Automated bimodal ultrasound device for preclinical testing of HIFU technique in treatment of solid tumors implanted into small animals

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In Poland cancer is the second cause of death overall, and the first before 65. Demand for new anticancer therapies is increasing every year. The main objective of studies on medical and technical aspects of new anticancer methods is to reduce unwanted side effects and costs associated with conventional methods of treatment. Percutaneous (noninvasive) HIFU (High Intensity Focused Ultrasound) technique gives the chance to radically reduce both of these factors. The main goal of this work is automation of HIFU technology for producing thermal damage to the entire volume of a solid breast tumor implanted into a rat mammary gland using the proposed bi-modal ultrasound equipment, enabling the ultrasonic heating of a small volume within the tumor under the ultrasonic imaging control, as well as 3D scanning of the heating beam focus throughout the entire tumor volume. Design of the proposed equipment includes the heating probe of low frequency (about 1MHz), allowing penetration of pulsed focused waves into tissues, and the linear phased array probe of high frequency (from 4 MHz to 10 MHz), allowing visualization of the locally heated area inside the tumor in real time. Automatic 3D scanning of the heating beam focus provides the thermal damage to its entire volume.

Keywords: High Intensity Focused Ultrasound beam, focal volume, tissue damage.

1. Introduction

The technique using pulsed High Intensity Focused Ultrasound (HIFU) to destroy primary solid tumors or their metastases located deep beneath the skin is a promising non-invasive therapeutic approach [1-6]. The main purpose of this study was to design an automated HIFU-based device suitable for damage of the entire volume of a solid tumor implanted into a rat at the depth of the order of 1-1.5 cm under the skin, without damaging the surrounding healthy tissues.

The essence of this technique is to heat a small volume of tissue inside the tumor to the temperature leading to coagulative necrosis, or to release the chemotherapeutic drug delivered by micro-carriers, such as liposomes or micelles. The extent of thermal tissue damage induced by the HIFU beam depends on the size of the ellipsoidal volume of its focal area. Because the typical sizes of this area (for -6 dB pressure drop) are λ x λ x (5-7)$\cdot\lambda$, where λ is the wavelength in tissue [7] it is necessary to scan the beam focus across the entire volume of the tumor to cover it with necrosis. Tumor scanning can be performed by positioning the beam focus in the nodes of the 3D grid covering the entire tumor volume by means of its electronic control. However, this is a costly solution, because it requires a multi-element phased array (several hundreds of transducers) as a heating probe, multi-channel electronic devices with delay lines, as well as an extensive software package for the beam focus control in space and time.

In a previous preclinical study on the effectiveness of the HIFU technique in inducing thermal damage of selected tissues *in vivo* in small animals, we proposed a solution that would reduce the number of transducers in the phased array probe. We built a 7-element phased annular array transducer with a selected radius of curvature capable of focusing the HIFU beam in a rat liver at depths between 5mm and 15mm under the skin. Control of the focal length of the beam was carried out electronically. Results from studies conducted with this transducer have shown that induction of coagulative necrosis in small tissue volume at different depths is feasible for both *in vitro* and *in vivo* tissues [8]. However, to destroy the entire tumor volume, the electronic movement of the beam focus along the nodes of the 2D grid covering the tumor cross-section as well as the mechanical movement of the beam from one cross-section to the other, distant from the previous one by the width of the focal spot, would be required.

In order to automate the process for HIFU beam positioning along the nodes of the 3D grid covering the entire tumor, we proposed a new device that would allow thermal damage to the small volume inside the tumor by means of a bimodal ultrasonic system, as well as automated mechanical scanning of the HIFU beam through the entire volume of the tumor. The bimodal ultrasound system consists of an ultrasonic bowl-shaped heating probe with a central opening for an ultrasonic imaging probe mounted coaxially, and allowing the HIFU beam focus to be targeted to the inside of the tumor. The mechanical system in the proposed device provides precise positioning of the beam focus in space and time using computer control. The implementation of the proposed HIFU technique for the treatment of solid tumors in humans will help to reduce the problems occurring in currently used conventional methods of treatment (surgery, radio- and chemotherapy). The advantages of this technique are its non-invasiveness, multiple use (no ionization), minimal side effects (complications after therapy) and lower costs.

2. Materials and methods

Schematic diagram of the acoustic-mechanical system in the proposed device is shown in Fig. 1. The HIFU beam will be generated by a spherical ultrasonic transducer H102 (Sonic Concepts Inc., Bothell, WA, USA) with a central opening. The transducer with selected geometry (outer diameter of 64mm, focal length of 62.6mm, central hole diameter of 22.6mm) is capable of operating at either the basic resonant frequency (1.1 MHz) or 3rd harmonics (3.3 MHz). To guide the HIFU beam to the inside of the tumor, a high frequency ultrasonic imaging probe Zonare P10-4 (operating at 4-10 MHz frequency) will be used. This linear phased array probe, compatible with the ultrasound scanner Zonare Medical Systems Inc.. (Mountain View, CA, USA), will be integrated with the heating probe coaxially. The integrated system of bimodal probes (heating + imaging) will be installed in the bottom of the rectangular tank filled with distilled water.

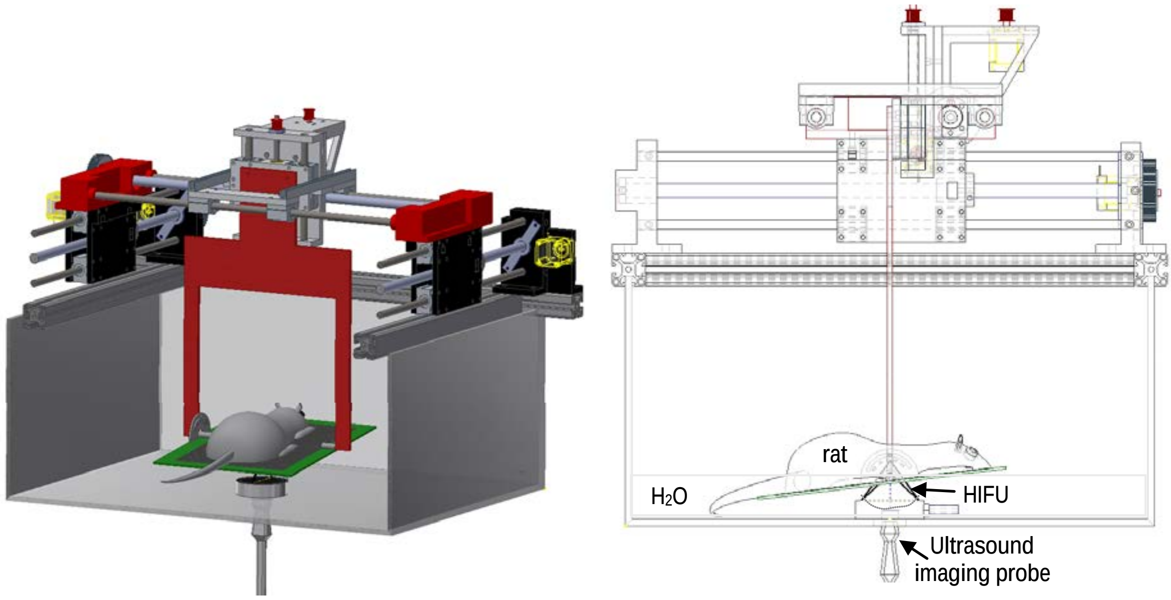

Fig. 1. View (left) and scheme (right) of the cross section of the automated bimodal ultrasonic device for the destruction of solid tumors implanted into various small animal organs.

An electronic transmission system comprising an Agilent 33250A function generator (Colorado Springs, USA) and an ENI 3100LA power amplifier (55 dB) (Rochester, New York, USA) will be used to drive the HIFU transducer with electrical pulses of the selected amplitude, duration and repetition frequency. In order to avoid interference, the work of both heads will be synchronized by means of a special electronic circuit.

To guide the focus of the heating beam to the inside of the tumor, and to scan it throughout the volume of the tumor, a computer-controlled precision positioning system is used. This system consists of a cradle in the form of a frame with a stretched grid, on which a rat (under anesthetic) lies on a shaved belly immersed in water. In the middle, the grid has a hole that forms an acoustic window for the HIFU beam. The cradle has 4 degrees of freedom of movement. Moving the cradle in the *X*, *Y* and *Z* directions is done automatically by a positioning system controlled by a computer, while its inclination at the proper angle enabling targeting of the focus of the heating beam on the inside of the tumor is done manually. To determine the path-length of the wave propagation in water between the center of the HIFU transducer and the cradle in its original position, the numerical model of nonlinear propagation for acoustic waves generated by the axially symmetric source in a layered system of thermo-viscous media, developed earlier in our laboratory [9], was used. The length of the propagation path in water was defined as the axial distance from the source at which the amplitude of the second harmonic component in the spectrum of the pulse propagating in water begins to rise rapidly. Fig. 2 shows the axial distribution of harmonic components contained in the nonlinear pulsed HIFU beam with an acoustic power of 16W (source pressure amplitude of 0.273MPa) generated in water. The length of the propagation path in water, determined on the basis of this distribution for the selected layered system of media of propagation, was equal to 50 mm (see Fig. 2).

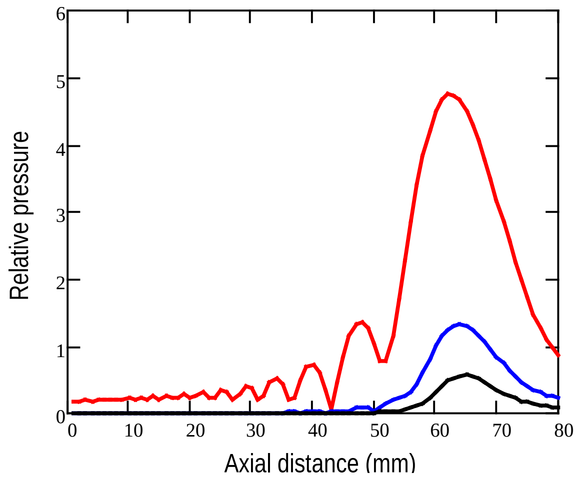

Fig. 2. Axial variations of the amplitude of the 1st, 2-nd and 3-rd harmonics in the pulsed nonliner beam of 16W acoustic power produced in water by the HIFU transducer used.

As the extent of thermal damage, induced locally within the tissue by the HIFU beam, depends on the sizes of the ellipsoidal volume of its focal spot, for their determination the axial and lateral pressure distributions in the beams generated in water by the applied HIFU transducer operating at the resonant frequency (1.08 MHz) or at the frequency of the 3-rd harmonics (3.21 MHz) were measured. The acoustic power of each beam used was changed between 4W and 16W. For measuring, the S/N 1664 needle hydrophone (Precision Acoustics Ltd, Dorchester, Dorset, UK) with the diameter of an active electrode of 0.075mm was used. Fig. 3 and Fig. 4 show examples of axial and lateral acoustic pressure distributions for HIFU beams with two different frequencies (resonance and 3rd harmonic) and varying acoustic power.

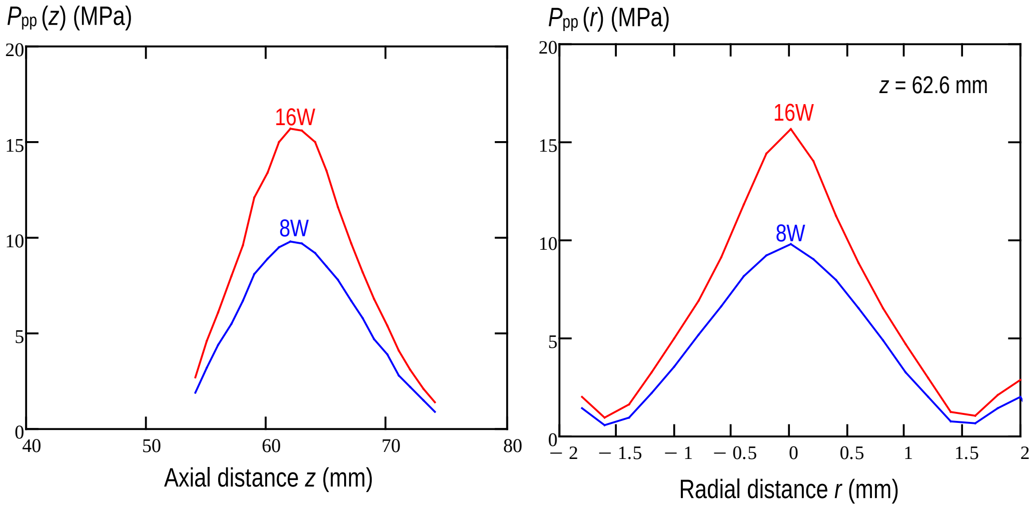

Fig. 3. Axial (left) and radial (right) peak-peak pressure distributions measured for the beam of 8W and 16W acoustic power generated in water by the HIFU transducer used.

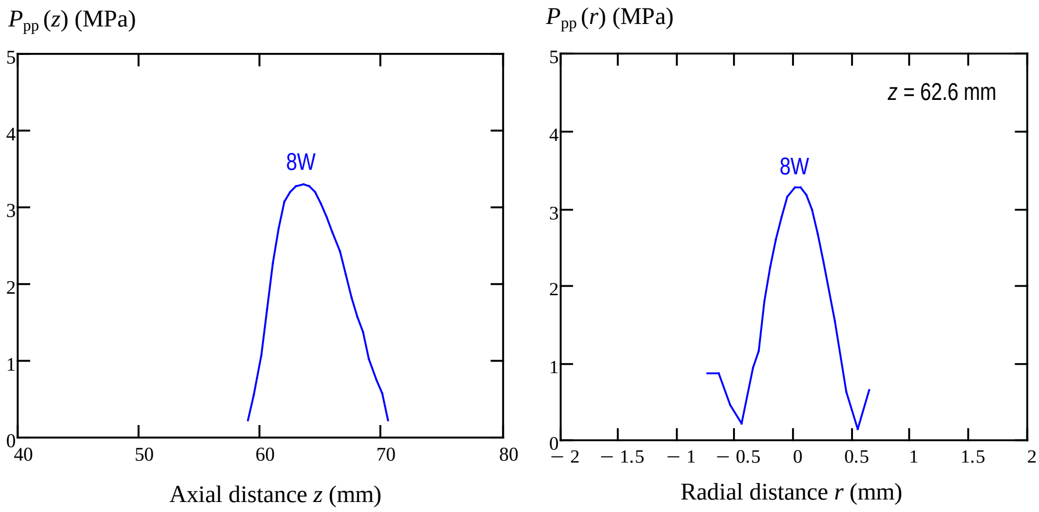

Fig. 4. Axial (left) and radial (right) peak-peak pressure distributions measured for the beam of 8W acoustic power generated in water by the HIFU transducer used and operating at the frequency of the 3-rd harmonics (3.21 MHz).

In order to determine the dependence of the acoustic power radiated by the applied transducer operating at the resonance frequency or at the 3-rd harmonic frequency, the measurements were performed using the UPM DT 1E ultrasonic power meter (Ohmic Instruments, St. Charles, MO, USA). Fig. 5 illustrates the results obtained.

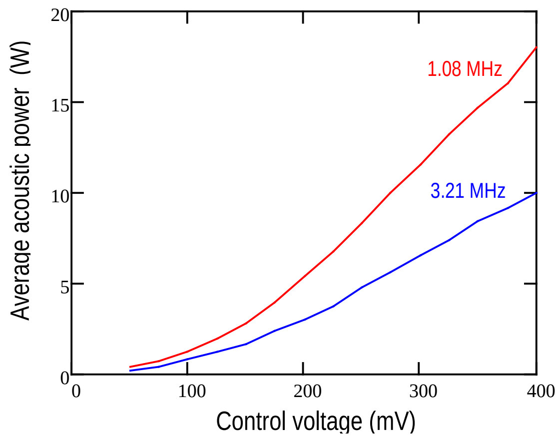

Fig. 5. The average acoustic power of the applied HIFU transducer operating at resonant frequency (1.08 MHz) or 3rd harmonic (3.21 MHz) measured as a function of the excitation control voltage.

3. Results

The measurements of the pressure distributions in the nonlinear beams generated in water by the applied transducer allowed us to determine sizes of the ellipsoidal focal volume for each beam. In the case of beams with resonance frequency (1.08 MHz), the sizes of the ellipsoidal focal volume (for a maximum pressure drop of -6dB) varied from 1.4 mm x 1.4 mm x 11 mm for the beams with the acoustic power of 16W to 1.6 mm x 1.6 mm x 12.3 mm for the beams with the acoustic power of 8W. This means that when the acoustic power is doubled, the volume of necrosis decreased from 31.49 mm^3 to 21.56 mm^3, being almost 1.5 times smaller.

Whereas, in the case of the HIFU beams of the same acoustic power (8W) generated by the applied transducer operating at the fundamental (1.08 MHz) or 3rd harmonic (3.21 MHz) frequency, these dimensions decreased from 1.6 mm x 1.6 mm x 12.3 mm to 0.6 mm x 0.6 mm x 4.4 mm. It means that the sizes of the ellipsoidal focal volume of the 3rd harmonic beam dropped nearly 14 times compared to the beam with the same acoustic power operating at the resonance frequency.

4. Conclusions

Because the designed device is intended for the automated destruction of primary solid tumors or their metastases in small animals, whose organs are in the order of a few centimeters, the use of the HIFU beam of the 3rd harmonic frequency will enable the tumor to be destroyed with greater accuracy, without damaging the surrounding healthy tissues.

Acknowledgments

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