World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
doi:10.5306/wjco.v2.i1.8

World J Clin Oncol 2011 January 10; 2(1): 8-27
ISSN 2218-4333 (online)

TOPIC HIGHLIGHT

E YK Ng, PhD, PGDTHE, Associate Professor, *Series Editor*

High intensity focused ultrasound in clinical tumor ablation

Yu-Feng Zhou

Yu-Feng Zhou, Division of Engineering Mechanics, School of Mechanical and Aerospace Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798, Singapore
Author contributions: Zhou YF solely contributed to this paper.
Correspondence to: Yu-Feng Zhou, PhD, Division of Engineering Mechanics, School of Mechanical and Aerospace Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798, Singapore. yfzhou@ntu.edu.sg
Telephone: +65-67904482 Fax: +65-67924062
Received: June 24, 2010 Revised: July 26, 2010
Accepted: August 2, 2010
Published online: January 10, 2011

Abstract

Recent advances in high intensity focused ultrasound (HIFU), which was developed in the 1940s as a viable thermal tissue ablation approach, have increased its popularity. In clinics, HIFU has been applied to treat a variety of solid malignant tumors in a well-defined volume, including the pancreas, liver, prostate, breast, uterine fibroids, and soft-tissue sarcomas. In comparison to conventional tumor/cancer treatment modalities, such as open surgery, radio- and chemo-therapy, HIFU has the advantages of non-invasion, non-ionization, and fewer complications after treatment. Over 100 000 cases have been treated throughout the world with great success. The fundamental principles of HIFU ablation are coagulative thermal necrosis due to the absorption of ultrasound energy during transmission in tissue and the induced cavitation damage. This paper reviews the clinical outcomes of HIFU ablation for applicable cancers, and then summarizes the recommendations for a satisfactory HIFU treatment according to clinical experience. In addition, the current challenges in HIFU for engineers and physicians are also included. More recent horizons have broadened the application of HIFU in tumor treatment, such as HIFU-mediated drug delivery, vessel occlusion, and soft tissue erosion ("histotripsy"). In summary, HIFU is likely to play a significant role in the future oncology practice.

Key words: High intensity focused ultrasound; Thermal ablation; Image-guided therapy; Cancer; Bubble cavitation; Bioeffects

Peer reviewer: Nathalie Lassau, MD, PhD, Imaging Department, Institut Gustave Roussy, 39 Rue Camille Desmoulins, 94800 Villejuif, France; Ali Syed Arbab, MD, PhD, Associate Scientist and Director, Cellular and Molecular Imaging Laboratory, Department of Radiology, Henry Ford Hospital, 1 Ford Place, 2F, Box 82, Detroit, MI 48202, United States; Ravi Murthy, MD, Interventional Radiology, UT MD Anderson Cancer Center, 1400 Pressler Street, Unit 1471, Houston, TX 77042, United States; Ronald Xiaorong Xu, PhD, Assistant Professor, Biomedical Engineering Department, The Ohio State University, 270 Bevis Hall, 1080 Carmack Rd., Columbus, OH 43210, United States

Zhou YF. High intensity focused ultrasound in clinical tumor ablation. *World J Clin Oncol* 2011; 2(1): 8-27 Available from: URL: http://www.wjgnet.com/2218-4333/full/v2/i1/8.htm DOI: http://dx.doi.org/10.5306/wjco.v2.i1.8

INTRODUCTION

Cancer is a major public health problem for human beings in both developed and developing countries. Currently, one in four deaths in the United States is due to cancer[1]. Cancer therapy demand in the United States will grow annually by 10% through 2009. Increases will be driven by more incidence and detection of cancer coupled with a range of highly effective, but expensive, new treatment modalities. $16.8 billion are spent each year for cancer therapies in the United States[2]. This represents historical demand data from 1994, 1999 and 2004 and forecasts to 2009 and 2014 by cancer type (e.g. breast, digestive system, genital system, leukemia, lymphoma), by product/procedure (e.g. chemotherapy drugs, surgery, radiation therapy, biotechnology-based drugs, hormonal therapy, vaccines, nanotechnology, stem cells), and by institution/provider

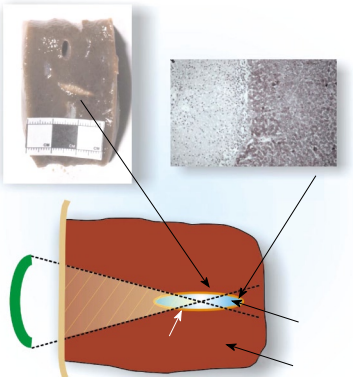

Figure 1 The high intensity focused ultrasound beam passes through overlying skin and other tissues without harming them and is focused to necrose a localized tumor region, which may lie deep within the body. There is a very sharp boundary between dead and live cells at this contour.

(e.g. hospitals, outpatient facilities, physicians' offices, home health care). The conventional therapy modalities are open surgery, chemo- and radio-therapy, which carry significant morbidity and mortality, and may be associated with long in-patient stays and recovery periods. A major goal of technological and medical research in fighting cancer is to significantly reduce local, regional, and systemic side effects, as compared with conventional therapies and to provide additional therapeutic options in cases where conventional therapies fail. New modalities have been introduced in recent years, such as radiofrequency, laser, microwaves, and cryoablation therapies.

The application of ultrasound in clinics is no longer limited to diagnosis. High intensity focused ultrasound (HIFU) is being promoted as the only completely noninvasive and extracorporeal method to treat primary solid tumors and metastatic disease. The key of HIFU treatment is to deliver the energy required to raise the tissue temperature to a cytotoxic level sufficiently fast such that the tissue vasculature does not have a significant effect on the extent of cell killing (Figure 1). Coagulative necrosis caused by heat differs in microscopic appearance and host response from the classical ischemic-type coagulative necrosis: heat coagulation favors giant cell reaction with chronic inflammation whereas ischemic-type necrosis causes healing mainly with granulation tissue. In addition, with heat coagulation, the surrounding normal fatty tissue frequently shows histological signs of fat necrosis. The boundary between apparently totally disrupted cells and normal tissue is no more than 50 μm in width[3]. However, lethal complications may develop if some vital blood vessels adjacent to the tumors are severely damaged. This indicates that large blood vessels are probably less vulnerable to HIFU damage than solid tissues (such as tumor tissue), presumably due to the blood flow dissipating the thermal energy from the vessel wall. Therefore, HIFU is a relatively safe method to ablate tumors in close proximity to major blood vessels, where surgical resection is often contraindicated and may be hazardous. The clinical applications for HIFU have been widely explored in neurosurgery, ophthalmology, urology, gynecology, and oncology[3-5] for about 100 000 patients to date, mainly in Asia and Europe. Preliminary reports suggest that there is reduced toxicity with HIFU ablation compared with other ablation techniques, such as cryotherapy, percutaneous alcohol ablation, and either percutaneous or laparoscopic radiofrequency because of the noninvasive nature of the procedure[6]. In addition, there is an upper size limit for tumors that can be treated, approximately 3-4 cm in diameter, with minimally invasive methods.

HIFU technology has the following advantages that justify research efforts: pain is minimized (the procedure is minimally- or non-invasive); the procedure cost is low as compared with traditional surgery; there are no remaining scars; recovery is faster than with traditional surgical methods; if any hemorrhage occurs, ultrasound (US) has the potential to stop the bleeding; the therapy can be repeated, theoretically, an infinite number of times because there is no dose limit; there is no ionizing radiation from magnetic resonance imaging (MRI) and diagnostic US, as opposed to other systems that are guided by X-rays; and maintenance of the system is low. Unpleasant side effects of current cancer therapies are often the limiting factor for treatment. For example, neurotoxic effects may limit the dose of a cytotoxic agent in chemotherapy. Similarly, in radiotherapy some critical surrounding normal tissues may receive an irradiation dose causing irreversible damage. Clinical trials, in which 68 patients have been treated at the Royal Marsden Hospital in London, have demonstrated that HIFU treatment for liver cancer is well tolerated by fully conscious patients who are treated on an outpatient basis and have not needed local anesthesia or sedation[7]. Altogether, HIFU has been becoming a viable thermal tissue ablation modality for solid tumors and an interesting topic for ultrasound researchers and engineers.

This article initially introduces the principles of HIFU, its history and development from a technical viewpoint. Secondly, clinical outcomes of current HIFU applications in the treatment of prostate, breast, liver, renal tumors, and uterine fibroids are reviewed. It is noted that, with the development and wide acceptance of HIFU ablation, its application is not limited to the diseases mentioned above. Finally, the practical experiences of successful tumor ablation and technical challenges met in clinical applications are summarized from numerous trials. Furthermore, other HIFU-related technologies, which may play an important role in future cancer treatment, are also introduced.

HIFU BACKGROUND

History

The first therapeutic trial of high intensity ultrasound beams was carried out in 1942[8]. The Fry brothers are credited with the first application of HIFU for neurologic disorders in humans[9]. Early attempts to generate HIFU lesions in the brain through the intact skull bone were unsuccessful[8,10]. Small lesions were found in the brain, but there was profound damage to the scalp. Although

it was claimed that the symptoms of Parkinsonism were eliminated, this treatment was not taken further, probably because of the concurrent development of the drug L-dopa. The requirement to remove a section of the skull bone and the lack of imaging sophistication limited the progress of this neurosurgical research in its earlier days. In 1970s, US was used to induce hyperthermia (elevation of tissue temperature to about 43℃) in the entire tumor volume for an extended time (about 1 h)[11]. A rediscovery of HIFU for the treatment of tumors occurred in the 1990s with the refinement of modern technologies in transducer design, modes of energy delivery, and real time imaging. Precise targeting and good treatment follow-up techniques (with anatomical and functional imaging) were available with diagnostic US scanning and MRI techniques, which paved the way to realizing the full potential of HIFU treatment. The ability of HIFU to target subcutaneous tissue volumes and produce almost instantaneous cell death by coagulation necrosis in the selected regions of deep-seated soft tissue tumors has made it a candidate for direct and rapid treatment of tumors[3-5].

HIFU principles

HIFU relies on the same principles as conventional US. The time-averaged intensities of typical diagnostic US (B-mode, pulsed or continuous Doppler) can be up to 720 mW/cm^2 according to United States Food and Drug Administration (USFDA) regulations. In contrast, the intensity of HIFU in the focal region is about several orders higher, 100-10 000 W/cm^2, with peak compression pressures of up to 70 MPa and peak rarefaction pressures up to 20 MPa.

Two main mechanisms are involved in the HIFU ablation: a thermal effect and a mechanical effect. The thermal effect of HIFU is heat generation due to absorption of the acoustic energy with a rapid elevation of temperature in the local tissue. Tissue temperature elevated to more than 60℃ for 1 s will generally lead to instantaneous and irreversible cell death *via* coagulation necrosis in most tissues, which is the primary mechanism for tumor cell destruction in HIFU therapy. Ultrasound beam focusing results in high intensities only at a specific location within a small volume (e.g. about 1 mm in diameter and about 10 mm in length), which minimizes the potential for thermal damage to tissue outside the focal region. Since the thermal mechanism is better understood and its effect is easier to control, it is preferred in tissue ablation.

Tissue thermal damage at high-temperature exposures can be predicted by using an Arrhenius analysis or the Sapareto-Dewey iso-effect thermal dose relationship, which demonstrate that tissue thermal damage is approximately linearly dependent on exposure time and exponentially on the temperature elevation[12]. For convenience, a thermal dose, which is expressed in equivalent minutes at 43℃ (EM43℃ or t_{43}), is usually applied in hyperthermia or high-temperature hyperthermia. Thermal doses of 120-240 min at 43℃ irreversibly damage and coagulate critical cellular protein, tissue structural components and the vasculature leading to immediate tissue destruction, however, the threshold varies with tissue type[13]. At the borders of the thermal coagulated lesion, the tissue will die within 2-3 d.

Mechanical effects induced by HIFU are associated with acoustic pulses only at high intensities, including cavitation, micro-streaming, and radiation force. Cavitation is defined as the creation or motion of a gas cavity in an acoustic field due to alternating compression and expansion of tissue as an ultrasound burst propagates through it. There are two forms of cavitation: stable and inertial cavitation[14]. Stable cavitation is the stable oscillation of the size of the bubble when exposed to a low-pressure acoustic field. Inertial cavitation is violent oscillations of the bubble and rapid growth of the bubble during the rarefaction phase when they reach their size of resonance, eventually leading to the violent collapse and destruction of the bubble. The violent collapse will produce shock waves of very high pressure (20-30 000 bars) and high temperature (2000-5000 K) in the microenvironment[14]. The oscillating motion of stable cavitation causes the rapid movement of fluid near the bubble due to its oscillating motion, which is called the "micro-streaming" effect. Micro-streaming can produce high shear forces that can cause transient damage to cell membranes and may play a role in US-enhanced drug or gene delivery[15]. Meanwhile, radiation force is developed when an acoustic wave is either absorbed or reflected. If the medium is liquid and can move freely, the liquid motion will lead to the generation of microscopic streaming, which can also induce cell apoptosis[16]. In apoptotic cells, the nucleus of the cell self-destructs with rapid degradation of DNA by endonucleases. Apoptosis may be an important delayed bioeffect in tissue exposed to HIFU, especially in cell types that regenerate poorly, such as neurons.

HIFU system

HIFU devices for clinical use fall into three main categories: extracorporeal, transrectal, and interstitial. Extracorporeal transducers are used for targeting organs that are readily accessible through an acoustic window on the skin, whereas transrectal devices are used for the treatment of the prostate and interstitial probes are being developed for the treatment of biliary duct and esophageal tumors.

Focusing a high-intensity US beam can be achieved by a concave self-focusing transducer (e.g. Sonablate-500, Focus Surgery, USA), or arranging multiple piston transducers on the truncated surface of a spherical bowl (e.g. FEP-BY02, Beijing Yuande Biomedical Engineering, China), or fronting a flat transducer with a suitably designed acoustic lens (e.g. Model-JC, Chongqing HAIFU™, China). The -6 dB beam size of HIFU system in its focal region is usually 1-3 mm in width and about 10 mm in length, depending on the geometrical size and acoustic parameters of the HIFU transducer applied. However, the detectable and treatable tumor/cancer in HIFU is at least 1 cm in size. In order to treat the target, HIFU focus should be scanned throughout the entire volume. Moving and/or rotating the HIFU transducer with a fixed focus in a mechanical way

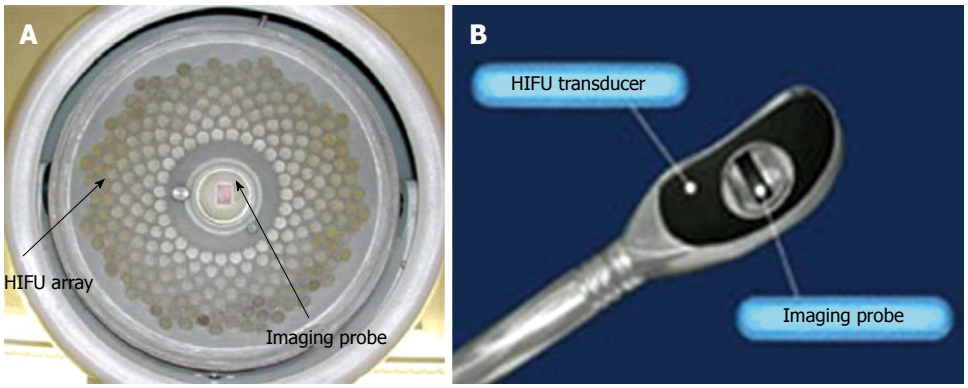

Figure 2 The structure of (A) an extracorporeal (FEP-BY02) and (B) a transrectal (Ablatherm) high intensity focused ultrasound transducer. HIFU: High intensity focused ultrasound.

was the common method used in the first generation of HIFU systems because of the simplicity in control regardless of the system type. Thanks to developments in electrical control and US transducer fabrication, another focusing and scanning approach became available in the second generation by utilizing phased array technology and adjusting the amplitude and phase of each element individually. Phased array allows more rapid and electrical steering of the HIFU focus through tissue, and greater flexibility in focal geometry. Tissue inhomogeneity in abdominal-pelvic (e.g. uterine fibroids and renal tumors) or transcranial applications might cause focal beam distortion and might largely decrease the focusing ability in deep-seated tissues. Focal beam patterns can be virtually restored by using the phase correction procedure as in US imaging. Subsequently, significant improvement on the shape of temperature profiles and the accuracy of temperature control are expected.

The acoustic energy may be delivered in two ways in HIFU ablation. A single exposure may be made with the transducer held stationary. When larger volumes are to be ablated, the transducer may be moved in discrete steps either mechanically or electronically, and fired at each position, where the distance between "shots" will determine whether lesions are overlapped or separated, depending on the necessity to achieve confluent regions of cell killing (e.g. FEP-BY02 and Sonablate-500 systems). An alternative exposure strategy is to move the active therapy transducer in pre-determined trajectories (e.g. linear tracks or spirals) to conform to the required treatment volume. If the correct combination of transducer velocity and US energy is used, these result in confluent volumes of cell damage (e.g. Model-JC system).

The optimal choice of therapeutic US frequency is application-specific, and represents a compromise between treatment depth and the desired rate of heating. Frequencies near 1 MHz have been found to be most useful for heat deposition, with frequencies as low as 0.5 MHz being used for deep treatments or with large absorption portion in the propagation path (e.g. transcranial application) and as high as 8 MHz for superficial treatments (e.g. prostatic application)[17]. Usually an extracorporeal device has a wide aperture and a long focal length and is driven at high power. Wide aperture sources have the advantage of distributing the incident energy over a large skin area, thus reducing the acoustic intensity at the wave entry site and the consequent possibility of skin burn. Transrectal and interstitial sources operate at lower powers and higher frequencies as they can be placed closer to the target volume. Typical HIFU systems are shown in Figure 2.

An extracorporeal HIFU device is usually used for targets lying within the breast, abdomen, brain or limbs. Transcutaneous treatments require an appropriate acoustic window on the entry site that provides a propagation path for the focused US beam that is uninterrupted by intervening gas. In addition, it must be possible to couple the US energy to the skin surface using coupling gel, a water balloon, or other suitable liquid path. Extracorporeal HIFU treatments are guided using either US (e.g. FEP-BY02 of Beijing Yuande Biomedical Engineering and Model-JC of Chongqing HAIFU™ Co.) or a MRI modality (ExAblate 2000 of InSightec, Israel).

MRI has excellent anatomical resolution and high sensitivity for tumor detection, thereby offering accurate planning of the tissue to be targeted. In order to be used in the high magnetic fields of MRI, HIFU transducers must be specially designed for compatibility. The lead zirconate titanate (PZT) ceramic material, commonly used for US transducers, contains nickel, which is necessary for the high levels of electrical excitation and mechanical stress induced. However, nickel causes magnetic field distortion. Therefore, the new piezo-composite materials are usually used to develop MRI-compatible transducers. Using MR thermometry, it enables calculation of thermal dose and superimposes a representation of the regions in which the thermal dose has achieved cytotoxic levels on the anatomical MR image. The phase-shift image used to visualize the temperature-dependent changes in proton-resonance frequency using a fast spoiled gradient-recalled echo sequence (SPGR)[18] is more reliable than T1-weighted imaging[19]. MR proton resonance frequency thermometry at 1.5 T with segmented gradient-echo echo planar imaging (GRE-EPI) sequences has been evaluated during liver tumor radiofrequency (RF) ablation. It was found that MR proton resonance frequency thermometry at 1.5 T yields precise

and accurate measurements of temperature increments (1.3 ± 0.4℃ with frame rate of 0.6 s/image). Rapid GRE-EPI sequences minimize intra-scan motion effects and can be used for MR thermometry during RF ablation in moving organs[20]. In addition, T1 or T2 weighted fast spin-echo (FSE) were proven successful to image thermal lesions created by HIFU in rabbit liver *in vivo*. The contrast to noise ratio (CNR) with T1-weighted FSE was significantly higher than T2-weighted FSE (25 *vs* 14). With T1-weighted FSE, the range of repetition time (TR) under which CNR is high ranges from 400 to 900 ms[21]. Therefore, during the HIFU procedure, the temperature-sensitive MRI provides the ability of closed-loop control of energy deposition, with temperature accuracy of 1℃, spatial resolution of 1 mm, and temporal resolution of 1 s. Immediate post-treatment assessment of the therapy is also available.

Although MRI has the advantage of providing temperature data within seconds after HIFU exposure and it is superior to sonography in obese patients[22], MRI guidance is expensive, labor-intensive, and of lower spatial resolution in some cases. The temporal and spatial averaging effect of the MRI thermometry cannot be ignored and leads to the underestimation of temperature. The temperature measured in a single MRI voxel by water proton resonance frequency shift attained a maximum value of only 73℃ after 7 s of continuous HIFU exposure when boiling started, which was detected by visual observation and appearance on the MR images. Theoretical simulation predicted 100℃ after 7 s of exposure and the averaged temperature field over the volume of the MRI voxel 0.3 mm × 0.5 mm × 2 mm yielded a maximum of 73℃, which agreed with the MR thermometry measurement[23]. In comparison, US imaging modality is generally more convenient and mechanically compatible. US guidance provides the benefit of imaging using the same form of energy that is being used for therapy. The most significant is that the condition of the acoustic window can be verified with sonography in real-time (usually 30 Hz frame rate depending on the imaging depth and configuration). Therefore, if the target cannot be well visualized with sonography before or during the HIFU ablation, it is unlikely that HIFU therapy will be effective in the target region, and it may potentially cause thermal injury to unintended tissue (e.g. skin on the acoustic wave entry site). An US diagnostic transducer is usually incorporated into the treatment head (Figure 2), which allows real time imaging of the ablation process. However, the thermally ablated region is not visible on standard B-mode images unless gas bubbles have been induced as hyperechoic spots. In addition, the US image quality may be less than optimal.

HIFU with MRI and US guidance have their advantages and shortcomings. US guidance is good for preprocedural tumor localization, but not good for intraprocedural assessment of therapeutic boundaries because the non-specific acoustic contrast generated by heat-induced tissue bubbles. MRI is good for transient tissue temperature measurement, but cannot effectively measure the "lethal thermal dose" and is not sensitive to fat tissue[24]. In recent years, magnetic resonance-guided focused US surgery (MRgFUS) has been developed as an integrated system for HIFU therapy. Heat sensitive microbubbles have also been explored for enhanced US imaging of lethal thermal doses[25].

The transrectal devices that have been developed for the treatment of benign and malignant prostate disease can be inserted per rectum. The two commercially available devices, the Ablatherm© (Edap Technomed, France) and the Sonablate™ (Focus Surgery, USA), incorporate therapy and imaging transducers into a treatment head mounted at the end of a transrectal probe. Prostate ablation is achieved by placing touching lesions side by side. In the Ablatherm device, lesion length is varied by adjustment of the US power. However, thicker prostates are ablated using two layers of lesions in the Sonablate system, the deeper layer being created using a longer focal length than the more superficial layer. The different focal lengths are achieved by rotating the transducer since the two sides have different geometries. Usually coupling water is circulated and cooled during the HIFU therapy to avoid thermal damage to the interface tissue due to the temperature increase on the surface of the HIFU transducer and to maintain working stability of the HIFU transducer. In contrast, because of the large size of the water balloon in the extracorporeal HIFU system, water cooling in real-time is not required and the degassed water is suggested to be changed every 1-2 h.

There has been increasing interest in the development of high intensity US probes for interstitial use, and volume destruction is obtained by rotating the probe[26]. Usually plane transducers, rather than focusing elements, are used. Once 360° of rotation has been achieved the probe can be repositioned under fluoroscopic or MRI guidance to create other adjacent rings. The interstitial devices can be used for biliary and esophageal tumors, or bloodless partial nephrectomy. It can also be developed into a MR compatible device, or percutaneous and laparoscopic devices. Commercial products are expected to enter the market in the near future.

Popular HIFU systems that have been reported in clinical use are listed in Table 1. With development of the HIFU market, more devices are being developed or are in different stages of clinical trials. Therefore their performance and specifications have not been offered to the public.

System characterization

Conventionally, US exposures are characterized in terms of the acoustic field determined in the free field. The parameters necessary for describing HIFU exposures are frequency, exposure time, transducer characteristics (geometry and configuration), total power delivered, acoustic pressure and intensity, and energy delivery mode. The total acoustic output power is usually determined using a radiation force balance method[27]. The acoustic exposure power is proportional to the discrepancy of force applied to an absorbing target between HIFU on and off, and depends on the beam convergence angle, the shape and properties of the absorbing target, and the HIFU transducer configuration. Other important factors

Table 1 Summary of most popular high-intensity focused ultrasound system for clinical use

Model	Manufacturer	Size (mm)	Focal length (mm)	Frequency (MHz)	Focusing method	Imaging guidance	Clinical applications
FEP-BY02	Beijing Yuande Biomedical Engineering Inc, China	OD = 370 ID = 120	255	1	251 elements driven in phase	GE Logiq series ultrasound system	Liver, kidney, breast, pancreatic, bone tumor and uterine fibroid
Model-JC	Chongqing Haifu Tech Ltd, China	D = 120 or 150	90, 130, 160	0.8, 1.6, 3.2	Flat ceramics with acoustic lens	AU3 ultrasound imaging system	Liver, kidney, breast, pancreatic, bone tumor and uterine fibroid
ExAblate 2000	InSightec Ltd, Israel	120	150	0.9, 1.3	Phased array 208 hexagonal elements, 3 cavitation detector	GE Signa 1.5/3.0T MR imaging system	Uterine fibroids, breast tumor, liver cancer, bone metastases, neurosurgery, prostate cancer
Sonalleve	Philips, USA	N/A	N/A	1.2, 1.4	Phased array	Philips Achieva 1.5/3.0T MR imaging system	Uterine fibroids
Sonablate 500	Focus Surgery Inc., USA	30 × 22	30 and 40 or 45/50	4	2 elements mounted back-to-back	Element for both therapy and imaging	Prostate cancer
Ablatherm	Edap-Technomed, France	40 × 22 ID = 8	45	3	Single concave element	7.5 MHz integrated ultrasound imaging	Prostate cancer
TH-One	Theraclion, France	56	38	3	Single concave element	B-K Medical ultrasound imaging system	Hyperparathyroidism

N/A: Not available; GE: General electronics; MR: Magnetic resonance.

affecting the measurement are the distance of the target from the source, absorption of energy in the water bath between the transducer and the target, and acoustic streaming effects. The radiation force balance method is particularly useful when very strongly focused transducers and phased arrays are being characterized.

Acoustic pressure is measured using a hydrophone. Both needle and polyvinylidene fluoride (PVDF) membrane hydrophones have been used widely in the calibration acoustic field at low (e.g. US diagnostic system) and intermediate (e.g. physiological US devices) power level. PVDF hydrophones have the advantage of only minimally disturbing the field and high sensitivity, but may be prone to cavitation damage at their surface in a high intensity field. Once damaged, the PVDF and needle hydrophone will not be usable until recalibration. Beam profiles are usually measured at much lower output levels than are used for clinical HIFU treatment and it is assumed that a linear extrapolation to high levels is valid[28]. This method introduces errors since it ignores the effects of nonlinear propagation occurring at high pressures, which increases the amplitude of peak positive pressure significantly, reduces the wave front rise time (formation of shock wave), and introduces harmonic components. Recently, a fiber optic probe hydrophone (FOPH) was used in the HIFU acoustic field measurement[29]. FOPH is robust to the cavitation damage to sensor and has a broad bandwidth (up to 100 MHz after deconvolution) to guarantee the accurate measurement of all harmonics. A new tip can be prepared easily with self-calibration even after damage (optical fiber included in the FOPH is supposed to be used for a life time). With use, the acoustic pressure at high power can be measured directly and operation is rather straight-forward. Once the position of the focal peak has been established, the peak acoustic pressure amplitude can be measured, from which intensity will be calculated. The hydrophone is scanned in the focal region under the automatic control of the three-dimensional translational stage, and measured waveforms are transferred to a computer for further off-line processing. The beam size (usually -6 dB/half of maximum pressure in the lateral and axial directions) can be determined from the pressure distribution. Hill *et al*[28] defined a parameter, I_{SAL}, which is the acoustic intensity spatially averaged over the area enclosed by the half pressure maximum contour. It was demonstrated that there was a correlation between lesion diameter and I_{SAL}[30].

CLINICAL APPLICATION

Prostate tumor

Transrectal HIFU treatment of prostate tumors is one of the pilot investigations. Both benign prostate hyperplasia (BPH) and prostate carcinoma have been targeted at a few medical centers in Europe and Japan in the past decade. Initial clinical trials for BPH treatment were encouraging[31,32], with increases in flow rate and decreases in post-void residual volume. However, the long-term results were disappointing[33], with 43.8% of patients requiring a salvage trans-urethral resection of the prostate (TURP) within 4 years. Therefore, HIFU has not been proved significantly better than the "gold standard" treatment (TURP), and is not recommended for treatment of this condition[34].

In contrast, treatment of prostate cancer presents different problems from those associated with BPH treatment[35]. Prostate cancer is a multi-focal disease, with the foci difficult to detect with diagnostic US. The most successful HIFU treatments have been those that have ab-

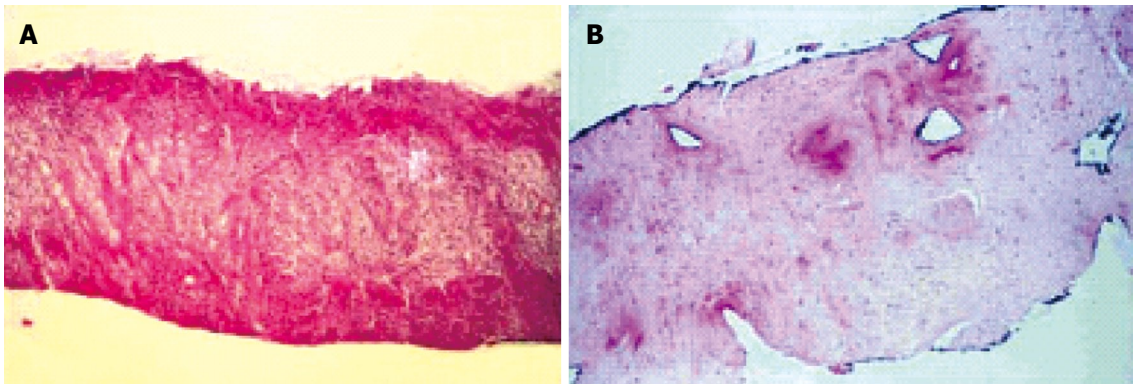

Figure 3 Complete destruction of the glandular tissue due to coagulation necrosis lesion which reaches the capsula and the periprostatic fat 48 h after high intensity focused ultrasound treatment (A) and the necrotic prostatic tissue is replaced by a fibrotic tissue, including the capsula, 3 mo after high intensity focused ultrasound therapy (B).

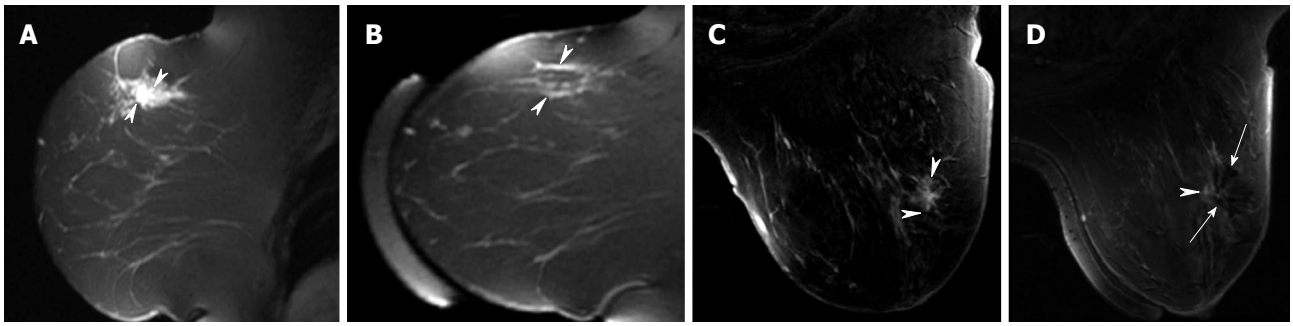

Figure 4 Sagittal contrast-enhanced T1-weighted fat-saturated magnetic resonance sagittal (A) and axial (C) images of a 1.8-cm poorly differentiated invasive ductal carcinoma in a 44-year-old woman before MRgFUS. An irregular enhancing mass is seen in the upper outer quadrant of the right breast (arrow heads). Three days after magnetic resonance-guided focused US surgery (MRgFUS), minimal strikes of enhancement are seen without mass like enhancement in the sagittal image (arrow heads in B), which may represent hyperemia due to reactive inflammation or residual tumor. On the axial image (D), dark signal void area is seen at the site of the prior enhancing mass (long arrows). At histopathology, about 50% of the carcinoma and adjacent normal tissue showed thermal effects and the remaining portion of the carcinoma appeared viable.

lated the whole gland[31,32]. With experience, control rates for the treated tumor have risen from 50% at 8 mo in the early days to 90% more recently[36,37]. Mid-term follow-up (2-5 years) has shown that the prostate specific antigen (PSA) levels remain low and that the negative biopsy rate remains around 90%[36,38,39]. Success rates for the treatment of prostate cancer range from 60%[4] to 80%[40] of patients being disease-free at repeat biopsy and show a reduction of serum PSA values to less than 4 ng/mL[41]. Whole-gland versus focal treatment resulted in a reduced incidence of recurrent tumor of 35% to 17% in one series; in patients not found to be disease-free, reductions in tumor volume greater than 90% have been reported[40]. A representative complete destruction of the glandular tissue due to coagulation necrosis lesion is shown in Figure 3.

Complications reported from prostate HIFU include urinary retention, incontinence, urinary infection, impotence, chronic pain, rectal anal fistulas, and incomplete treatment of disease[42]. Repeat treatment with HIFU is associated with much higher complication rates than single treatments[43,44]. To mitigate urinary retention associated with prostate HIFU, transurethral resection was performed before treatment[45,46]; and in these patients, the length of time with indwelling catheters remaining in the bladder has been reduced from 40 to 7 d[36]. Prostate HIFU seems most appropriate in men older than 65 years, those who are not candidates for surgery, and those who are obese[47,48].

Breast tumor

The standard treatment for women with breast cancer desiring breast conservation is lumpectomy followed by external radiation therapy. There is increasing interest in recent years to use nonsurgical ablation as part of a breast-conservation therapy in patients with early breast cancer. The cosmetic results and side effects after conventional breast-conservation treatment are acceptable to most patients; however, the nonsurgical ablation methods are thought to be psychologically and cosmetically more satisfactory. HIFU is one of the noninvasive and effective techniques to induce local tumor necrosis, and is also suitable for treating patients who are at high risk for surgery with less anesthesia, reduced in-hospital recovery time and cost, less risk of infections, and no scar formation[49] (Figure 4).

The HIFU can precisely deliver energy to a given point in soft tissue without interrupting skin integrity. Very few severe (3rd-degree skin burn) and a few minor adverse events were reported. Proximity to the skin should be avoided, and it is important to keep safety margins during

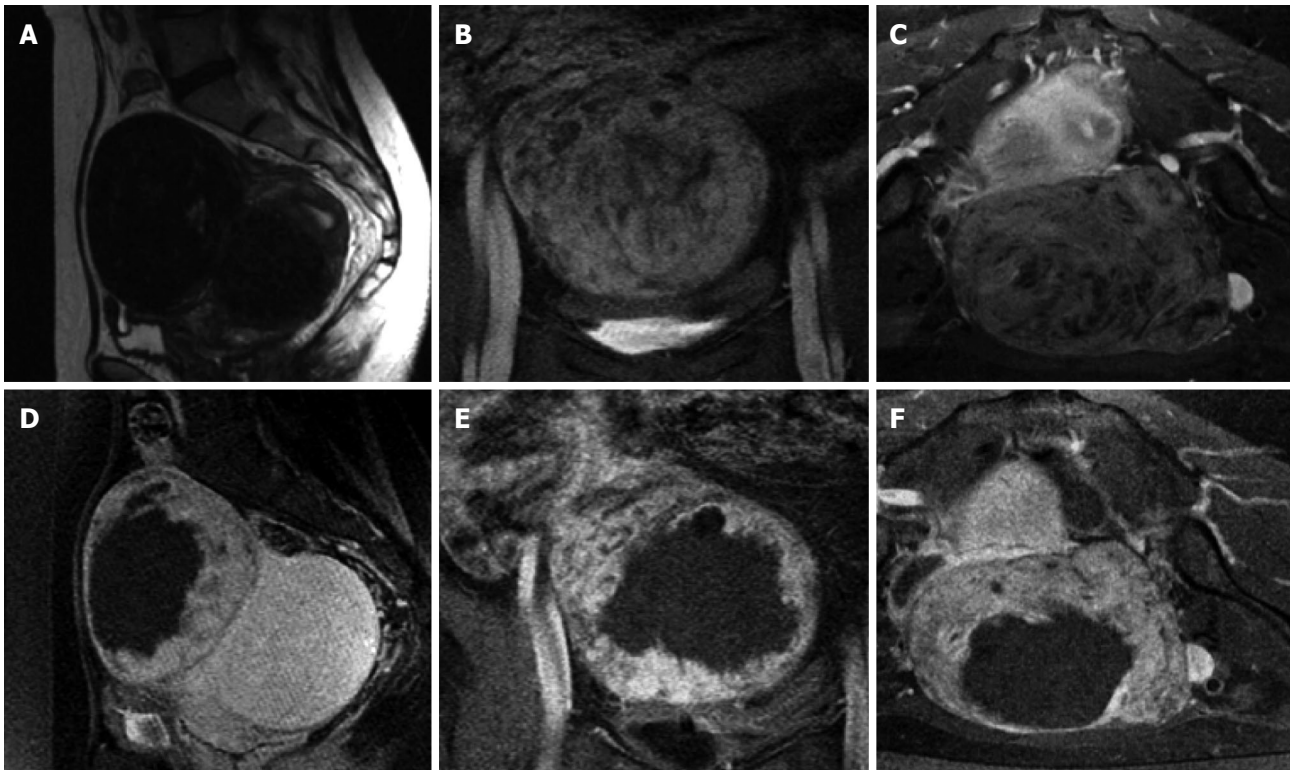

Figure 5 Images of a uterine fibroid pretreatment and posttreatment with MRgFUS. Top, Sagittal T2 fast spin-echo (A), coronal spoiled gradient-recalled echo sequence (SPGR) postgadolinium (B), and axial SPGR postgadolinium (C) are obtained pretreatment. The low SI homogenous fibroid depicted in Figure 3A demonstrates slight heterogenous enhancement pretreatment (Figure 3B, C). Bottom, Sagittal SPGR post-gadolinium (D), coronal SPGR post-gadolinium (E), and axial SPGR post-gadolinium (F) are obtained immediately post-treatment. A new large nonperfused area is identified, consistent with treatment-induced necrosis.

the HIFU treatment of breast carcinomas. In total, 19 of 24 patients were considered to have undergone successful treatment (breast biopsy free of neoplasia after 1 or 2 sessions of HIFU). All patients remained free of metastasis on routine follow-up (mean follow-up, 20.2 mo)[50]. The main argument against noninvasive treatments of breast cancer, including HIFU, is that the margin status cannot be assessed due to lack of pathological specimen. Radiological assessment, mainly post-procedure contrast-enhanced MRI, must replace histopathology.

Uterine fibroids

Uterine leiomyomas (fibroids) are gonadal steroid-dependent benign smooth-muscle tumors and are one of the most common female pelvic tumors, occurring in approximately 25% of women[51]. Whereas many patients remain asymptomatic, others experience symptoms such as pelvic pain, menorrhagia, dysmenorrhea, dyspareunia, urinary frequency, and infertility. The most common organ of origin is the uterus, although fibroids can also arise from the fallopian tubes, broad ligament, or cervix. Women are, however, increasingly seeking less invasive treatment options, perhaps motivated toward fertility preservation and a reduction in procedure recovery time. MRI is an optimal modality for further characterizing fibroids because of its good inherent tissue contrast. The addition of post-intravenous gadolinium imaging further characterizes these benign tumors, detecting homogenous enhancement or areas of internal necrosis, which may affect treatment decisions. Gadolinium helps differentiate cellular from degenerating fibroids; cellular lesions usually demonstrate diffused early homogenous enhancement with dynamic imaging, whereas degenerating fibroids demonstrate irregular, delayed, or no enhancement (Figure 5).

MRgFUS was approved by the USFDA in October 2004, with more than 2000 patients treated to date worldwide. Clinical trials were carried out at 5 medical centers across the United States[52,53], in addition to centers in Japan[54], the United Kingdom, Germany, and Israel. Enrollment of phase Ⅰ/Ⅱ began in 1999. The purpose of this study was to assess the safety and feasibility of MRgFUS in the treatment of fibroids. Suitable symptomatic candidates were chosen using an 8-item symptom severity score (SSS) of the Uterine Fibroid Quality of Life Questionnaire[55]. An SSS of 21 of a possible 40 points were required for entry into the clinical trial, as a reflection of the significant fibroid-related symptom burden. Premenopausal women with symptomatic uterine fibroids who have no desire for future pregnancy were included. This treatment is not indicated for pregnant women, postmenopausal women, or those with contrast-enhanced MRI contraindications. The MRgFUS did indeed result in hemorrhagic necrosis in the area of non-perfusion on the post-treatment MR. Only 10% of patients reported taking pain medication within 72 h of treatment. The phase Ⅲ clinical trial involved treatment of larger volumes in the fibroids of women with

symptomatic uterine fibroids. Seventy-nine percent of treated patients reported a 10-point reduction in their SSS, at 6 mo post-treatment, with a 13.5% mean reduction in treated fibroid volume. Most of the improvement in SSS occurs within the first 3 mo of treatment. However, at 12 mo post-treatment, only 51% of those evaluable reported a 10-point reduction in SSS and 28% of patients underwent an alternative treatment by 12 mo[56]. These results should be interpreted in view of the fact that on average only 10% of the fibroid volume was treated, as this FDA-approved study design sought to maximize safety. Gonadotrophin-releasing hormone agonists (GnRHa) are well known to cause a reduction in fibroid size when administered in a continuous fashion. It has recently been demonstrated that the pretreatment of patients who have fibroids measuring 10 cm or greater with GnRHa, before MRgFUS, has a beneficial effect, enhancing the tissue response to HIFU[57].

Although the clinical outcome is best assessed using a disease-specific questionnaire, symptom relief and fibroid volume reduction cannot be assessed until some period later. Immediately post-treatment with MRgFUS, it was found that apparent diffuse coefficient (ADC) values were significantly lower within the area of treatment, which may suggest cell necrosis and loss of membrane integrity due to this treatment. Long-term changes in ADC values on follow-up studies, and the reason for these changes, remain to be determined. In 109 patients studied, leg and buttock pain were reported after treatment. Although the MR neurography and electromyography studies failed to show any intrinsic damage, the sciatic nerve was revealed in the far field of the sonication region.

Liver tumor

Hepatocellular carcinoma (HCC) is rapidly becoming the most common malignancy worldwide. Surgery, particularly liver transplantation, offers the only real hope for cure; but survival rates are only 25%-30% at 5 years. Despite considerable advances in diagnostic modalities, the overall prognosis of primary and metastatic liver cancer remains dismal. The poor outcome is attributed mainly to the characteristic biological behavior of hepatic cancer: multiple foci of origin, resulting in low rates of respectability and a high risk of postoperative recurrence. For such a multi-focal and frequently recurrent malignancy, a logical and attractive method of treatment would be using a noninvasive therapeutic modality that can selectively destroy multiple tumor nodules scattered throughout the liver without impairing liver function. A noninvasive therapeutic system would also allow repeated application when necessary. Tumors can be destroyed by producing a contiguous lesion lattice encompassing the tumor and appropriate margins of surrounding tissue determined by computer coordination.

Small animal models have established that HIFU can ablate areas of normal liver[58], and energy thresholds for liver tissue destruction have been published[59]. A maximum lesion size was observed on the third day after treatment, and its replacement by a thin fibrous scar after several months[58]. When intensity was kept constant and exposure time increased, the lesion size increased to a maximum, after which longer exposure times did not cause larger lesions. An optimal result was reached when the necrosis area in the liver had the same dimensions as the desired volume at the desired location. After treatment of normal rabbit livers, hyperechogenic patterns at the target location were rarely observed, even when a homogenous lesion was observed at autopsy. When this hyperechogenic pattern was present immediately, it disappeared 3 wk later. In contrast, the hyperechogenic pattern was always present after successful treatment of rabbits bearing a liver tumor. However, there was no correlation between the size of the hyperechogenic area and the volume of the coagulation necrosis at autopsy[58].

Studies of the treatment of HCC and secondary liver metastasis in human clinical trials have also been published[60,61]. Destruction rates as estimated by quantitative microscopy on millimetric tissue slices ranged from 42.5% to 100%. Histology showed a homogenous dwell-delineated coagulation necrosis corresponding to the target volume in the depth of the liver. No viable tumor tissue remained in the treated area[62]. A model-JC HIFU device has been used to treat 68 patients with liver malignancies in China. In 30 cases in which surgical excision followed HIFU ablation, the tumor was totally ablated[63]. Subsequently, 474 patients with HCC were treated using the same device[64]. HIFU has also been used for palliation in patients with advanced-stage liver cancer[65]. After treatment, 87% of patients reported symptomatic improvement. Patients were also randomized between transarterial chemoembolization (TACE) and HIFU[66]. The median patient survival times were 11.3 mo in the combined HIFU-TACE group and 4 mo in the TACE-only group ($P = 0.0042$). Overall, HIFU has been shown significant promise in the treatment of hepatic malignancies. Tumor growth inhibition rates from 65%-93% were seen in the HIFU-treated group. They also showed a longer median survival in groups treated with HIFU or HIFU combined with doxorubicin[67].

Renal tumor

Surgery remains as the mainstay of treatment for renal tumors, with 5-year survival rates greater than 80% after resection[68]. Because most renal tumors are small, a noninvasive approach for their treatment would be attractive. Currently HIFU ablation of renal tumors in humans remains in the early stages of clinical trials. A clinical feasibility study has been performed on 8 patients who showed histological evidence of ablation in the treated areas after excision[69]. Wu *et al*[70] reported a series of 13 patients with renal cell carcinoma. Nine of 10 patients treated for palliation reported a reduction in pain. No side effects occurred after ablation using an experimental handheld device. Further investigations continue to study the efficacy of HIFU treatment of renal cell carcinoma for both cure and palliation[70].

Pancreatic cancer

More than 32000 people are diagnosed with pancreatic

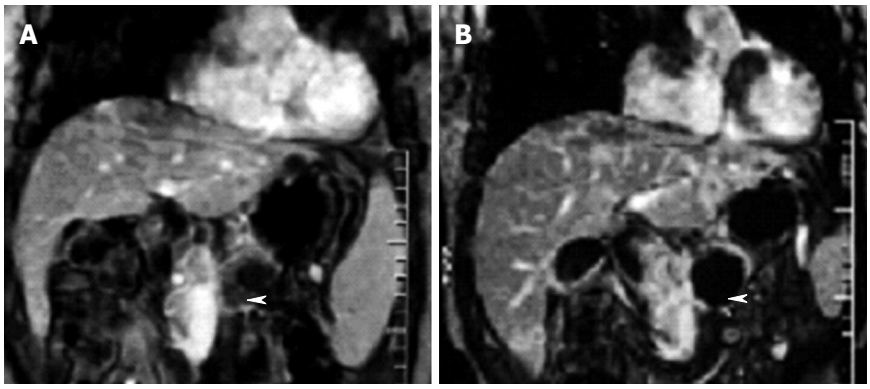

Figure 6 Dynamic contrast-enhanced gradient-echo T1-weighted magnetic resonance images (180/6.0, 90° flip angle, 128 × 256 matrix, 10-mm-thick sections, 2-mm intersection gap, one signal acquired, and 18-s acquisition time) obtained with breath holding in 48-year-old man who underwent high-intensity focused ultrasound ablation for advanced pancreatic cancer. The tumor was 4.5 cm × 4.5 cm in diameter and located in the body of the pancreas. A: Image obtained before high-intensity focused ultrasound shows the blood supply in the pancreatic lesion (arrowhead); B: Image obtained 2 wk after high-intensity focused ultrasound shows no evidence of contrast enhancement in the treated lesion (arrowhead), which is indicative of complete coagulation necrosis in the pancreatic cancer.

cancer annually in the United States and as many as 200 000 patients annually worldwide; the 5-year survival rate is less than 5%[1,71]. Pancreatic adenocarcinoma accounts for 5% of cancer deaths in the United States and is the fourth leading cause of cancer mortality. However, only less than 20% of pancreatic cancer patients can undergo open surgery. Two hundred and twenty-three patients with advanced pancreatic cancer (Tumor Node Metastasis stages Ⅱ-Ⅳ) have been treated in China, and the results from this open-label study suggested that HIFU can reduce the size of pancreatic tumors without causing pancreatitis and thus prolong survival[72]. Before HIFU treatment, all patients had obvious visceral pain that necessitated management with oral analgesic drugs. The pain associated with unresectable pancreatic cancer in 84% of patients, however, had resolved significantly within 24-48 h after a single session of HIFU treatment and the pain relief persisted during the follow-up period. 223 patients were followed up from 8 to 36 mo. The average survival time was 12.5 mo and 6 patients survived more than 3 years. No skin burns caused directly by HIFU were observed in this group, and no deaths had occurred 1 mo after HIFU therapy (Figure 6). During the hospital stay, no signs of tumor hemorrhage, large blood vessel rupture, or gastrointestinal perforation were detected in any patient. No dilatation of the common bile duct or pancreatic duct was visible at follow-up imaging. There was no evidence of postinterventional pancreatitis, peritonitis, or jaundice in any patient during the follow-up period[72,73]. Other initial nonrandomized open-label human studies have provided additional evidence that HIFU treatment of pancreatic tumors indeed relieves pancreatic adenocarcinoma-related pain and focally ablates malignant tissue[66].

Bone tumor

Surgical removal and radiation therapy are commonly used strategies to treat bone tumors. The former is often used for primary bone tumors, whereas the latter is more often than not adopted for bone metastases. Initially HIFU was not considered as a suitable modality for bone diseases because of the great difference of acoustic impedance of bone from that of the surrounding soft tissue. However, Smith *et al*[74] found that focused US beams can target bone tissues and induce necrosis of osteocytes in normal rabbits. In fact, after the bone was destroyed by a lesion, such as an aneurismal bone cyst, the lesion inside the marrow cavity could be verified by diagnostic US imaging[75]. In the targeted region, the destruction of endothelium cells of microvessels and thrombosis was readily detected, suggesting that HIFU could potentially prevent hematogenous dissemination of the tumor cells[76]. The treatable diameters of bone tumor increased with the absorption ratio of bone marrow to tumor, acoustic window of surface skin, and diameter of bone, but decreased with muscle depth and specific absorption rate ratio (SARR) of the bone tumor to the surface skin, bone marrow, and bone[77]. The optimal driving frequency was dependent on tumor depth, US absorption of bone marrow, and bone diameter, but was independent of the acoustic window area and SARR ratio under the three SARR criteria[77].

Ninety-six cases of bone tumors have been successfully treated using HIFU technology as of 2002 in China[78]. 4 patients with primary stage Ⅱ malignant bone tumors, including 3 chondrosarcoma and 1 malignant giant cell tumor of bone, and 4 patients with breast cancer bone metastases were treated with HIFU ablation alone[79]. All treated regions after HIFU had no intensification and there was an even, thin intensification rim around the region (Figure 7). In ^{99m}Tc-MDP bone scan, disappearance of radioactive uptake was found and a radioactive cold region was produced, suggesting complete inactivation of the tumor foci. After an average follow-up of 23.1 mo, no local recurrence was found in any of the cases, which shows HIFU can be an effective stand-alone therapy to manage malignant bone tumors. However, when diagnostic US was used for guidance of HIFU treatment, nerves might not always be clearly detected. In clinics, there were no significant changes in ECG, renal function, and blood electrolytes of patients before and after HIFU. Although ALP activity (a measure of liver function) increased 3 d after HIFU, it returned to the same or lower pre-HIFU

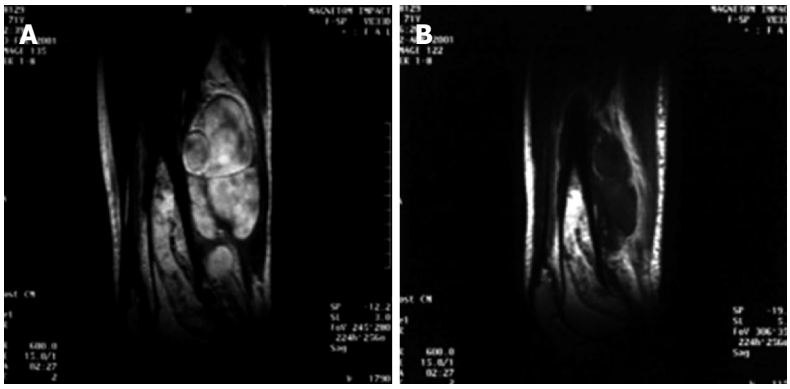

Figure 7 Contrast-enhanced magnetic resonance images (A) before and (B) 14-d after high intensity focused ultrasound ablation in a 45-year-old patient with osteosarcoma at the upper right tibia.

level 1 wk later. Those findings indicated that HIFU ablation had no significant influence on the vital organs.

Further studies were also done using the combination of HIFU and chemotherapy for managing malignant bone tumors in a total of 44 patients[80]. After a mean follow-up time of 17.6 mo, the overall survival rate was 84.1%. For the 34 cases of stage Ⅱb, 30 cases continued to survive disease-free, 2 died of lung and brain metastases, and the other 2 had local recurrence. Among 10 of the stage Ⅲb cases, 5 survived with tumor, 1 had local recurrence, and 5 died of lung metastases. It is conceivable that a limb salvage procedure can be carried out to treat malignant bone tumors of limbs using HIFU and chemotherapy because the preliminary results demonstrated that HIFU is effective and well tolerated. HIFU ablation results in fewer complications and well-preserved limb function because there were no surgical traumas and blood vessels > 2 mm in diameter were retained, which could be beneficial to revascularization and the repair of inactivated tumor bones. In addition, because surgical trauma and repair of the trauma are not involved with HIFU treatment, there would be no delay of postoperative chemotherapy, which is beneficial to ensure the efficacy of chemotherapy and to improve the prognosis[81].

Overall, representative HIFU clinical trials are summarized in Table 2. Although the summation is not complete because of unfinished publication collection, current results show HIFU as a safe and effective modality in multiple cancer treatment.

CLINICAL EXPERIENCE

Among the most important factors that determine the success of HIFU is patient selection. General exclusion criteria are: women who are pregnant or nursing, clinical evidence of brain metastases, subjects with tumors lying < 5 mm from vital structures or either adjacent to the skin or the chest wall, concurrent antiarrhythmic, disease with good prognostic factors, anticoagulant or immunosuppressive medication, ductal carcinoma *in situ* (DCIS) and cancers with an extensive intraductal component or lymphovascular invasion, tumors with very irregular margins, too large size, scattered multiple foci, or in proximity to the nipple, more than one focal breast lesion per quadrant, previous radiation or local thermal therapy, significant background illness or underlying medical condition (e.g. congestive heart failure, chronic obstructive pulmonary disease), metallic implants or other incompatibility with MRI (e.g. permanent implanted pacemakers), an inability to lie still for up to 150 min, and those who had previously documented severe intra-abdominal adhesions.

Critical to the performance of HIFU is the ability to obtain an adequate and optimal acoustic window and ultrasonic beam conformation, including, if possible, algorithms for correcting beam distortion in the presence of interfaces. There are a limited number of such acoustic windows because bone, air, and gas interfere with the propagation of US beams into the body, thus obscuring targets beyond these interfaces. In addition, unavoidable microscopic bubbles in the coupling media and local anesthesia caused scattering of the US beam and thus limited the power delivered to the target. It is therefore recommended that, if local anesthesia is used, it should be placed not in front rather beyond the lesion. The effect of interfaces requires particular attention because it is known that an interface is a potential site of cavitation. The skin of the HIFU entry site must be hair-free, the patient having been instructed to shave all hair the night before the procedure. Although patients with extensive skin scarring in the beam path are excluded, it may, however, be possible to treat patients with non-extensive abdominal wall scarring by angling the beam path, ensuring that the scar is not traversed. Placement of a gel spacing device may allow the bowel loops to be "pushed" out of the treatment field, thereby enlarging the acoustic window and allowing for greater treatment volume. Care should be taken to ensure that the pathway of the treatment beam does not traverse any critical structures (such as bowel loops anterior to the selected outlined sub-volume).

Definition of the target volume by the radiologist or/and operator is of the highest importance because tumor margins must be correctly identified and included in the target volume. During any cancer surgery or abla-

Table 2 Summary of high-intensity focused ultrasound clinical outcomes

Cases	Authors	HIFU system	Patients	Outcomes
BPH	Sullivan *et al*[32]	Sonablate	25 patients (mean age 67 years, range 47-84)	5 patients with large glands were withdrawn; the remaining 20 patients had improvements in the AUA symptom score (20.25 to 9.56), Qmax (9.2 to 13.7 mL/s) and QOL score (4.75 to 2.50)
	Uchida *et al*[34]	Sonablate Sonablate 200	35 patients mean age 68.5 ± 7.7 (52-84) treated by Sonablate; 22 patients mean age 68 ± 6.8 (57-81) treated by Sonablate 200	IPSS and QOL scores showed significant improvement at 3, 6, and 12 mo follow-up (P < 0.001-0.01); maximum flow rate (8.9-15.5 mL/s, P < 0.001) and prostatic volume (32.2-22.8 mL, P < 0.01) were significantly improved at 12 moths follow-up treated by Sonablate 200
Prostate cancer	Chaussy *et al*[36]	Ablatherm	271 patients were selected: 96 in the HIFU group and 175 in the TURP + HIFU group	A significant impact was observed on catheter time (40.0 d *vs* 7.0 d), incontinence (15.4% *vs* 6.9%), urinary infection (47.9% *vs* 11.4%), and the evolution of the post-treatment IPSS (8.91 *vs* 3.37) in favor of TURP + HIFU group; no significant changes were observed regarding efficacy during short-term follow-up, 25% and 4% retreatment rate in the HIFU and TURP + HIFU group, respectively
	Gelet *et al*[37]	Ablatherm	14 patients (mean age 72.5 years) with clinical stage T1 (3) and T2 (11) prostatic cancers	Early complications occurred in 6 (rectal burns 3, urinary retention 2, transient incontinence 1) and late complications in 5 (incontinence 2, bladder neck stenosis 3) patients; the PSA nadir value (1.79 ± 2.35 ng/mL) was achieved at 6 mo and the final PSA value was 2.94 ± 3.27 ng/mL (mean follow-up 380 d); No residual cancer was observed in 7 patients; Residual cancer was found in 7 patients: 4 required complementary treatment (orchidectomy 2, external beam radiation therapy 2)
	Gelet *et al*[40]	Ablatherm	82 patients (mean age 71 ± 5.7 years) with biopsy-proven localized (stage T1-T2) cancer	62% of patients exhibited no disease progression at 60 mo follow-up; the disease-free rate was 68% for the moderate-risk group of 50 patients (PSA < 15.0 ng/mL, Gleason sum < 8, prostate volume < 40 cm^3, and number of positive biopsies < 5); for the low-risk group of 32 patients (PSA < 10 ng/mL and Gleason sum < 7), the disease-free survival rate was 83%
	Chaussy *et al*[41]	Ablatherm	184 patients (mean age of 72 years, range 59-81)	Cancer free in 80% of patients and the tumor mass was reduced more than 90% in the residual cancer; the nadir value of PSA was < 4 ng/mL in 97%, including 61% who had values < 0.5 ng/mL; no severe side effects (fistula, grade 2 or 3 incontinence, rectal mucosal burn) were seen
	Uchida *et al*[41]	Sonablate-500	181 patients (median age of 70 years, range 44-88) and pretreatment PSA was 9.76 ng/mL (range 3.39-89.60)	The disease-free survival rates at 1, 3 and 5 years in all patients were 84%, 80% and 78%, respectively; the disease-free survival rates at 3 years for patients with pretreatment PSA less than 10 ng/mL, 10.01-20.0 ng/mL and more than 20.0 ng/mL were 94%, 75% and 35%, respectively (P < 0.0001)
	Blana *et al*[42]	Ablatherm	223 patients with age of 68.2 ± 6.8 years, PSA 11.3 ± 10 ng/mL (range 0.5-81.2), Gleason score 5.3 ± 1.5 and a prostate volume of 23.5 ± 10.7 cm^3 (range 3-62.5)	The complications rates were: urinary tract infection 0.4%, chronic pelvic pain 0.9%, infravesical obstruction 19.7%, stressincontinence 7.6%, impotence 49.8%; among the 49 patients who received a second HIFU therapy, the cumulative incontinence rate (12.2%, P = 0.024) and cumulative impotence rate (55%, P < 0.001) were significantly increased
	Blana *et al*[43]	Ablatherm	146 patients with a mean age of 66.9 ± 6.7 years, mean PSA of 7.6 ± 3.4 ng/mL, mean Gleason score of 5 ± 1.2, and prostate volume of 23 ± 7.7 cm^3	The median PSA nadir 3 mo after treatment was 0.07 ng/mL (0-5.67); The median PSA at 22 mo follow-up was 0.15 ng/mL (0-12.11), and 87% of patients had constant PSA < 1 ng/mL; 93.4% of patients had negative control biopsies; Of all the patients, 12% underwent transurethral resection because of obstruction with no severe stress incontinence (grade 2-3)
	Vallancien *et al*[45]	Ablatherm	30 patients with a mean age of 72 years, a median prostate volume of 30 cc, a median Gleason score of 6, a median PSA of 7 ng/mL	At a mean of 20 mo of follow-up 86% of patients had negative biopsies after HIFU; Median PSA was 0.9 ng/mL; At 1 year of follow-up the mean International Prostate Symptom Score was 8; Regarding sexual function, 73% of previously potent patients reported preserved sexual activity
	Lee *et al*[45]	Ablatherm	62 patients with clinical stage T1-2, PSA value < 30 ng/mL	After HIFU treatment, 78% of patients had a decreased PSA level to < 0.5 ng/mL within 3 mo; the median value of the last PSA was 0.6 ng/mL and the median nadir PSA was 0.2 ng/mL; The success rates of HIFU were 85, 77 and 47% in low-, intermediate- and high-risk groups, respectively
	Thüroff *et al*[39]	Ablatherm	402 patients with localized (stage T1-2N0-xM0) prostate cancer at 6 sites, mean age of 69.3 ± 7.1 years, mean prostate volume 28.0 ± 13.8 cc, mean PSA 10.9 ± 8.7 ng/mL	Negative biopsy rate in T1-2 primary cancer population was 87.2%, 92.1% in low-risk patients
Breast cancer	Wu *et al*[50]	JC	22 patients (4 in TNM stage Ⅰ, 9 in stage ⅡA, 8 in stage ⅡB, and 1 in stage); Tumor size ranged from 2 to 4.8 cm in diameter (mean 3.4 cm)	After a median follow-up of 54.8 mo, 1 patient died, 1 was lost, and 20 were still alive; 2 of 22 patients developed local recurrence; 5-year disease-free survival and recurrence-free survival were 95% and 89%, respectively; cosmetic result was judged as good to excellent in 94% of patients
	Furusawa *et a*[49]	ExAblate 2000	21 cases median age is 54 years (range 34-72), median diameter of tumor is 15 mm (range 5-50)	1 case of recurrence of pure mucinous carcinoma; 2 cases of skin burns

Uterine fibroids	LeBlang *et al*[52]	ExAblate 2000	147 symptomatic leiomyomas in 80 women (average age: 46, range: 34-55) with average fibroids volume of 175 ± 201 cm^3	The average nonperfused volume ratio was 55% ± 25% immediately after treatment; 6 mo after treatment, the average volume of treated fibroids had decreased to 112 ± 141 cm^3 (n = 81) (P < 0.0001) with an average volume reduction of 31% ± 28%
	Funaki *et al*[54]	ExAblate 2000	91 Japanese women (45 of Type 1-2 and 46 of Type 3)	The mean volume change ratios of Type 1-2 myomas were -36.5% and -39.5% at 6 and 24 mo follow-up, respectively; SSS value for patients with Type 1-2 myomas before MRgFUS was 35.1 ± 21.0, and the values diminished significantly during the 24-mo follow-up period to a mean value of ~15.0; Type 3 myomas did not decrease in size 6 mo after MRgFUS; The reintervention rates were 14.0% for Type 1-2 patients and 21.6% for Type 3 patients at 24 mo follow-up, respectively
Liver cancer	Li *et al*[65]	JC	100 patients (80 male, 20 female, mean age of 56, ranging 30-74 years) including 62 primary and 38 metastatic liver cancers	Clinical symptoms were relieved in 86.6% (71/82) of patients; the ascites disappeared in 6 patients; ALT (95 ± 44) U/L and AST (114 ± 58) U/L were reduced to normal in 83.3% (30/36) and 72.9% (35/48) patients after HIFU, respectively; AFP was lowered by more than 50% in 65.3% (32/49) patients
	Wu *et al*[66]	JC	50 patients with stage IVA HCC (T4N0-1M0) The tumors were 4-14 cm in diameter (mean, 10.5 cm)	The 6-mo and 1-year survival rate was 80.4%-85.4%, and 42.9%, respectively; median reductions in tumor volume at 1, 3, 6, and 12 mo after treatment were 28.6%, 35.0%, 50.0%, and 50.0%, respectively
Renal cancer	Wu *et al*[70]	JC	12 patients with advanced stage renal cell carcinoma and 1 patient with colon cancer metastasized to kidney	After HIFU hematuria disappeared in 7 of 8 patients and flank pain of presumed malignant origin disappeared in 9 of 10 patients; it showed decrease in or absence of tumor blood supply and significant shrinkage of the ablated tumor; 7 patients died (median survival 14.1 mo, range 2-27) and 6 were alive with median follow-up of 18.5 mo (range 10-27)
Pancreatic cancer	Wu *et al*[73]	JC	8 patients mean of 62 years range 48 to 86 years	No complications were observed, and preexisting severe back pain disappeared after intervention; Follow-up images revealed an absence of tumor blood supply and shrinkage of the ablated tumor; a median survival time was 11.25 mo
	He *et al*[72]	FEP-BY02	251 (147 men and 104 women) patients in 25 hospitals with mean age of 59, range 39-82, 3-12 cm tumor diameter; TNM grade Ⅱ 7%, Ⅲ 34%, Ⅳ 59%; Concurrent jaundice 18.7% and pain 68%; Head 183, body 53, 14 trail	21.5% cases exhibited a remarkable effect, 64% exhibited a general effect; survival time is 12.5 mo; 6 patients survived more than 3 years; no complications, such as skin burn, gastrointestinal perforation and pancreatic fistula were observed
Bone metastases	Liberman *et al*[81]	ExAblate 2000	31 patients in 3 medical centers	25 patients underwent the planned treatment and were available at 3 mo follow-up; 72% of the patients reported significant pain improvement; average VAS score was reduced from 5.9 to 1.8 at 3 mo follow-up; 67% of patients reported a reduction in their opioid usage

HIFU: High intensity focused ultrasound; BPH: Benign prostate hyperplasia; AUA: American Urology Association; QOL: Quality of life; PSA: Prostate specific antigen; AFP: α-fetoprotein; MRgFUS: Magnetic resonance-guided focused US surgery.

tion, tumors are excised or ablated along with a surrounding margin of normal tissue, usually no less than 1 cm. The radiological analysis of HIFU-treated liver tumors shows that the median area of ablation seen on MRI is 45% smaller than that predicted at the time of treatment, which is greater than the difference between histological ablation and intended area, 6%[61]. If a target tour is situated at a depth greater than 10 cm from the skin, the attenuation of the normal tissues in the beam-path reduces the likelihood of successful ablation with current devices. Additional factors, such as obstruction of the incident ultrasound energy by the ribs or reflection by tissue interfaces, can also lead to under-treatment. Computation of the optimal planning for dosimetry must be performed as fast as possible (in minutes) and *in situ* (patient installed in the final setup for treatment), to deliver a uniform lethal dose over the entire target volume and to spare as many as possible thermal lesions in healthy tissue. The HIFU planning should include, if possible, physiological information (perfusion) and border conditions.

Performing the HIFU ablation should be under active feedback control of the temperature evolution. On-line adjustment of the acoustical power level and/or of the spatial distribution of heat deposition is therefore necessary. Thermal safety in those regions where the delivered thermal dose is close to the lethal threshold and the stability of the temperature controllers for thermal dose feedback require both very accurate thermometry. The MR thermometry measurements have been used in real time to control the power of a stationary, focused US transducer to achieve the desired treatment outcome in minimum time without violating the imposed safety constraints.

Mis-registration, due to respiratory or bulk patient movement, may be problematic. Detection and compensation of physiological or accidental motion of the patient during the treatment provides significant advantage for accurate control of the delivered thermal dose. Therefore, the tumor location should be monitored throughout therapy. Before the start of an HIFU procedure, an anxiolytic can be given to reduce movement, and an analgesic can be administered to counter the associated discomfort. Patients should be under sedation and local anesthesia

during HIFU ablation, but avoiding general anesthesia (because the procedure is to stay minimally invasive as much as possible). In addition, digestive peristaltic motion was reversibly blocked during the HIFU ablation using a common antispasmodic administrated intramuscularly (tiemonium methylsulfate, Visceralgine).

When addressing cancer applications, the accurate spatial control of the delivered thermal dose is mandatory. Geometrical information from diagnostic imaging and from the positioning system of the HIFU probe must be co-registered to provide referencing of the HIFU probe orientation. The HIFU probe is moved using the freedom degrees of the positioning system (translation and rotation) with the focus of the transducer coinciding with the center of the target volume. A checkup for the correct location of the focal point is preferred, with one or several low-power sonications prior to the high-power ablation.

Immediate post-treatment assessment of the therapy is typically performed with contrast-agent uptake, to assess for local perfusion within the tumor and the neighboring tissues. The best time for follow-up MRI may be approximately 1 wk after HIFU. It was found that more than 90% of the identified tumor volume was treated and the residual cancer was predominantly identified at the periphery of the tumor mass. This shortcoming indicated the need to increase the total targeted area at the periphery. Microbubble contrast-enhanced sonography is also being used to evaluate the treatment effect of HIFU[82]. Another method currently being examined in oncologic applications is the use of PET to assess changes in metabolic activity after HIFU treatment.

The HIFU ablation was well tolerated by patients, with the exception of minor skin burns, and no complications occurred. However, high rate of overall side effects on the diaphragm, abdominal wall or skin at relatively low intensities may be explained by the fact that the skin is close to the focus area (e.g. the target HCC is close to the proximal surface of the liver). Autopsy revealed a perforation of the diaphragm in 50% of the cases and a gastric perforation in 25%[67]. Such complications seem to be related to the size of the target volume: with a large target area, some of the volume may be more frequently located outside of the liver so damaging adjacent organs. Although the majority of patients experienced some discomfort, this was generally transient. Skin toxicity was treated with cool-packs and aloe gel. All adverse events were local to the treatment site and self-limiting. Solution is establishing artificial ascites by injecting normal saline solution or 0.2% hyaluronan water solution into the abdominal cavity or under skin. The method of artificial ascites increases the distance between the skin surface and target and serves as a heat sink to cool overlying structures. It has been illustrated that this method not only reduces the probability and extent of thermal damage to intervening structures but also has no adverse affect on the efficacy of HIFU ablation[83].

LIMITATIONS AND CHALLENGES

Despite its promising noninvasive and nonionizing effects in the therapy of malignancies, particularly those that are widespread or inoperable, the application of HIFU has certain limitations. Continuing research is still in great need in the area of focusing the HIFU pulses, the technique of gradual pulsed exposures to achieve a cumulative therapy result, improving imaging quality for accurate tumor determination and post-treatment evaluation, and developing a real-time monitoring modality for lesion generation and temperature elevation.

Since HIFU is essentially US, any artifacts related to US, such as in US imaging, would apply to HIFU as well, such as acoustic shadowing, reverberation, and refraction. Hence, bones and lungs oppose the penetration of US and some areas of the liver parenchyma adjacent to a rib may be difficult to reach with the focused beam. Gas in the bowel cannot be penetrated by HIFU, and sound waves are reflected back toward the transducer, which have high energy and may produce burns in the intervening tissue. Even small amounts of gas in the gastrointestinal tract can produce burns in the wall of the bowel anterior to the gas and in the abdominal wall musculature overlying the gas. Refraction artifacts can result in energy deposition in the soft tissues adjacent to the target area, and energy deposition can occur superficially to the target.

Non-invasive transcranial HIFU therapy remains very limited due to the strong phase aberrations and absorption induced by the skull. To compensate this distortion, the idea of phased array corrections was introduced to US diagnostic imaging through the skull. Thomas and Fink proposed to use a time reversal mirror in therapeutic US. However, a hydrophone has to be inserted in the neighborhood of the tumor in order to record the signals relating this hydrophone to each element of the therapeutic array[84]. Recently, adaptive corrections of the distortions induced by the skull bone have been performed using a previously acquired 3D computational tomography (CT) scan of the skull bone structure. These CT scan data are used as entry parameters in a finite differences time domain (FDTD) simulation of the full wave propagation equation. A numerical computation is used to deduce the impulse response relating the targeted location and the ultrasound therapeutic array, thus providing a virtual time-reversal mirror[84,85]. Research on a fast algorithm of aberration correction (for both trans-abdominal and cranial applications) on site is still ongoing.

A treatment session lasting for 2 h for a superficial 2-3 cm tumor may be acceptable when compared to the alternative of surgical resection, but is less favorably in comparison to other minimally invasive techniques. The longer treatment time may be justified on the grounds of a lower morbidity and mortality than conventional surgery. Treatment time will be reduced with development of HIFU technology, experience, and in combination with methods to reduce tumor perfusion, such as trans-arterial embolization[66].

Nonsurgical ablation relies on imaging quality for an accurate determination of tumor extent, which is why MRI guidance for HIFU has initially become more rapidly accepted clinically than sonographically guided HIFU[22].

Although MRI is shown to be more accurate than mammography or US in size assessment, even MRI currently cannot exclude small amounts of residual invasive cancer. 3D sonography is likely to better delineate a volume of tissue to be treated than just a single plane or orthogonal planes, which provide valuable information to the performance of HIFU, and most commercially available HIFU systems display with 2D sonography systems. Therefore, the application of 3D sonography techniques is an exciting area of future opportunity, especially for HIFU treatment planning, monitoring, and post-treatment evaluation.

Currently the most important problem of US-guided HIFU ablation is the lack of reliable thermometry and lesion production monitoring. There have been several methods under investigation. A sonographic thermometry is being actively investigated and incorporated in FEP-BY02 system[86]. Elastographic techniques will measure the variation of tissue stiffness during the ablation process in real time[59], especially in some cases in which tissue contrast is not sufficient to visualize a tumor in the background of normal tissue. The speed of sound is temperature dependent, which causes the apparent change in position of echoes in the images of heated tissues in comparison to the unheated ones[87]. However, none of these techniques have achieved wide-spread clinical use yet, although some promising results have been provided with a smaller range of temperature elevation in *ex vivo* experiments.

A controversial question is the possibility of increased risk of metastases after the tumor has been disrupted by HIFU. In a report by Fry *et al*[88], a higher rate (17%-44%) of metastases was observed after HIFU treatment than in the control group. However, that feature was not found in other studies. Yang *et al*[67] described a lower rate of lung metastases in the HIFU-treated group. In a model of prostatic cancer, metastases in 16% of the treated rats was found as compared to 28% in the control group[62]. It was found that one of the most important biological consequences of HIFU treatment is the creation of a large amount of tumor antigens in the form of necrotic cells and the local release of a diverse array of endogenous danger signals from HIFU damaged tumor cells. This biological response has the potential to stimulate an anti-tumor immune response[89,90]. However, little is known about how such significant HIFU-induced changes in the tumor microenvironment may influence the host's anti-tumor immune response.

Clinical thermal ablation methods also include the application of radiofrequency (RF), laser, microwave, and their combination[91]. Currently RF is the front-runner and the most widely practiced and preferred technique. Laser has the advantage of being more MR compatible permitting direct MR monitoring. MR compatible RF electrodes are now available but the application of RF current and image acquisition are incompatible and have to be alternated. Microwave has been used particularly in China to treat small HCC. Current microwave applicators are large and several are usually required for open surgery; one of the focuses of development is to produce a smaller percutaneous probe. Most of these technologies are minimally invasive with almost the same effectiveness in small tumors as with a surgical approach (i.e. complications of 2%-10.6% and mortality of 0.1%-1.4%). In comparison, HIFU requires longer treatment times, limited depth of penetration, and an excellent acoustic window, and excludes the applications with overlying ribs or lung.

HIFU-RELATED TUMOR THERAPY METHODS

Thermal ablation HIFU technology can also be used in treating cancers in the following ways.

Immune response

Adjunctive thermal ablation with carmustine, cyclophosphamide and doxorubicin was found to be beneficial in improving the results of HIFU treatment. It has been postulated that sono-modification of the tumor tissue may enhance tumor immunogenicity and subsequently augment the host immune response against the tumor, although the mechanisms behind this phenomenon remain unknown. Animal experiments show that while there were a few HSP70 positive cells in rabbit VX2 bone tumors before HIFU ablation, HSP70 positive cells significantly increased up to 3 wk after HIFU treatment[92]. Furthermore, HIFU ablation also increased CD25 positive cells in the same rabbit bone tumor model. The increase of HSP70 and CD25 positivity in malignant bone tumors may facilitate tumor-specific antigen presentation to T lymphocytes, which stimulate the proliferation of T lymphocytes and enhance the anti-tumor immune response. In a clinical trial, 16 patients with solid malignancies, including 6 with osteosarcoma, were treated with HIFU. There were significant increases in the population of CD4 (+) lymphocytes ($P < 0.01$) and in the ratio of CD4 (+)/CD8 (+) ($P < 0.05$) after HIFU ablation[90]. Their findings suggest that HIFU ablation may eliminate or significantly reduce potential circulating tumor cells in patients with solid malignancies. While the long-term therapeutic benefits and molecular mechanisms of HIFU-treatment-elicited host immune responses in cancer patients require further investigation, it is conceivable that HIFU ablation may induce massive tumor cell death and/or necrosis, which could lead to the release of tumor antigens to stimulate a host anti-tumor immune response. These changes may ultimately enhance the immune function of tumor-bearing patients and improve their prognosis.

Drug delivery

Drug delivery across the blood-brain barrier (BBB) is one of the most important key factors in the treatment of diseases of the central nervous system (CNS). The BBB is a barrier system of the vessels in the brain that hampers various substances from leaking into the brain. Although this barrier system is important for the maintenance of homeostasis of the brain, it prohibits the delivery of therapeutic agents into the brain and complicates the treat-

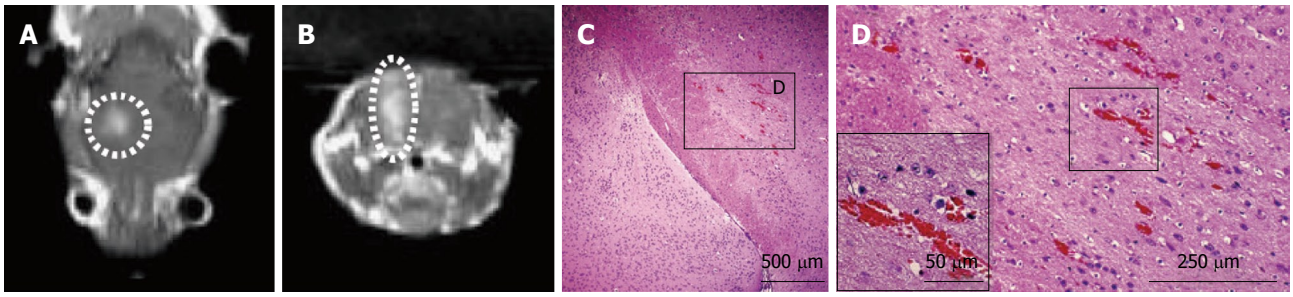

Figure 8 The axial (A) and the coronal magnetic resonance images (B) are presented with a tissue block showing the blood-brain barrier disruption from the mice, overview of the half hemisphere of a mouse with focused ultrasound-induced blood-brain barrier disruption (C) and high magnification of the lesions with severe damage (D).

ment of CNS disorders[93]. The intracellular space in the BBB is so tight that even one of the smallest molecules, such as ions, cannot easily cross the barrier. Current trans-BBB delivery methods include modifying drug formats or attaching with carriers, or focusing on delivery methods such as intracarotid injection and direct catheter insertion into the brain. The major disadvantage of drug modification is its lack of site specificity and not all drugs can be modified. The invasive techniques also limit the candidates for treatment[93].

Although the possibility of using US for BBB disruption has been previously documented, reproducible and reliable opening of the BBB remains difficult[94]. Creating BBB opening without or with only an acceptable magnitude of tissue damage is one of the most challenging issues. When BBB disruption was attempted by means of US with the combined use of microbubble US contrast agent (Optison, Amersham Health Inc., Princeton, NJ), a more reliable and reproducible BBB opening was achieved compared with that when US alone was used. The BBB disruption was achieved at both 1.0- and 3.3-MPa sonication with a burst length of 100 milliseconds[95]. When temperature elevation was measured using MR thermometry, temperature elevation was only 4.8℃ even at the highest amplitude tested. In addition, when the same procedure was performed without the injection of Optison, nearly no BBB opening was achieved (Figure 8). These results indicate that local temperature elevation is not the key mechanism for BBB disruption, and the presence of microbubbles is necessary for the reliable opening of the BBB. The time course study showed that the disrupted BBB repairs itself within approximately 6 h and that the BBB disruption is a transient and reversible event[96]. Long-term follow-up of the sonicated rabbit brain showed nearly no damage, suggesting that the long-term adverse effect of US-induced BBB disruption is minimal[97]. Altogether, it seems reasonable to assume that the parameters for BBB disruption in humans are similar to those used in animal studies. Electron microscopic study suggests that the transcellular pathway is enhanced with US treatment. Drugs were taken up by the endothelial cells by means of vesicle transportation through the endothelial cells and on the loosening or destruction of the tight junctions[96]. From an acoustic point of view, the BBB disruption occurred only with stable cavitation and without the presence of inertial cavitation[98]. US-induced BBB disruption technique can also deliver antibodies to the brain in a localized fashion and the delivered antibodies do not lose their innate function. Herceptin is an antibody against HER-2, which is a receptor for a growth factor and has been shown to be a powerful chemotherapeutic agent against breast tumor. When herceptin was injected into mice using ultrasound-induced BBB disruption technique, the agent was successfully delivered into the brain. Because brain metastases following breast tumors is a very common problem in the clinical field, these results seem promising in providing alternative options for curing patients with brain metastases following breast cancer.

Focusing the US through the intact skull is probably the most exciting and challenging application of the HIFU. CT-derived preliminary information must be coregistered with MR images to correct for wave distortion in bone, in particular, to determine the driving signal (amplitude and phase) for each transducer element to achieve a well-focused beam through the skull. However, until now, no clinical trials have been performed using US-induced BBB disruption techniques. In humans, the cranium is much thicker than that of mice or rats, which means that a more careful and delicate control of US is necessary to form a target inside the brain.

Beside the trans-BBB drug delivery, the cytotoxic potential of the anti-cancer drugs, such as bleomycin and adriamycin, may be restricted by its low membrane permeability. Morphological evaluation of US irradiated cells with scanning electron microscopy showed minor disruption of the cell surface and disappearance of microvilli. It suggests that low intensity US altered the cell membrane thus resulting in anticancer drug uptake into carcinoma cells[82]. Application of low-intensity US to growing tumors is found to enhance intracellular delivery after intraperitoneal or intratumoral administration, thereby potentiating its cytotoxicity. Cell death after treatment was shown to occur by an apoptotic mechanism[99,100]. HIFU was also delivered to a mouse model prior to doxorubicin hydrochloride liposomes. Mean doxorubicin concentration in tumors treated with HIFU pulses was significantly higher (124%) than in the control group. Extravasation of dextran-fluorescein isothiocyanate was observed in the vasculature of HIFU-

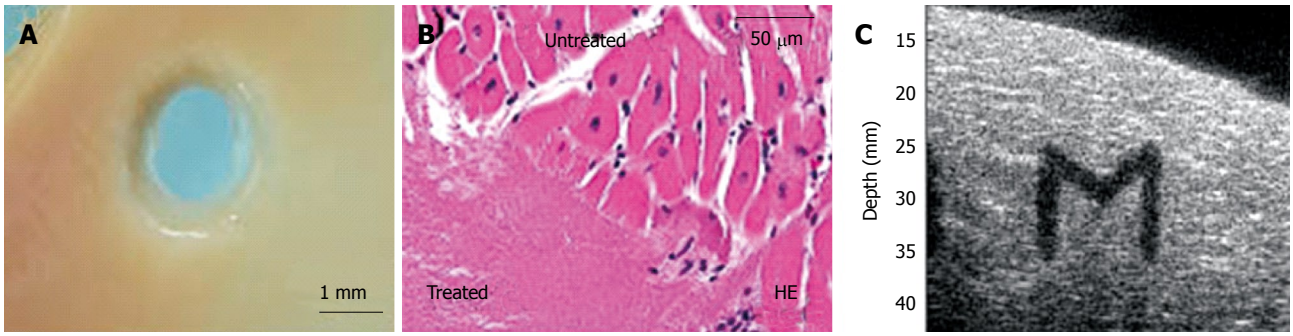

Figure 9 Representative (A) image and (B) histology of tissue erosion after histotripsy, and (C) "M" shape lesion generated by histotripsy shown in ultrasound imaging.

treated tumors but not in that of untreated tumors[101]. Meanwhile, addition of microbubbles in the ultrasound-mediated drug delivery can lower the threshold of bubble cavitation and transiently increase capillary permeability in tumor cells[102]. Although no clinical trials have been performed, this technique could be developed into a localized and effective anticancer treatment with little or no systemic toxicity with enhanced efficiency of thermal ablation.

Vessel occlusion

Blood vessel occlusion is useful for treating arteriovenous malformations (AVM) in different parts of the body for controlling abdominal, peritoneal and pelvic hemorrhage and also for treating some tumors with an identifiable blood supply. HIFU has recently been used to interrupt blood flow in experimental animals[92]. The renal artery branches of rabbits (diameter about 0.6 mm) were occluded by HIFU. Complete cessation of blood flow was observed by color Doppler imaging and MRI, and lack of perfusion was also observed in the renal cortex in the contrast-enhanced image. Postmortem histological evaluation showed an infracted tissue volume corresponding to the wedge shape seen in the ultrasound and MRI images. No damage to the surrounding soft tissue was noted[103]. These results demonstrated that HIFU can be used to induce arterial occlusion, thus producing infarction and necrosis of the perfusion tissue. HIFU may offer a non-invasive, non-surgical technique that effectively obliterates blood flow. However, before clinical applications can be considered, additional studies are needed to obtain data concerning the relationship between the intensity of HIFU required for flow occlusion, blood vessel diameter, and flow velocity, and to investigate possible long-term adverse effects. Blood vessel occlusion may be useful in cancer therapy, where interruption of flow to a tumor may lead to its shrinkage.

Histotripsy

A new technique, "histotripsy", has also been developed to achieve mechanical fractionation of tissue structure using a number of short, high intensity US pulses (20 μs duration, 1 kHz pulse repetition rate, 18 MPa rarefactional pressure)[104]. The transducer has similar geometry and acoustic intensity as the HIFU type, but its center frequency is around 750 kHz. At a fluid-tissue interface, histotripsy results in localized tissue removal with sharp boundaries, which is used to remove cardiac tissue in the treatment of congenital heart disease[105]. In bulk tissue, histotripsy produces mechanical fragmentation of tissue resulting in a liquefied core with very sharply demarcated boundaries. Histology demonstrates treated tissue within the lesion is fragmented to a subcellular level surrounded by an almost imperceptibly narrow margin of cellular injury. As shown in Figure 9B, at the lesion boundary, half of the cell is cut off, and the other half is still intact. The mechanism of histotripsy is acoustic cavitation and energetic microbubble activities fragment and subdivide tissue resulting in cellular destruction[106]. Histotripsy has vast clinical applications where precise tissue ablation and removal are needed (e.g. tumor treatment). Compared to non-invasive thermal therapy, histotripsy has some important advantages: (1) microbubbles produced at the US focus, shown as bright spots on US imaging; (2) energetic microbubble activities can be seen on imaging and provide real-time feedback; (3) the lesions appear darker on US imaging post-treatment; and (4) the lesions can be produced in a very controlled and precise manner. It suggests that in the near future, imaging guided histotripsy can be a potential non-invasive surgery tool. Current clinical targets are: kidney, breast cancer, prostate cancer, several cardiac applications (perforation of the arterial septum for congenital heart disease), BPH, and breast fibroadenoma[107,108].

CONCLUSION

The drive in modern medicine is towards the development of treatments and techniques that minimize intervention to the patient and length of hospital stay. Thermal ablation therapies provide a minimally invasive approach to cancer therapy that is gaining rapid clinical acceptance. Of the available ablative techniques, HIFU is the least invasive and, in many ways, the most attractive. HIFU is being increasingly used for limited applications in Asia and Europe; however, these studies have all been preliminary, and clinical trial results to date have demonstrated HIFU to be safe and clinically effective. Further studies will be necessary before the widespread use of HIFU can be rec-

ommended. Long-term medical benefit and perhaps the beneficial economic impact of this therapy for oncology are of clinical and social importance and will be an area of continuing interest. However, HIFU is still in its infancy, and there remain outstanding technical and treatment delivery questions to be addressed. With improving imaging, advances in transducer technology and energy delivery techniques, and better understanding of HIFU-induced bioeffects, it is probable that the versatility of HIFU will increase and its range of applicability will expand.

REFERENCES

1 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225-249
2 **The Freedonia Group**. Cancer therapies to 2009 - Market research, market share, market size, sales, demand forecast, market leaders, company profiles, industry trends, 2009
3 **ter Haar G**, Rivens I, Chen L, Riddler S. High intensity focused ultrasound for the treatment of rat tumours. *Phys Med Biol* 1991; **36**: 1495-1501
4 **Gelet A**, Chapelon JY, Bouvier R, Rouvière O, Lasne Y, Lyonnet D, Dubernard JM. Transrectal high-intensity focused ultrasound: minimally invasive therapy of localized prostate cancer. *J Endourol* 2000; **14**: 519-528
5 **Visioli AG**, Rivens IH, ter Haar GR, Horwich A, Huddart RA, Moskovic E, Padhani A, Glees J. Preliminary results of a phase I dose escalation clinical trial using focused ultrasound in the treatment of localised tumours. *Eur J Ultrasound* 1999; **9**: 11-18
6 **Dubinsky TJ**, Cuevas C, Dighe MK, Kolokythas O, Hwang JH. High-intensity focused ultrasound: current potential and oncologic applications. *AJR Am J Roentgenol* 2008; **190**: 191-199
7 **ter Haar G**. Acoustic surgery. *Phsics Today* 2001; **54**: 29-34
8 **Lynn JG**, Zwemer RL, Chick AJ, Miller AE. A new method for the generation and use of focused ultrasound in experimental biology. *J Gen Physiol* 1942; **26**: 179-193
9 **Fry WJ**, Barnard JW, Fry EJ, Krumins RF, Brennan JF. Ultrasonic lesions in the mammalian central nervous system. *Science* 1955; **122**: 517-518
10 **Lynn JG**, Putnam TJ. Histology of Cerebral Lesions Produced by Focused Ultrasound. *Am J Pathol* 1944; **20**: 637-649
11 **Hynynen K**, Lulu BA. Hyperthermia in cancer treatment. *Invest Radiol* 1990; **25**: 824-834
12 **Dewey WC**. Arrhenius relationships from the molecule and cell to the clinic. *Int J Hyperthermia* 1994; **10**: 457-483
13 **Diederich CJ**. Thermal ablation and high-temperature thermal therapy: overview of technology and clinical implementation. *Int J Hyperthermia* 2005; **21**: 745-753
14 **Mason TJ**. A sound investment. *Chem Ind* 1998; **21**: 878-882
15 **Pitt WG**, Husseini GA, Staples BJ. Ultrasonic drug delivery--a general review. *Expert Opin Drug Deliv* 2004; **1**: 37-56
16 **Lagneaux L**, de Meulenaer EC, Delforge A, Dejeneffe M, Massy M, Moerman C, Hannecart B, Canivet Y, Lepeltier MF, Bron D. Ultrasonic low-energy treatment: a novel approach to induce apoptosis in human leukemic cells. *Exp Hematol* 2002; **30**: 1293-1301
17 **Haar GT**, Coussios C. High intensity focused ultrasound: physical principles and devices. *Int J Hyperthermia* 2007; **23**: 89-104
18 **Chung AH**, Hynynen K, Colucci V, Oshio K, Cline HE, Jolesz FA. Optimization of spoiled gradient-echo phase imaging for in vivo localization of a focused ultrasound beam. *Magn Reson Med* 1996; **36**: 745-752
19 **Hynynen K**, Freund WR, Cline HE, Chung AH, Watkins RD, Vetro JP, Jolesz FA. A clinical, noninvasive, MR imaging-monitored ultrasound surgery method. *Radiographics* 1996; **16**: 185-195
20 **Cernicanu A**, Lepetit-Coiffe M, Roland J, Becker CD, Terraz S. Validation of fast MR thermometry at 1.5 T with gradient-echo echo planar imaging sequences: phantom and clinical feasibility studies. *NMR Biomed* 2008; **21**: 849-858
21 **Mylonas N**, Ioannides K, Hadjisavvas V, Iosif D, Kyriacou PA, Damianou C. Evaluation of fast spin echo MRI sequence for an MRI guided high intensity focused ultrasound system for in vivo rabbit liver ablation. *J Biol Sci Eng* 2010; **3**: 241-246
22 **Yagel S**. High-intensity focused ultrasound: a revolution in non-invasive ultrasound treatment? *Ultrasound Obstet Gynecol* 2004; **23**: 216-217
23 **Khokhlova TD**, Canney MS, Lee D, Marro KI, Crum LA, Khokhlova VA, Bailey MR. Magnetic resonance imaging of boiling induced by high intensity focused ultrasound. *J Acoust Soc Am* 2009; **125**: 2420-2431
24 **Jolesz FA**, McDannold N. Current status and future potential of MRI-guided focused ultrasound surgery. *J Magn Reson Imaging* 2008; **27**: 391-399
25 **Xu RX**, Povoski SP, Martin EW Jr. Targeted delivery of microbubbles and nanobubbles for image-guided thermal ablation therapy of tumors. *Expert Rev Med Devices* 2010; **7**: 303-306
26 **Makin IR**, Mast TD, Faidi W, Runk MM, Barthe PG, Slayton MH. Miniaturized ultrasound arrays for interstitial ablation and imaging. *Ultrasound Med Biol* 2005; **31**: 1539-1550
27 **Maruvada S**, Harris GR, Herman BA, King RL. Acoustic power calibration of high-intensity focused ultrasound transducers using a radiation force technique. *J Acoust Soc Am* 2007; **121**: 1434-1439
28 **Hill CR**, Rivens I, Vaughan MG, ter Haar GR. Lesion development in focused ultrasound surgery: a general model. *Ultrasound Med Biol* 1994; **20**: 259-269
29 **Zhou Y**, Zhai L, Simmons R, Zhong P. Measurement of high intensity focused ultrasound fields by a fiber optic probe hydrophone. *J Acoust Soc Am* 2006; **120**: 676-685
30 **Hill CR**. Optimum acoustic frequency for focused ultrasound surgery. *Ultrasound Med Biol* 1994; **20**: 271-277
31 **Gelet A**, Chapelon JY, Margonari J, Theillère Y, Gorry F, Souchon R, Bouvier R. High-intensity focused ultrasound experimentation on human benign prostatic hypertrophy. *Eur Urol* 1993; **23** Suppl 1: 44-47
32 **Sullivan LD**, McLoughlin MG, Goldenberg LG, Gleave ME, Marich KW. Early experience with high-intensity focused ultrasound for the treatment of begin prostatic hypertrophy. *British J Urol* 1997; **79**: 172-176
33 **Madersbacher S**, Schatzl G, Djavan B, Stulnig T, Marberger M. Long-term outcome of transrectal high- intensity focused ultrasound therapy for benign prostatic hyperplasia. *Eur Urol* 2000; **37**: 687-694
34 **Uchida T**, Muramoto M, Kyunou H, Iwamura M, Egawa S, Koshiba K. Clinical outcome of high-intensity focused ultrasound for treating benign prostatic hyperplasia: preliminary report. *Urology* 1998; **52**: 66-71
35 **Madersbacher S**, Pedevilla M, Vingers L, Susani M, Marberger M. Effect of high-intensity focused ultrasound on human prostate cancer in vivo. *Cancer Res* 1995; **55**: 3346-3351
36 **Chaussy C**, Thüroff S. The status of high-intensity focused ultrasound in the treatment of localized prostate cancer and the impact of a combined resection. *Curr Urol Rep* 2003; **4**: 248-252
37 **Gelet A**, Chapelon JY, Bouvier R, Souchon R, Pangaud C, Abdelrahim AF, Cathignol D, Dubernard JM. Treatment of prostate cancer with transrectal focused ultrasound: early clinical experience. *Eur Urol* 1996; **29**: 174-183
38 **Beerlage HP**, Thüroff S, Debruyne FM, Chaussy C, de la Rosette JJ. Transrectal high-intensity focused ultrasound using the Ablatherm device in the treatment of localized prostate carcinoma. *Urology* 1999; **54**: 273-277
39 **Thüroff S**, Chaussy C, Vallancien G, Wieland W, Kiel HJ, Le Duc A, Desgrandchamps F, De La Rosette JJ, Gelet A. High-intensity focused ultrasound and localized prostate cancer:

efficacy results from the European multicentric study. *J Endourol* 2003; **17**: 673-677
40 **Chaussy C**, Thüroff S. High-intensity focused ultrasound in prostate cancer: results after 3 years. *Mol Urol* 2000; **4**: 179-182
41 **Uchida T**, Ohkusa H, Yamashita H, Shoji S, Nagata Y, Hyodo T, Satoh T. Five years experience of transrectal high-intensity focused ultrasound using the Sonablate device in the treatment of localized prostate cancer. *Int J Urol* 2006; **13**: 228-233
42 **Blana A**, Rogenhofer S, Ganzer R, Wild PJ, Wieland WF, Walter B. Morbidity associated with repeated transrectal high-intensity focused ultrasound treatment of localized prostate cancer. *World J Urol* 2006; **24**: 585-590
43 **Blana A**, Walter B, Rogenhofer S, Wieland WF. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. *Urology* 2004; **63**: 297-300
44 **Chaussy C**, Thüroff S, Rebillard X, Gelet A. Technology insight: High-intensity focused ultrasound for urologic cancers. *Nat Clin Pract Urol* 2005; **2**: 191-198
45 **Vallancien G**, Prapotnich D, Cathelineau X, Baumert H, Rozet F. Transrectal focused ultrasound combined with transurethral resection of the prostate for the treatment of localized prostate cancer: feasibility study. *J Urol* 2004; **171**: 2265-2267
46 **Lee HM**, Hong JH, Choi HY. High-intensity focused ultrasound therapy for clinically localized prostate cancer. *Prostate Cancer Prostatic Dis* 2006; **9**: 439-443
47 **Rebillard X**, Gelet A, Davin JL, Soulie M, Prapotnich D, Cathelineau X, Rozet F, Vallancien G. Transrectal high-intensity focused ultrasound in the treatment of localized prostate cancer. *J Endourol* 2005; **19**: 693-701
48 **Vallancien G**, Prapotnich D, Cathelineau X, Baumert H, Rozet F. Transrectal focused ultrasound combined with transurethral resection of the prostate for the treatment of localized prostate cancer: feasibility study. *J Urol* 2004; **171**: 2265-2267
49 **Furusawa H**, Namba K, Nakahara H, Tanaka C, Yasuda Y, Hirabara E, Imahariyama M, Komaki K. The evolving non-surgical ablation of breast cancer: MR guided focused ultrasound (MRgFUS). *Breast Cancer* 2007; **14**: 55-58
50 **Wu F**, Wang ZB, Zhu H, Chen WZ, Zou JZ, Bai J, Li KQ, Jin CB, Xie FL, Su HB. Extracorporeal high intensity focused ultrasound treatment for patients with breast cancer. *Breast Cancer Res Treat* 2005; **92**: 51-60
51 **Stewart EA**. Uterine fibroids. *Lancet* 2001; **357**: 293-298
52 **LeBlang SD**, Hoctor K, Steinberg FL. Leiomyoma shrinkage after MRI-guided focused ultrasound treatment: report of 80 patients. *AJR Am J Roentgenol* 2010; **194**: 274-280
53 **Fennessy FM**, Tempany CM. A review of magnetic resonance imaging-guided focused ultrasound surgery of uterine fibroids. *Top Magn Reson Imaging* 2006; **17**: 173-179
54 **Funaki K**, Fukunishi H, Sawada K. Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up. *Ultrasound Obstet Gynecol* 2009; **34**: 584-589
55 **Spies JB**, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet Gynecol* 2002; **99**: 290-300
56 **Stewart EA**, Rabinovici J, Tempany CM, Inbar Y, Regan L, Gostout B, Hesley G, Kim HS, Hengst S, Gedroyc WM. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. *Fertil Steril* 2006; **85**: 22-29
57 **Smart OC**, Hindley JT, Regan L, Gedroyc WM. Magnetic resonance guided focused ultrasound surgery of uterine fibroids--the tissue effects of GnRH agonist pre-treatment. *Eur J Radiol* 2006; **59**: 163-167
58 **Linke CA**, Carstensen EL, Frizzell LA, Elbadawi A, Fridd CW. Localized tissue destruction by high-intensity focused ultrasound. *Arch Surg* 1973; **107**: 887-891
59 **Frizzell LA**. Threshold dosages for damage to mammalian liver by high intensity focused ultrasound. *IEEE Trans Ultrason Ferroelectr Freq Control* 1988; **35**: 578-581
60 **Vallancien G**, Harouni M, Veillon B, Mombet A, Prapotnich D, Brisset JM, Bougaran J. Focused extracorporeal pyrotherapy: feasibility study in man. *J Endourol* 1992; **6**: 173-181
61 **Wu F**, Wang ZB, Chen WZ, Zou JZ, Bai J, Zhu H, Li KQ, Jin CB, Xie FL, Su HB. Advanced hepatocellular carcinoma: treatment with high-intensity focused ultrasound ablation combined with transcatheter arterial embolization. *Radiology* 2005; **235**: 659-667
62 **Chapelon JY**, Prat F, Sibille A, About El Fadil F, Henry L, Theilliere Y, Cathignol D. Extracorporeal selective focused destruction of hepatic tumours by high intensity ultrasound in rabbits bearing VX-2 carcinoma. *Min Inv Ther* 1992; **1**: 287-293
63 **Wu F**, Chen W, Bai J. Effect of high-intensity focused ultrasound on patients with hepatocellular cancer: preliminary report [in Chinese]. *Chin J Ultrasonog* 1999; **8**: 213-216
64 **Wu F**, Wang Z, Chen W, Zou JZ, Bai J, Zhu H, Li KQ, Xie FL, Jin CB, Su HB, Gao GW. Extracorporeal high-intensity focused ultrasound for treatment of solid carcinomas: four-year Chinese clinical experience. 2nd International Symposium on Therapeutic Ultrasound, Seattle, University of Washington, 2003
65 **Li CX**, Xu GL, Jiang ZY, Li JJ, Luo GY, Shan HB, Zhang R, Li Y. Analysis of clinical effect of high-intensity focused ultrasound on liver cancer. *World J Gastroenterol* 2004; **10**: 2201-2204
66 **Wu F**, Wang ZB, Zhu H, Chen WZ, Zou JZ, Bai J, Li KQ, Jin CB, Xie FL, Su HB. Feasibility of US-guided high-intensity focused ultrasound treatment in patients with advanced pancreatic cancer: initial experience. *Radiology* 2005; **236**: 1034-1040
67 **Yang R**, Reilly CR, Rescorla FJ, Faught PR, Sanghvi NT, Fry FJ, Franklin TD Jr, Lumeng L, Grosfeld JL. High-intensity focused ultrasound in the treatment of experimental liver cancer. *Arch Surg* 1991; **126**: 1002-1009; discussion 1009-1010
68 **Reddan DN**, Raj GV, Polascik TJ. Management of small renal tumors: an overview. *Am J Med* 2001; **110**: 558-562
69 **Vallancien G**, Chartier-Kastler E, Harouni M, Chopin D, Bougaran J. Focused extracorporeal pyrotherapy: experimental study and feasibility in man. *Semin Urol* 1993; **11**: 7-9
70 **Wu F**, Wang ZB, Chen WZ, Bai J, Zhu H, Qiao TY. Preliminary experience using high intensity focused ultrasound for the treatment of patients with advanced stage renal malignancy. *J Urol* 2003; **170**: 2237-2240
71 **Parkin DM**, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. *Int J Cancer* 1993; **54**: 594-606
72 **He SX**, Wang GM, Niu SG, Yao B, Wang XJ. The noninvasive treatment of 251 cases of advanced pancreatic cancer with focused ultrasound surgery. 2nd International Symposium on Therapeutic Ultrasound, Seattle, 2002
73 **Wu F**, Wang ZB, Zhu H, Chen WZ, Zou JZ, Bai J, Li KQ, Jin CB, Xie FL, Su HB. Feasibility of US-guided high-intensity focused ultrasound treatment in patients with advanced pancreatic cancer: initial experience. *Radiology* 2005; **236**: 1034-1040
74 **Smith NB**, Temkin JM, Shapiro F, Hynynen K. Thermal effects of focused ultrasound energy on bone tissue. *Ultrasound Med Biol* 2001; **27**: 1427-1433
75 **Gómez J**, Pinar A, Vallcanera A, Moreno A, Cortina H. Sonographic findings in aneurysmal bone cyst in children: correlation with computed tomography findings. *J Clin Ultrasound* 1998; **26**: 59-64
76 **Wu F**, Chen WZ, Bai J, Zou JZ, Wang ZL, Zhu H, Wang ZB. Pathological changes in human malignant carcinoma treated with high-intensity focused ultrasound. *Ultrasound Med Biol* 2001; **27**: 1099-1106
77 **Lu BY**, Yang RS, Lin WL, Cheng KS, Wang CY, Kuo TS.

Theoretical study of convergent ultrasound hyperthermia for treating bone tumors. *Med Eng Phys* 2000; **22**: 253-263
78 **Chen W**, Zhou K. High-intensity focused ultrasound ablation: a new strategy to manage primary bone tumors. *Curr Opin Orthop* 2005; **16**: 494-500
79 **Chen W**, Wang Z, Wu F, Bai J, Zhu H, Zou J, Li K, Xie F, Wang Z. [High intensity focused ultrasound alone for malignant solid tumors] *Zhonghua Zhongliu Zazhi* 2002; **24**: 278-281
80 **Chen W**, Wang Z, Wu F, Zhu H, Zou J, Bai J, Li K, Xie F. [High intensity focused ultrasound in the treatment of primary malignant bone tumor] *Zhonghua Zhongliu Zazhi* 2002; **24**: 612-615
81 **Liberman B**, Gianfelice D, Inbar Y, Beck A, Rabin T, Shabshin N, Chander G, Hengst S, Pfeffer R, Chechick A, Hanannel A, Dogadkin O, Catane R. Pain palliation in patients with bone metastases using MR-guided focused ultrasound surgery: a multicenter study. *Ann Surg Oncol* 2009; **16**: 140-146
82 **Kennedy JE**. High-intensity focused ultrasound in the treatment of solid tumours. *Nat Rev Cancer* 2005; **5**: 321-327
83 **Wu CC**, Chen WS, Ho MC, Huang KW, Chen CN, Yen JY, Lee PH. Minimizing abdominal wall damage during high-intensity focused ultrasound ablation by inducing artificial ascites. *J Acoust Soc Am* 2008; **124**: 674-679
84 **Thomas JL**, Fink MA. Ultrasonic beam focusing through tissue inhomogeneities with a time reversal mirror: application to transskull therapy. *IEEE Trans Ultrason Ferroelectr Freq Control* 1996; **43**: 1122-1129
85 **Marquet F**, Pernot M, Aubry JF, Montaldo G, Marsac L, Tanter M, Fink M. Non-invasive transcranial ultrasound therapy based on a 3D CT scan: protocol validation and in vitro results. *Phys Med Biol* 2009; **54**: 2597-2613
86 **Qian ZW**, Xiong L, Yu J, Shao D, Zhu H, Wu X. Noninvasive thermometer for HIFU and its scaling. *Ultrasonics* 2006; **44** Suppl 1: e31-e35
87 **Annand A**, Kaczkowski PJ. Monitoring formation of high intensity focused ultrasound (HIFU) induced lesions using backscattered ultrasound. *Acoustical Research Letters Online* 2004; **5**: 88-94
88 **Fry FJ**, Johnson LK. Tumor irradiation with intense ultrasound. *Ultrasound Med Biol* 1978; **4**: 337-341
89 **Hu Z**, Yang XY, Liu Y, Sankin GN, Pua EC, Morse MA, Lyerly HK, Clay TM, Zhong P. Investigation of HIFU-induced anti-tumor immunity in a murine tumor model. *J Transl Med* 2007; **5**: 34
90 **Wu F**, Wang ZB, Lu P, Xu ZL, Chen WZ, Zhu H, Jin CB. Activated anti-tumor immunity in cancer patients after high intensity focused ultrasound ablation. *Ultrasound Med Biol* 2004; **30**: 1217-1222
91 **Gillams AR**. Liver ablation therapy. *Br J Radiol* 2004; **77**: 713-723
92 **Si HP**, Xiang LK, Wang Z, Li YY, Wang ZB. Immune changes in bone neoplasm rabbits transplanted with VX2 before and after high intensity focused ultrasound therapy. *Chin J Exp Surg* 2003; **20**: 823-824
93 **Kinoshita M**. Targeted drug delivery to the brain using focused ultrasound. *Top Magn Reson Imaging* 2006; **17**: 209-215
94 **Patrick JT**, Nolting MN, Goss SA, Dines KA, Clendenon JL, Rea MA, Heimburger RF. Ultrasound and the blood-brain barrier. *Adv Exp Med Biol* 1990; **267**: 369-381
95 **Hynynen K**, McDannold N, Vykhodtseva N, Jolesz FA. Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. *Radiology* 2001; **220**: 640-646
96 **Hynynen K**, McDannold N, Sheikov NA, Jolesz FA, Vykhodtseva N. Local and reversible blood-brain barrier disruption by noninvasive focused ultrasound at frequencies suitable for trans-skull sonications. *Neuroimage* 2005; **24**: 12-20
97 **McDannold N**, Vykhodtseva N, Raymond S, Jolesz FA, Hynynen K. MRI-guided targeted blood-brain barrier disruption with focused ultrasound: histological findings in rabbits. *Ultrasound Med Biol* 2005; **31**: 1527-1537
98 **McDannold N**, Vykhodtseva N, Hynynen K. Targeted disruption of the blood-brain barrier with focused ultrasound: association with cavitation activity. *Phys Med Biol* 2006; **51**: 793-807
99 **Larkin JO**, Casey GD, Tangney M, Cashman J, Collins CG, Soden DM, O'Sullivan GC. Effective tumor treatment using optimized ultrasound-mediated delivery of bleomycin. *Ultrasound Med Biol* 2008; **34**: 406-413
100 **Yu T**, Wang Z, Jiang S. Potentiation of cytotoxicity of adriamycin on human ovarian carcinoma cell line 3AO by low-level ultrasound. *Ultrasonics* 2001; **39**: 307-309
101 **Yuh EL**, Shulman SG, Mehta SA, Xie J, Chen L, Frenkel V, Bednarski MD, Li KC. Delivery of systemic chemotherapeutic agent to tumors by using focused ultrasound: study in a murine model. *Radiology* 2005; **234**: 431-437
102 **Bekeredjian R**, Kroll RD, Fein E, Tinkov S, Coester C, Winter G, Katus HA, Kulaksiz H. Ultrasound targeted microbubble destruction increases capillary permeability in hepatomas. *Ultrasound Med Biol* 2007; **33**: 1592-1598
103 **Delon-Martin C**, Vogt C, Chignier E, Guers C, Chapelon JY, Cathignol D. Venous thrombosis generation by means of high-intensity focused ultrasound. *Ultrasound Med Biol* 1995; **21**: 113-119
104 **Parsons JE**, Cain CA, Abrams GD, Fowlkes JB. Pulsed cavitational ultrasound therapy for controlled tissue homogenization. *Ultrasound Med Biol* 2006; **32**: 115-129
105 **Xu Z**, Fowlkes JB, Rothman ED, Levin AM, Cain CA. Controlled ultrasound tissue erosion: the role of dynamic interaction between insonation and microbubble activity. *J Acoust Soc Am* 2005; **117**: 424-435
106 **Xu Z**, Hall TL, Fowlkes JB, Cain CA. Optical and acoustic monitoring of bubble cloud dynamics at a tissue-fluid interface in ultrasound tissue erosion. *J Acoust Soc Am* 2007; **121**: 2421-2430
107 **Roberts WW**, Hall TL, Ives K, Wolf JS Jr, Fowlkes JB, Cain CA. Pulsed cavitational ultrasound: a noninvasive technology for controlled tissue ablation (histotripsy) in the rabbit kidney. *J Urol* 2006; **175**: 734-738
108 **Xu Z**, Fowlkes JB, Cain CA. A new strategy to enhance cavitational tissue erosion using a high-intensity, Initiating sequence. *IEEE Trans Ultrason Ferroelectr Freq Control* 2006; **53**: 1412-1424

S- Editor Cheng JX **L- Editor** Lutze M **E- Editor** Ma WH