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A brief review of development of high intensity focused ultrasound (HIFU) in Chongqing Medical University of the past 21 years

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ABSTRACT

Basic research and clinical applications of HIFU to treat many life-threatening diseases such as uterine fibroids, osteosarcoma, liver cancer, breast cancer, and many others have attracted broad interests in global medical communities (Nat Rev Cancer. 2005; 5(4): 321-327; Nature Reviews Drug Discovery. 2005; 4:255-260). HIFU has been considered as one of the most important developing technologies of modern medicine (Nature News. February 17, 2004). Since 1988, researchers and medical doctors in Chongqing Medical University, China have been performing fundamental research, animal experiments, and clinical trials on HIFU technology. This presentation will serve a brief review of this development of the past 21 years. Due to the multi-disciplinary nature of this technology, this talk will focused on the inter-linkage of the three aspects: engineering, biology and clinical protocol. Examples of clinical treatments of liver, bone and breast cancers will be introduced; our treatment record shows that patients have survived longer than ten year after treatments. In addition, we also will report on applications of HIFU in the treatment of gynecological non-neoplastic diseases such as nonneoplastic epithelial disorders of vulva, chronic cervicitis and HPV infections.

In the last 20 years, High Intensity Focused Ultrasound (HIFU) has been widely recognized as a non-invasive yet effective extracorporeal method for treating tumors. This "non-invasive surgery" presents great potential applications in medical science. The principle of this technology is focusing ultrasoundic energy inside a human body and forming a local high-intensity region, the in situ target tissue absorbs the sound energy and transform it into thermal energy which can induce a rapid rise of tissue temperature to $\geq$ 65ºC within 1 second, causing protein denaturation and resulting in irreversible coagulative necrosis, while the surrounding normal tissue remains intact.

Since 1998, professionals at Chongqing Medical University have been applying this HIFU technology for the treatment of bone, breast, liver and kidney cancers successfully. This article focuses on the researches conducted by Chongqing Medical University in the field of HIFU.

1. How to induce a single coagulative necrosis within deep tissue non-invasively

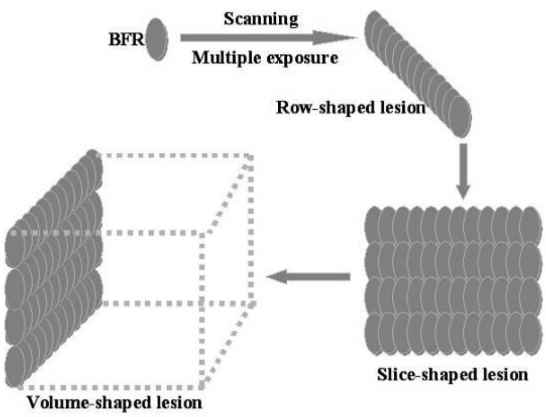
The principle of HIFU treatment is based on focusing ultrasound energy into a target tissue and inducing a single coagulative necrosis. In terms of technology, focusing of ultrasound has been already achieved in water and the distribution of focal sound field can be detected and verified by using hydrophones. However, due to heterogeneity of biological tissue, the variations of ultrasonic attenuation and speed of sound in layers of tissue have serious effects on focusing. Additionally, acoustic caviation and boiling occurring in tissues induced by high intensity ultrasound can also affect ultrasound propagation. The combination of all these factors makes use of the uniform and isotropic medium model as a toolto evaluate the focusing effects of focused ultrasound in biological tissues invalid.

Through a large quantity of experimental studies using *in vitro* and *in vivo* tissues, Wang *et al* [1, 2] proposed the concept of Biological Focal Region (BFR) Which corresponds to the acoustic focal region (AFR) in vivo. The energy deposition from a single HIFU exposure of biological tissue induces a region of coagulative necrotic tissue which is called HIFU BFR. In general, it is a complex concept and a function of the size and shape of AFR, ultrasound intensity (I), ultrasound exposure time (t), depth of focus (D), tissue structure (TS), and tissue function (Tf) [3] . This can be represented by the following formula:

$$BFR = f\,(AFR, I, t, D, Ts, Tf). \qquad (1)$$

2. How to achieve a complete coagulative necrosis of a tumor tissue

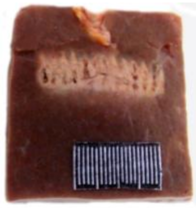
Relative to a tumor with a large volume, the cogulative necrotic tissue induced from single HIFU exposure is too small. In order to completely "remove" a large tumor, a "surgical procedure" must be followed. The extracorporeal transducer must follow a certain combination of movements in order to completely ablate the entire tumor (same as normal surgery). A complete "surgery" in this case usually includes tissue ablation of dots, lines, slices and volume; i. e., many single coagulative necrotic dots making a line, several lines forming a slice and a few slices making a block etc. The procedure starts from deep tissue and moves up to superficial tissue with a set spacing between each line to form a slice of necrotic tissues, combining multiple slices of necrotic tissue to form a block of necrotic tissue. The key is the formation of line necrosis, which is based on the size and location of individual necrotic lesions (Figure 1).

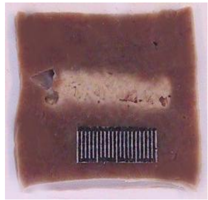


Source: (Z.B. Wang, 1998)

Figure 1.Mehod of ablating a tissue volumn through dot to line lesion, slice lesion and volume lesion

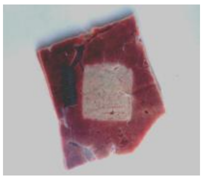
A. BFR (coagulative necrosis generated by a single ultrasound exposure)





B1 B2

B. line lesion (B1.multiple pulses, B2.linear scanning)



C. slice lesion D.volume lesion

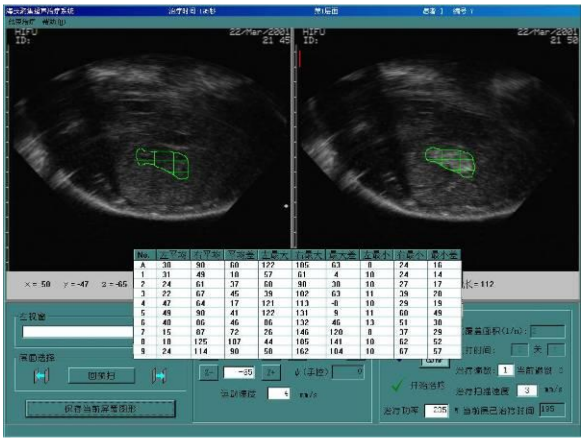
Source: (Faqi Li, 2003)

Figure 2.HIFU induced dot, line, slice, and volume lesion in tissue respectively

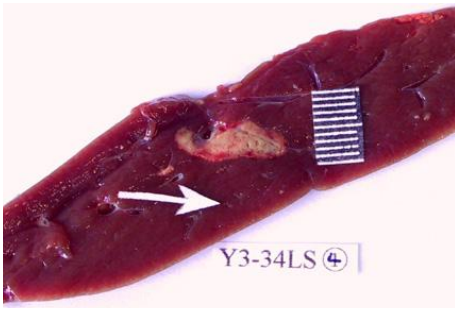
Experiments done in bovine liver have shown that following the procedure line necrosis, slice necrosis and volume necrosis can be generated. Closer examination by slicing open the treated liver shows clear boundaries between the complete cogulative necrotic tissue and normal tissue (Figure 2). This "surgery procedure" can avoid "lesion-lesion interaction" (damage-damage interference effect). The movement of the extracorporeal transducer which forms multiple coagulative necrotic points within the target lesion, instead of increasing the size of necrotic tissue at single point, is the major difference between HIFU technology, microwave and radiofrequency method.

3. Image-guided HIFU treatment

Clinical HIFU treatment of tumors must be conducted under precise image monitoring. At present, two methods of monitoring are achieved by using real-time ultrasound imaging and Magnetic Resonance Imaging (MRI). Regardless of which means of monitoring is utilized, they must be able to guide, locate, monitor changes in target lesion and evaluate the therapeutic efficacy. In clinical applications, it is important to monitor changes at target region and how this would relate to pathological changes as well as how the therapeutic efficacy can be evaluated from these changes. Research has shown that, immediately post-HIFU exposure, real-time ultrasound monitoring on the target region show hyperecho, which diminished in its intensity and range with time [4]. Compared with pre-HIFU exposure, the strength of this echo can be calculated using computer software which analysis gray-scale value (Figure 3).



Source: (Faqi Li, 2007)
Figure 3.Gray scale at the focus before and after HIFU treatment



Source: (Faqi Li, 2007)
Figure 4.Shape and size of coagulative necrotic tissue is comparable to the scope of hyperecho in figure 3.

This gray scale value is the result of HIFU exposure induced cavitation and bubble formation which causes rapid temperature rise in tissues and the structural changes in coagulative necrotic tissues. When the grayscale value reaches a certain value, it represents coagulative necrosis. The largest cross-section of the scope of hyperecho is the same as the cross-section of the coagulative necrotic tissue (Figure 4). During HIFU treatment, real-time evaluation of grayscale value determines whether coagulative necrosis has occurred. If the grayscale value of the target lesion has not reached certain value, it is necessary to treat this lesion again, until the grayscale value reached that of coagulative necrosis. Therefore, it is possible to utilize real-time ultrasound to guide, locate, monitor and give real-time evaluation of treatment efficacy in HIFU tumor therapy.

4. HIFU Treatment system

After 10 years of basic research, the first ultrasound guided focused ultrasound tumor therapy system (JC-model Focused Ultrasound Tumor Therapy System) was developed in 1998. This system consisted of high frequency power generator, mechanical motion systems, integrated transducer with ultrasound probe, control console and water treatment system. This system was awarded the SFDA Certification in 1999 and the CE Certification in 2005. Based on this system, JC200-model was developed, as well as CZF-model which specialized in the treatment of white lesions of vulva and chronic cervicitis. As of 2005, a collaboration with Siemens to develop MRI-guided focused ultrasound tumor therapy system (JM-model Focused Ultrasound Tumor Therapy System), which is undergoing clinical trials.

5. Clinical applications of HIFU

Since 1997, the HIFU therapy system developed by Chongqing Medical University has been used in more than 10 countries worldwide for the treatment of liver cancer, breast cancer, malignant bone cancer, soft tissue sarcoma, kidney cancer, pancreatic cancer and uterine fibroids. The safety and efficacy of this treatment is evident in more than 10,000 cases [5]. The clinical feedback of the HIFU therapeutic system from these countries is all positive. They all agree that HIFU is a novel, safe and effective non-invasive treatment technology. RO Illing [6-8] has used JC-model Focused Ultrasound Tumor Therapy System to treat 30 Western patients with liver or kidney cancer and stated that HIFU treatment on these Western patients is safe and feasible. Zhang *et al* [9] have used the JM-model Focused Ultrasound Tumor Therapy System to treat 23 patients with uterine fibroids. Their studies showed that MR images obtained at 3 month follow-up from 12 patients indicated shrinkage of treated fibroid volume by 31.4%.

In 2009, on the first Non-Invasive Ultrasound Treatment Summit, results of 10 year follow-up of HIFU treated liver cancer, bone cancer and breast cancer patients were presented [10].

In addition, focused ultrasound is also used to successfully treat gynecological diseases such as white lesion of vulva and chronic cervicitis of more than 10,000 cases, showing both safety and efficacy. Li *et al* [11] used HIFU to treat 76 cases of white lesions of vulva and vulvar dystrophies. After 2 years follow-up, 49 patients were successfully treated and 23 patients had improved symptoms. Jinyun Chen [12] compared ultrasound therapy and laser therapy for symptomatic cervical ecotopy, showing ultrasound therapy with a better outcome and little damage to the normal tissue.

CONCLUSION

High Intensity Focused Ultrasound is recognized as an effective non-invasive treatment in the 21st Century. Chongqing Medical University has always insisted on integrating basic research, engineering technology and clinical trials as a new way to develop a medical modality. HIFU provides physicians with a truly non-invasive treatment and its application is not limited to only treatment of cancer. It can also be used to treat benign and other diseases and symptoms such as palliative relief of chronic pain caused by malignant cancer as well as inducing surgical coagulation. Recent technological advances show that HIFU will play a pivotal role in future surgical applications.

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