Comparison of pathway in high intensity focused ultrasound (HIFU) lesion production

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High intensity focused ultrasound (HIFU) is being evaluated for non-invasive treatment of solid tumors. The temperature at the HIFU focus can reach over 65 deg C denaturing cellular proteins and resulting in coagulative necrosis and lesion formation. One common method for delivering HIFU therapy clinically is using the spot accumulation method that delivers sequential individual treatment spots. Because of thermal diffusion from nearby treatment spots, the size of subsequent lesions will gradually become larger as the HIFU therapy progresses, which may cause insufficient treatment of the initial spots, and over-treatment of later spots unless parameters are changed during treatment. A new pathway for HIFU treatment is proposed and compared with the conventional sequential path. Modeling, in vitro phantom and ex vivo bovine liver experiments demonstrate that the new treatment path produces more uniform lesions than the conventional treatment path (p<0.05). The relationship between lesion area/volume and delivered ultrasound energy and dose-dependent discrepancies between scanning paths were also studied. In addition, the temperature changes in the ex vivo system were measured using a thermocouple array. Altogether, the new treatment path appears to be advantageous for producing more uniform lesions without modifying HIFU parameters during treatment or significantly increasing the scanning time.
Comparison of Pathway in High Intensity Focused Ultrasound Lesion Production

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1. Introduction

High intensity focused ultrasound (HIFU) is emerging as a new modality for ablat ing solid tumors, such as uterine fibroids and cancers of the prostate, kidney, liver, breast, and pancreas [1-4]. In China and Europe more than 100,000 cases have already been carried out in clinics with promising results. The principle of the HIFU therapy is focusing a high intensity ultrasound beam into a small region, where a tumor is located [5]. The acoustic intensity at the focus can be several 1,000 W/cm\textsuperscript{2} with the temperature reaching over 65 °C within seconds to coagulate the tissue. In comparison to traditional cancer treatment methods, such as open surgery, radiotherapy, and chemotherapy, HIFU ablation has the advantages of being non-invasive, does not expose patients to ionizing radiation, and is a local treatment. Theoretically this may reduce the risk of metastasis and lead to fewer treatment related complications.

Despite its uniqueness and encouraging preliminary clinical results, HIFU is still a developing technology yet to be accepted as a therapeutic modality by both patients and physicians. Engineers and scientists are improving the technology with the goals of achieving accurate focusing, developing appropriate treatment planning methods, and providing real-time monitoring of the thermal field and lesion formation. Since tumors are typically several centimeters in diameter, much larger than the size of the focus of the HIFU transducer (which is on the order of millimeters in diameter and approximately 1 cm in length), treatment of the entire volume of tumor requires multiple treatment spots. Individual treatment spots are administered in a raster pattern in a treatment layer. Subsequent layers are treated moving proximal to the HIFU source. Because of thermal diffusion from nearby treatment spots, the lesion size of individual treatment spots will gradually become larger as the HIFU therapy progresses, which may cause insufficient treatment of the initial spots and over-treatment of later ones. In this study, two new scanning pathways are proposed and compared with the conventional raster scanning method with the same HIFU parameters (acoustic power and exposure duration). It is found that the scanning pathway affects the lesion production with the new pathways producing more uniform lesions. Therefore, by selecting the appropriate scanning pathway and varying treatment parameters as treatment progresses, HIFU therapy can achieve uniform lesions while minimizing the total delivered energy and treatment time.

2. Methods

A conventional scanning approach used in clinical HIFU therapy is raster scanning (Fig. 1a). Here, only one treatment layer is considered for simplicity. Besides the raster scan, 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) are evaluated. In this study, there are total 25 treatment spots arranged in the shape of a diamond with a grid size of 4 mm. The treatment parameters are all the same for each spot: the HIFU on time is 150 ms, the HIFU off time is 150 ms, there are 60 pulses per spot, interval time between treatment spots is 6 s, and the acoustic energy at the target is 1,000 J.
A theoretical model was established to simulate the lesions produced by using different scanning pathways. The Khokhlov-Zaboltskaya-Kuznetsov (KZK) nonlinear evolution equation has been used widely to model high intensity acoustic beams numerically [5]. The KZK model was applied to simulate the acoustic field generated by the HIFU array,

$$\frac{\partial p}{\partial z} - \frac{\beta}{c_0^3 \rho_0} p \frac{\partial p}{\partial \tau} - \frac{b}{2c_0^3} \frac{\partial^2 p}{\partial \tau^2} = \frac{c_0}{2} \int_{\tau'}^{\tau} \Delta_{\perp} p(\tau') d\tau', \quad (1)$$

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, $\beta$ is the coefficient of nonlinearity, $b$ is the dissipative parameter, and $\Delta_{\perp}$ is the Laplacian operator with transverse coordinates $r=(x,y)$. In the frequency-domain schemes the solution of Eq. (1) is represented in the form of a Fourier series expansion,

$$p(z,r,t) = \sum_{n=-\infty}^{\infty} C_n(z,r) \exp(-in\omega_0 \tau), \quad (2)$$

where $\omega_0$ is the fundamental frequency of the HIFU pulses, $C_n$ is the complex amplitude of the $n$th harmonic. The mathematical model for temperature elevation in the tissue is based on the BioHeat transfer equation (BHTE) [5],

$$\frac{\partial T}{\partial t} = k \Delta T - \frac{T - T_0}{t_p} + \frac{Q}{c_v K}, \quad (3)$$

where $t$ is the time, $t_p$ is the perfusion time, $T(r,t)$ is the tissue temperature, $T_0$ is the equilibrium temperature, $k = K / c_v$ 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,

$$Q = 4 \sum_{n=0}^{\infty} \alpha_n |C_n|^2 / c_0 \rho_0, \quad (4)$$

where $\alpha_n = (n \omega_0)^2 b / 2c_0^3 \rho_0$ is the attenuation coefficient, which exhibits quadratic frequency dependence according to Eq. (1).
The HIFU system used in this study (FEP-BY02, Yuande Bio-Engineering, Ltd., Beijing, China) consists of 251 individual PZT elements, driven all in phase and arranged in a concave spherical holder. Each PZT element has a center frequency of ~1 MHz and diameter of 16 mm. The HIFU transducer has an outer diameter of 33.5 cm and an inner diameter of 12 cm with integrated ultrasound imaging probe (S3, Logiq 5, GE, Seongnam, Korea) mounted in the central hole co-axial to the HIFU beam. An optically transparent gel phantom (L×W×H=5.5 cm×5.5 cm×5 cm), composed of polyarylamide hydrogel and bovine serum albumin (BSA) that becomes optically opaque when denatured by heat [6], surrounded by a tissue phantom that contains 6.5% Alginate (Jeltrate, Dentsply International, York, PA), was put into a sample holder. The holder was mounted to the treatment table. The center of the transparent gel phantom was aligned with the HIFU focus under the guidance of B-mode ultrasound imaging. A LabVIEW (National Instruments, Austin, TX) 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 delivery of HIFU pulses. After the treatment, the HIFU phantom was taken out and the lesions were recorded photographically 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).

3. Results

The simulated thermal fields from the theoretical model are shown in Fig. 3. Using the raster scanning method, the produced lesions were asymmetric, with lesions becoming progressively larger as the treatment progressed. However, by using the new spiral scanning pathways, the lesions were more symmetric. The maximum temperature elevations using these 3 pathways were 50 °C, 44 °C, and 58 °C, respectively.
The simulated thermal fields generated by using different scanning pathways, (a) raster scan, (b) spiral scanning from the center to the outside, and (c) spiral scanning from the outside to the center. The scale shows the temperature rise from 0 to 60 °C.

The lesions generated in the gel phantom were found to have similar pattern and characteristics as predicted by the simulations, validating our theoretical model. By using the raster scanning method, the lesion can only be visualized beginning with the 3rd treatment spot (Fig. 4a). In addition, two other spots on the boundary of the treatment area, 5th and 10th treatment spots, also were not visible. With the progress of the HIFU treatment the lesion size became larger because of the thermal diffusion from nearby spots. Merging of lesions occurred toward the end of the treatment. However, the change of lesion size is not in monotonic in nature. For example, the 16th spot is still relatively small and the largest spot is not the last treatment spot, but the 23rd treatment spot. When using the spiral scanning pathway from the center to the outside, only the first lesion was not visible (Fig. 4b). However, the other lesions were smaller in comparison to those generated in raster scanning pathway, and no merging of lesions was observed. The lesion pattern using the spiral scanning, from the outside to the center, had different characteristics (Fig. 4c) with all treatment spots along the outside boundary (first 12 spots) not being visible. Since thermal energy is concentrated toward the center of the treatment area, the last few lesions merged to form a large lesion. The lesion areas are calculated to be 96.8 mm², 26.1 mm², and 67.1 mm², respectively, using these 3 scanning pathways.

The patterns of lesion production and their characteristics can also be assessed by observing the lesions from the lateral direction (Figs. 5 and 6). The maximum lesion lengths using the raster scanning, spiral scanning (inside-out), and spiral scanning (outside-in) were 10.1 mm, 6.9 mm, and 12.2 mm, respectively.
4. Discussion

HIFU has been used in the clinical setting in China and Europe with promising results. However, it remains a developing technology. 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 Co., Ltd., Chongqing, China) [1]. Treatment parameters are typically not adjusted during the treatment unless adjustment is necessary for patient tolerance. 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 parts treated toward the end of the therapy may be overexposed, increasing the potential of unintended collateral thermal injury. This asymmetric lesion production pattern has been observed in our ex vivo studies (data not shown). Although no in vivo study has been performed to confirm this phenomenon, it is reasonable to extrapolate this lesion production pattern to the clinical environment. From the viewpoint of the physician, predictable uniform lesion formation is desired. In this study, two new pathways, spiral scanning from the center to the outside and from the outside to the center, are evaluated and compared with the conventional raster scanning. It is found that more uniform lesions are produced by using these new spiral pathways, although resulting in different lesion patterns. Therefore, the scanning pathway has a great impact on the lesion production. However, the consequences on HIFU therapy outcomes require further investigation.

A considerable body of research has been undertaken to understand the mechanisms of HIFU lesion production [8-11]. In these experiments, usually a single lesion was studied. However, clinically, HIFU treatment of tumors requires multiple lesions for effective ablation. The multi-lesion production is more complex than simply summing
multiple single lesions. Tissue at the focal region of the HIFU transducer absorbs the acoustic energy and then converts it into thermal energy. As a result, temperature can reach over 65 °C within seconds causing necrosis. Owing to the thermal diffusion phenomenon the thermal energy at the focal region will spread towards the surrounding space and the ambient temperature will be raised. It has already been shown that larger lesions are formed with the same delivered energy at a higher background temperature. Therefore, the lesion size will gradually increase as the HIFU therapy progresses. If the lesion size is larger than the interval distance between spots, lesions may coalesce. All together, it is illustrated that thermal accumulation and diffusion effects are critical in multi-lesion treatments. Accounting for thermal accumulation and diffusion effects is of importance in HIFU planning in order to produce uniform lesions and minimize the total acoustic energy used during the treatments. In addition, lesion formation by HIFU in tissue depends on the physical properties of the tissue, such as perfusion time and heat capacity. A hyper-vascular tumor, such as hepatocellular carcinoma, has a short perfusion time. Its thermal accumulation and diffusion effects may not be as significant as in hypo-vascular tissues, such as pancreatic cancer. Thus tissue type also needs to be considered in HIFU therapy planning.

In order to generate uniform lesions, delivered acoustic energies should be adjusted for each treatment spot. In our gel phantom study, the first lesion was never visible no matter which pathway is used. A rational approach to HIFU treatment would be to have the first treatment spot receive the highest acoustic energy and to gradually decrease the acoustic energy for subsequent treatment spots. How to dynamically adjust the HIFU treatment parameters depends on the specific scanning pathway used. Optimization of specific treatment patterns and HIFU parameters will be the focus of future studies.

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References and links