temperature elevation (i.e., from 54 °C to 51.7 °C when $h = 100$ W/m²/K to 51.7 °C at $h = 10,000$ W/m²/K, respectively). However, the total HIFU energy delivered in uniform lesion production seems more sensitive to specific heat capacity (i.e., 551 pulses at $C_v = 1000$ J/kg/K increasing to 2594 pulses at $C_v = 6000$ J/kg/K) than the connective heat transfer coefficient (i.e., 1831 pulses at $h = 100$ W/m²/K increasing to 2164 pulses at $h = 10,000$ W/m²/K). In comparison, the reliance of thermal ablation on the thermal conductivity, $k$, was different. The maximum temperature elevation decreased from 163.5 °C to 47.2 °C at $k = 0.1$ W/m/K to 47.2 °C at $k = 0.7$ W/m/K. The minimal number of total pulses, 1874, occurred at $k = 0.4$ W/m/K.

### 3.4. Gel phantom and ex vivo experiment

In order to generate uniform lesions in the BSA-embedded gel phantom, the number of pulses delivered to each treatment spot was calculated using the proposed algorithm and temperature-threshold model. BSA is assumed to denature at a temperature higher than 65 °C with equilibrium temperature of 25 °C [5]. It is found that the corresponding treatment planning was different from those in the tissue using the thermal dose-threshold model (Fig. 8). The total numbers of pulses delivered using these three scanning pathways are 1832, 2261, and 2105, respectively. Although the thermal diffusion effect from nearby spots led to a rise of background temperature and consequently, a decrease of the number of pulses for lesion production, 35 and 21 pulses (not a single exposure) were required for the last two treatment spots, respectively, at a grid spacing of 4 mm and motion time of 6 s when using the spiral scanning pathway from the outside to the center. The experimental results recorded photographically agreed well with our expectation, although lesion coalescence was also observed.

Ex vivo experiment also confirmed the validity of the algorithm in generating uniform lesions in the bovine liver by dynamically adjusting the HIFU exposure energy (Fig. 9) rather than using the same energy output [5]. However, exact size and location of lesions in the bovine liver cannot be determined photographically as in the gel phantom. Although the histological method could show the existence of coagulative tissue in a microscope, our current facility is only available for a small area (1 cm × 1 cm). At least 5 gel phantom and ex vivo samples were used for each HIFU delivery protocol in a month with the same conclusion. The lesion area produced by these 3 scanning protocols in the gel phantom are 412.7 ± 15.3 mm², 399.6 ± 20.2 mm², and 434.9 ± 17.6 mm², respectively, which are close to the theoretical simulation results (421.5 mm², 402.8 mm², and 420 mm², respectively in Fig. 3). However, there are larger variations of lesion area in the bovine liver samples (484.3 ± 58.1 mm², 465.8 ± 45.9 mm², and 500.4 ± 76.2 mm², respectively), which is due to the inhomogeneous and inconsistent tissue properties (i.e., presence of artery).

### 4. Discussion

HIFU has been used in clinics in Asia and Europe with promising results. However, it is still in its infancy, and there remain outstanding technical and clinical questions to be addressed [16]. Currently, the HIFU focus is scanned throughout the tumor in either discrete spots (i.e., the FEP-BY02 system) or pre-determined scanning trajectories (i.e., the model JC system of Chongqing Haifu Technology Ltd., Chongqing, China) [1]. HIFU parameters are typically the same during the treatment unless an adjustment is necessary due to patient’s intolerance. Because of the 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 for coagulation while over-sized at the end observed in both gel phantom

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**Fig. 2.** (a) Flow chart of generating uniform lesions in HIFU treatment planning, and (b) the method of determining whether lesion reaches the predetermined size.
and ex vivo studies [5], increasing the potential of unintended collateral thermal injury. From the viewpoint of the physician, predictable and uniform lesion formation is desired. In this study, an algorithm of uniform lesion production was proposed, the effects of scanning protocol (i.e., scanning pathway, grid spacing and interval motion time between spots) and tissue's properties (i.e., specific heat capacity, convective heat transfer coefficient, and thermal conductivity) on the outcome were investigated, and lesion production was confirmed in the BSA gel and bovine livers. There are two approaches of changing HIFU energy delivered to the

Fig. 3. The maximum temperature elevation (left) and the subsequent lesions produced (right) at (a) XY plane, (b) XZ plane, and (c) YZ plane using raster scanning for uniform lesion production with a grid spacing of 4 mm and an interval motion time of 6 s between treatment spots.
target, adjusting the acoustic power and the number of pulses or exposure duration [17]. According to clinical experience, the patient’s pain to HIFU pulses was mainly relevant to the acoustic output power, not the energy [9]. Before starting HIFU therapy, the tolerance was determined as the starting of pain from each patient’s subjective evaluation by gradually increasing the output power of HIFU trial pulses (usually 300–500 W). Then 70–80% of the power for pain threshold was empirically set for the subsequent tumor ablation as a tradeoff between therapeutic efficiency and safety. No discomfort of patients was found in the preliminary clinical trials using this protocol although more data are needed for validation. Therefore, the latter method was applied in this study.

Because the focal zone of a single HIFU beam is usually a narrow cigar-shaped volume (i.e., 1–2 mm in width and 10 mm in length), it is inadequate for the whole tumor ablation by itself. Several strategies have been evolved by scanning a small focal zone, including mechanical motion, either continuously or discretely [18], and electronic steering of the transducer [19–21]. The advantages of mechanical steering are the low cost, high reliability, high resolution, and easy control. However, the motion speed (i.e., a few mm/s) may not be sufficient to compensate the respiration (i.e., 10–40 mm and 30–80 mm in the superior–inferior direction of liver in the shallow and deep breathing mode, respectively [22]). In contrast, HIFU focus can be steered rapidly by an electronic approach to track the target in real-time, whose accuracy depends on the number of phased arrays and the phase resolution applied to each element. However, when the shift from the geometrical focal point is large (i.e., 5–10 mm), the appearance of grating lobe will affect the safety of HIFU ablation even using the sparse random elements [23]. Therefore, phased array system still needs some mechanical motion, which is assumed to reduce the coagulation efficiency of HIFU. In this study, it is found that the interval motion time between treatment spots, if less than 10 s, may not affect the outcome in a typical tissue (i.e., $C_v = 4270$ J/kg/K, $h = 2500$ W/m²/K, $k = 0.59$ W/m/K). In addition, the presence of interval time would allow to detect the HIFU-induced lesions by using B-mode ultrasound image [24,25] or acoustic radiation force imaging (ARFI) [26] without interferences from HIFU pulses [27].

Bubble cavitation is an important phenomenon in the strong acoustic field. Bubbles, from boiling of fluid or by the growth of tiny gaseous nuclei due to the negative pressure of the acoustic wave, are strong scatters of acoustic waves. As a result, more energy will be absorbed in the pre-focal region, and the lesion distortions from cancer to taphole shape and moves towards the transducer [28]. The bubble dynamics and wave scattering in the HIFU field can be modeled and coupled with BHTE, and its effect on the lesion formation was theoretically investigated [29]. Although the trend of lesion shape as the output power agrees with

![Fig. 4. The lesions produced using (a) spiral scanning from the outside to the center, (b) spiral scanning from the center to the outside, and (c) the number of pulses delivered to each treatment spot for uniform lesion production with a grid spacing of 4 mm and an interval motion time of 6 s between treatment spots.](image-url)
Fig. 5. The number of pulses delivered to each treatment spot (left column) and the corresponding lesion patterns (right column) with a grid spacing of (a) 1 mm, (b) 2 mm, (c) 6 mm with an interval motion time of 6 s between treatment spots in a raster scanning, and (d) the comparison of total number of pulses delivered and the maximum temperature elevations.
in vivo experiment, the bubble size and concentration used in the simulation is difficult to measure using current technologies. Passive cavitation mapping by an array of passive receivers can be used to monitor cavitation distribution during HIFU exposure [30]. With the knowledge of 2D cavitation and subsequent lesion formation, which is absent in the current model, HIFU treatment planning could compensate smaller lesion in the post-focal and avoid over-treatment in the pre-focal region.

The transport of thermal energy in living tissue is a complex process involving multiple phenomena, including conduction, convection, radiation, metabolism, evaporation, and phase change [9]. The convective heat transfer depends on the rate of perfusion and the vascular anatomy, which vary widely among the tumor and cancer. Therefore, predicting heat-transfer in biomaterials requires the accurate knowledge of both tissue thermal properties and perfusion. Thermal probe techniques are used frequently to determine the thermal conductivity and diffusivity of biomaterials [31,32]. Blood perfusion is determined by the temperature response for power deposition although low perfusions are hard to estimate because of the dominance of conduction. However, determining the thermal properties and blood perfusion of deep-seated cancer or solid tumor accurately and noninvasively on site is a challenge. Furthermore, color Doppler ultrasound images showed an abrupt interruption, followed by the cessation of blood flow within the tumor vessels after HIFU treatment [33–35]. The vacuolar degeneration destruction of elastic fibers of the tunica media of the artery reduced the vascular diameter and finally led to the occlusion of the blood flow due to both the thermal and mechanical effects of HIFU. Subsequently, the reduced “heat sink” effect of blood perfusion would result in lesion production using less energy.

Open-loop delivery strategy (i.e., treatment planning) has the technical limitation and difficulty in measuring thermal properties, blood perfusion, spatial and temporal variation of tissue properties and bubble concentration. Therefore, a great discrepancy between the simulation and in vivo results is expected. Various approaches have been used to develop algorithms by using MRI thermometry as feedback for closed-loop ultrasound heating [36–38]. It takes MRI a few seconds to detect the lesion formation and measure the temperature elevation during HIFU therapy in a high accuracy and resolution, so temperature underestimation may occur [39]. Averaging of the thermal field over the volume of the MRI voxel (0.3 × 0.5 × 2 mm³) yielded a maximum of 73 °C after 7 s of continuous HIFU exposure when boiling (100 °C) started. To improve the control strategy the advantages of these two planning strategies may be combined. The lesion can be calculated accurately from the thermal dose using MRI thermometry after compensating the spatial and temporal averaging effect. With the progress of HIFU ablation, the varying trend of the shape and location of a new lesion may be predicted from the previous lesion information using neural network or expert system. Then the treatment plan will be adapted in real time for desired lesion pattern production. This approach will be developed and tested in the next stage.

Fig. 6. The uniform lesion pattern generated with a grid spacing of 4 mm and an interval motion time of: (a) 0 s, (b) 25 s, (c) 200 s between treatment spots in a raster scanning, and (d) the comparison of total number of pulses delivered and the maximum temperature elevations.
Fig. 7. The effect of (a) specific heat capacity, (b) perfusion, and (c) thermal conductivity of target on the uniform lesion production with a grid spacing of 4 mm and an interval motion time of 6 s in a raster scanning.
5. Conclusion

In comparison to conventional planning method (delivering the same HIFU energy to every treatment spot), dynamically adjusting HIFU parameters as determined by the proposed algorithm could produce uniform lesions in the whole tumor volume, and subsequently enhance both the therapeutic efficiency and safety. Treatment planning depends on the scanning protocol and thermal properties of the target. It is found that the spiral scanning from the outside to the center with a grid spacing of 2 mm and an interval motion time of 6 s.
interval motion time less than 10 s requires the least numbers of pulses or HIFU energy by making use of the thermal diffusion effect. The dynamic HIFU adjustment method proved valid in the both transparent gel phantom and ex vivo bovine liver experiments. The performance of this algorithm in vivo will be evaluated in the future study.

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References