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1aBA5. Generating Uniform Lesions in High Intensity Focused Ultrasound Ablation

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During high intensity focused ultrasound (HIFU) therapy, the operation parameters are usually kept the same for each treatment spot. Because of the thermal diffusion from nearby spots, the lesion size will gradually increase. In this study, an algorithm was developed to determine the number of HIFU pulses delivered to each spot for uniform lesion production. The exposure energies required using different scanning pathways, spot spacing and motion time 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. Effects of thermal properties of tissue (i.e., specific heat capacity, convective heat transfer coefficient and thermal conductivity) on HIFU ablation were investigated to determine the corresponding treatment planning. Uniform lesion production in the gel phantom and ex vivo bovine liver using the proposed algorithm was accord with the simulation. 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.
1. Introduction

High-intensity focused ultrasound (HIFU) is emerging as an effective oncology treatment modality in Asia and Europe in the last decade (Meaney et al. 2000, ter Haar 2001). Despite its technical advantages (i.e., noninvasiveness and nonionization) and encouraging preliminary clinical results with few complications and in-patient stays, HIFU is still a developing technology. 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. 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 and over exposure of the later ones. From the viewpoint of the physician, there are three basic requirements for the HIFU ablation: 1) ability to generate a predictable lesion for every treatment spot; 2) all generated lesions need to be uniform; 3) complete coverage of the entire target volume.

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. 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 was proved effective for different scanning pathways by an extracorporeal clinical HIFU system. It is suggested that the HIFU energy needs 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. Materials and Methods

2.1. HIFU System

A clinical extracorporeal HIFU system (FEP-BY02, Yuande Bio-Engineering Ltd., China), which has a center frequency of 1 MHz, an outer diameter of 33.5 cm and an inner diameter of 12 cm with integrated ultrasound imaging probe (S3, GE, Korea) mounted in the central hole co-axial to the HIFU beam, was used in this study. A 7% bovine serum albumin (BSA) of polyacrylamide hydrogel phantom, which becomes optically opaque when denatured by heat, was surrounded by a tissue mimicking phantom that contains 6.5% Alginate (Jeltrate, Dentsply International, PA). Ex vivo studies were performed using freshly excised bovine liver using established protocol (Zhou et al. 2011). Briefly, the samples were immersed in PBS solution, degassed in a vacuum chamber for at least 30 minutes, and then inserted into the central hole of the tissue mimicking phantom. Center of the gel phantom or liver sample was aligned with HIFU focus under the guidance of B-mode ultrasound imaging. A LabVIEW (National Instruments, TX) program controlled the motion of treatment table and delivery of HIFU pulses. Thermal lesions were recorded photographically.

2.2. Treatment Planning

BioHeat transfer equation (BHTE) was used to calculate temperature elevation in the tissue (Pennes 1948),

\[ \rho C_v \frac{\partial T}{\partial t} = k \Delta T - h(T - T_0) + Q \] (1)

where \( \rho \) is the density, \( C_v \) is the heat capacity, \( T(r, t) \) is the tissue temperature, \( t \) is the time, \( k \) is the thermal conductivity, \( h \) is the convective heat transfer coefficient, \( T_0 \) is the equilibrium temperature (37 °C as in vivo) and \( \Delta \) 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
\[ Q = 4 \sum_{n=0}^{20} \alpha_n |C_n|^2 / c_0 \rho_0 \]  

where \( C_n \) is the amplitude of the \( n \)-th harmonic in the measured pressure waveform, \( \alpha_n \) is the attenuation coefficient. 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

\[ TD_{43°C}(t) = \int_0^t R^{43-T(t)} \, dt \]

with \( R = 0.25 \) if \( T(t) < 43 °C \) and 0.5 otherwise. A 240-minute exposure at 43 °C could create irreversible damage in tissue (Damaniou and Hynynen 1994). However, temperature-threshold model and the equilibrium temperature of 25 °C were used to predict lesions in the BSA gel phantom (Zhou et al. 2011).

An algorithm was proposed to determine the HIFU treatment planning. Briefly, the thermal field and the corresponding lesion were calculated by the end of each pulse delivery by solving the BHTE. If the lesion size along any Cartesian coordinates (i.e., \( \pm x \) or \( \pm y \)) 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 and the transducer focus would be moved to the next location.

3. Results

3.1 Effect of Scanning Pathway

The numbers of pulses delivered to each treatment spot for uniform lesion production using three 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. 1. Although all lesions covered the target region uniformly, those 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 smaller. Using the spiral scanning from the outside to the center, the number of pulses gradually decreased with the progress of HIFU ablation. The total numbers of pulses delivered using these three scanning pathways are 1910, 1834 and 2061 with the maximum temperature elevation 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 proposed. 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.

![Figure 1. The lesions produced using (a) raster scanning, (b) spiral scanning from the outside to the center, (c) spiral scanning from the center to the outside for uniform lesion production with a grid spacing of 4 mm and an interval motion time of 6 s between treatment spots.](image)

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 (Zhou et al. 2011), 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. Smaller grid spacing resulted in a smoother lesion boundary (Fig. 2).

![Figure 2](image)

Figure 2. The uniform lesion patterns with a grid spacing of (a) 1 mm, (b) 2 mm and (c) 6 mm with an interval motion time of 6 s between treatment spots in a raster scanning.

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. 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. With the increase of interval motion time, the lesion coalescence, especially in the diagonal directions, became less significant.

3.2 Effect of Thermal Properties

Effect of tissue’s properties on the uniform lesion production was investigated (Fig. 3). Increases of specific heat capacity, $C_v$, and convective 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 (from 54°C at $C_v = 1000$ J/kg/K to 51.7°C at $C_v = 6000$ J/kg/K, and from 52.3°C at $h = 100$ 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 (551 pulses at $C_v = 1000$ J/kg/K increasing to 2594 pulses at $C_v = 6000$ J/kg/K) than the convective heat transfer coefficient (1,831 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 minimal number of total pulses, 1874, occurred at $k = 0.4$ W/m/K.
Figure 3. 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.

3.3 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. The corresponding treatment planning was different from those in the tissue (Fig. 4). 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 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 agree 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 rather than the same energy output (Zhou et al. 2011). However, exact size and location of lesions in the bovine liver cannot be determined photographically as in the gel phantom.

Figure 4. The generated lesions in the BSA phantom (top row) and in the bovine liver (bottom row) by using the dynamically adjusted energies and different scanning pathways of (a) raster scanning, (b) spiral from the center to the outside, (c) spiral from the outside to the center with a grid spacing of 4 mm and an interval motion time of 6 s.
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 (Zhou 2011). Currently, the HIFU focus is scanned throughout the tumor in either discrete points/spots as with the FEP-BY02 system or pre-determined scanning trajectories as with the model JC system (Chongqing Haifu Technology Ltd., Chongqing, China). 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 to cause tissue necrosis while those areas treated toward the end of the therapy may be overexposed, increasing the potential of unintended collateral thermal injury (Zhou et al. 2011). 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 treatment spots) and tissue’s properties (i.e., specific heat capacity, convective heat transfer coefficient, and thermal conductivity) on the uniform lesion production were investigated, and lesion production was confirmed in the BSA gel phantoms and ex vivo bovine livers. There are two approaches of changing HIFU energy delivered to the target, adjusting the acoustic power and the number of pulses. According to clinical experience, the patient’s tolerance to HIFU pulse was mainly determined by the output power, not the total energy. Therefore, the latter method was applied in this study.

The transport of thermal energy in living tissue is a complex process, including conduction, convection, radiation, metabolism, evaporation and phase change (Valvano 1995). 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. 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, noninvasively determining the thermal properties and blood perfusion of deep cancer or solid tumor accurately and noninvasively in situ remains a challenge.

Because the focal zone of a single HIFU beam is usually a narrow cigar-shaped volume, it’s inadequate for the whole tumor ablation by itself. Several strategies have evolved for treating a clinically relevant tumor volume, including mechanical steering of the transducer, either continuously or discretely, and electronic steering of the transducer (Ebbini and Cain 1991, Daum and Hynynen 1999). The advantages of mechanical steering are the low cost, high reliability, high resolution (i.e., the minimum step size on the order of µm) and easy control. However, the motion speed of motors (i.e., a few mm/s) may not be sufficient to compensate the respiratory motion (i.e., 10-40 mm and 30-80 mm motion in the superior-inferior direction of liver in the shallow and deep breathing mode, respectively). In contrast, HIFU focus can be steered rapidly by an electronic approach to track the target in real-time, whose steering 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 design of sparse random elements (Goss et al. 1996). Therefore, for full 3D coverage of target in clinics, some mechanical motion is still required for phased array system. In this study, it is found that the interval motion time between treatment spots, if less than 10 seconds, may not affect the outcome in a typical tissue. In addition, the interval time would allow the detection of the HIFU-induced lesions by using B-mode ultrasound image or acoustic radiation force imaging (ARFI) without interferences from HIFU pulses. If the generated lesion is smaller than planned, more energy will be delivered for compensation immediately.

In this study, an algorithm was proposed to determine HIFU treatment planning (the number of HIFU pulses delivered to each treatment spot in the thermal ablation) in order to produce uniform lesions in the whole tumor volume. In comparison to conventional planning method, delivering the same HIFU energy to every spot, the dynamical adjustment approach could 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 less than 10 s requires the least numbers of pulses or HIFU energy by making use of the thermal diffusion effect. The proposed method was proved valid in the transparent gel phantom experiment. The performance of this algorithm in vivo will be evaluated in a future study.

References and links


