HIFU for palliative treatment of pancreatic cancer

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ABSTRACT High intensity focused ultrasound (HIFU) is a novel non-invasive modality for ablation of various solid tumors including uterine fibroids, prostate cancer, hepatic, renal, breast and pancreatic tumors. HIFU therapy utilizes mechanical energy in the form of a powerful ultrasound wave that is focused inside the body to induce thermal and/or mechanical effects in tissue. Multiple preclinical and non-randomized clinical trials have been performed to evaluate the safety and efficacy of HIFU for palliative treatment of pancreatic tumors. Substantial tumor-related pain reduction was achieved in most cases after HIFU treatment, and no significant side-effects were observed. This review provides a description of different physical mechanisms underlying HIFU therapy, summarizes the clinical experience obtained to date in HIFU treatment of pancreatic tumors, and discusses the challenges, limitations and new approaches in this modality.

KEY WORDS therapeutic ultrasound; focused ultrasound; HIFU; pancreas cancer; review

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Introduction

Within the last year more than 42,000 people in the United States were newly diagnosed with pancreatic cancer, which makes it the fourth leading cause of cancer mortality (1). A majority of patients diagnosed with pancreatic cancer are considered inoperable at the time of the diagnosis due to locally advanced disease or the presence of metastasis, and the efficacy of systemic chemotherapy is limited (2). The prognosis for these patients is one of the worst among all cancers: according to EUROCARE study, based on over 30,000 cases, overall survival at 1,3 and 5 years was 16%, 5% and 4%, respectively (3). Pain is often reported by patients with advanced disease, and palliative treatment methods are commonly employed and include opioid therapy and celiac plexus neurolysis (4). However, opioids may produce a range of side-effects from dysphoria to respiratory depression, and celiac plexus neurolysis provides limited benefit in pain relief, in addition to being an invasive procedure (5,6).

No potential conflict of interest.

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High intensity focused ultrasound (HIFU) therapy is a non-invasive ablation method, in which ultrasound energy from an extracorporeal source is focused within the body to induce thermal denaturation of tissue at the focus without affecting surrounding organs (Figure 1). HIFU ablation has been applied to treatment of a wide variety of both benign and malignant tumors including uterine fibroids, prostate cancer, liver tumors and other solid tumors that are accessible to ultrasound energy (7-10). Preliminary studies have shown that HIFU may also be a useful modality for palliation of cancer-related pain in patients with advanced pancreatic cancer (11-14). The objective of this article is to provide an overview of the physical principles of HIFU therapy and to review the current status of clinical application of HIFU for pancreatic cancers.

Physical mechanisms underlying HIFU therapy

Ultrasound is a form of mechanical energy in which waves propagate through a liquid or solid medium (e.g., tissue) with alternate areas of compression and rarefaction. The main parameters that are used to describe an ultrasound wave are its frequency, or the number of pressure oscillations per second, and pressure amplitude, as illustrated in Figure 2C. Another important characteristic of an ultrasound wave is its intensity, or the amount of ultrasound energy per unit surface, which is proportional to the square of the wave amplitude.

Both HIFU devices and diagnostic ultrasound imagers

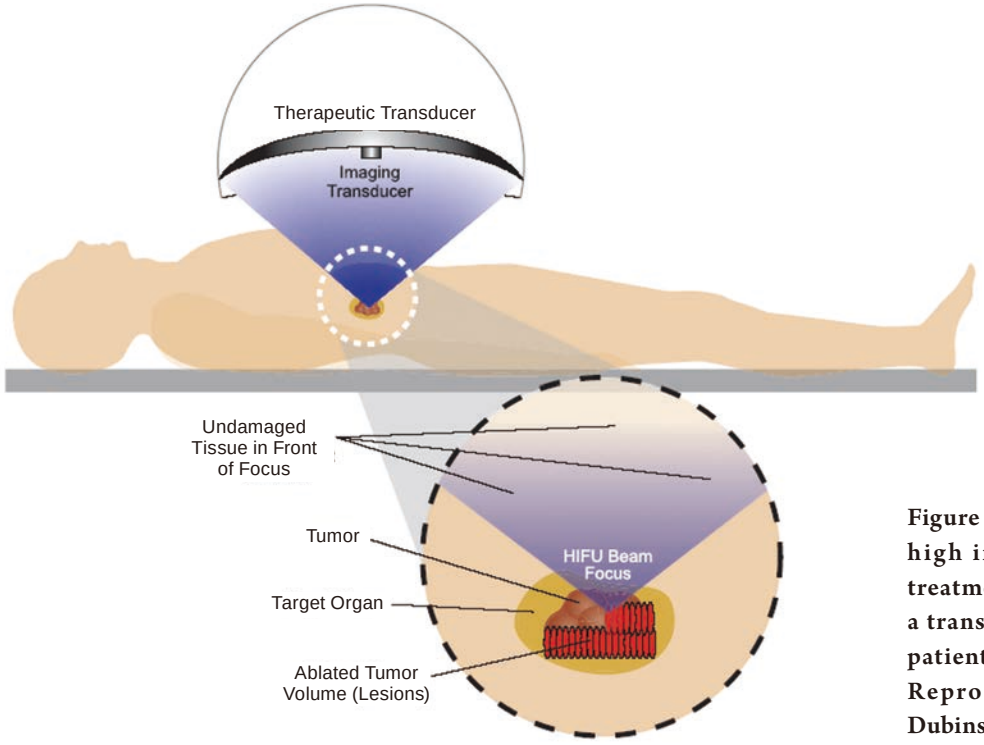

Figure 1 Illustration of extracorporeal high intensity focused ultrasound treatment of a pancreatic tumor using a transducer that is located above the patient that is in the supine position. Reproduced with permission from Dubinsky et al. (10).

utilize ultrasound waves with frequencies typically ranging from 0.2–10 megahertz (MHz), but the difference is in the amplitude and in how the ultrasound waves are transmitted. Diagnostic ultrasound probes transmit plane or divergent waves that get reflected or scattered by tissue inhomogeneities and are then detected by the same probe. In HIFU the radiating surface is usually spherically curved, so that the ultrasound wave is focused at the center of curvature in a similar fashion to the way a magnifying lens can focus a broad light beam into a small focal spot (Figure 2A). This can result in amplification of the pressure amplitude by a factor of 100 at the focus. Another method of focusing is using ultrasound arrays, as illustrated in Figure 2B: each element of the array radiates a wave with a pre-determined phase, so that waves from all elements interfere constructively only at a desired focal point. The size and shape of the focal region of most clinically available transducers is similar to a grain of rice: 2-3 mm in diameter and 8-10 mm in length.

As mentioned above, diagnostic ultrasound and HIFU waves differ in amplitude. Typical diagnostic ultrasound transducers operate at the pressures of 0.001 – 0.003 MPa which corresponds to time-averaged intensity of 0.1-100 mW/cm^2. HIFU transducers produce much larger pressure amplitudes at the focus of the transducer: up to 60 MPa peak compressional pressures and up to 15 MPa peak rarefactional pressures, which corresponds to intensities of up to 20000 W/cm^2. For comparison, one atmosphere is equal to 0.1 MPa. Ultrasound of such intensities is capable of producing both thermal and mechanical effects on tissue, which will be discussed below.

Tissue heating

The fundamental physical mechanism of HIFU, ultrasound absorption and conversion into heat, was first described in 1972 (15). Absorption of ultrasound, the mechanical form of energy, in tissue is not as intuitive as absorption of electromagnetic radiation (e.g., light or RF radiation) and can be simplistically explained as follows. Tissue can be represented as viscous fluid contained by membranes. When a pressure wave propagates through the tissue, it produces relative displacement of tissue layers and causes directional motion or microstreaming of the fluid. Viscous friction of different layers of fluid then leads to heating (16).

Both diagnostic ultrasound and HIFU heat tissue, however, since the heating rate is proportional to the ultrasound intensity, the thermal effect produced by diagnostic ultrasound is negligible. In HIFU the majority of heat deposition occurs at the focal area, where the intensity is the highest. The focal temperature can be rapidly increased causing cell death at the focal region. A threshold for thermal necrosis, the denaturing of tissue protein, is calculated according to the thermal dose (*TD*) formulation:

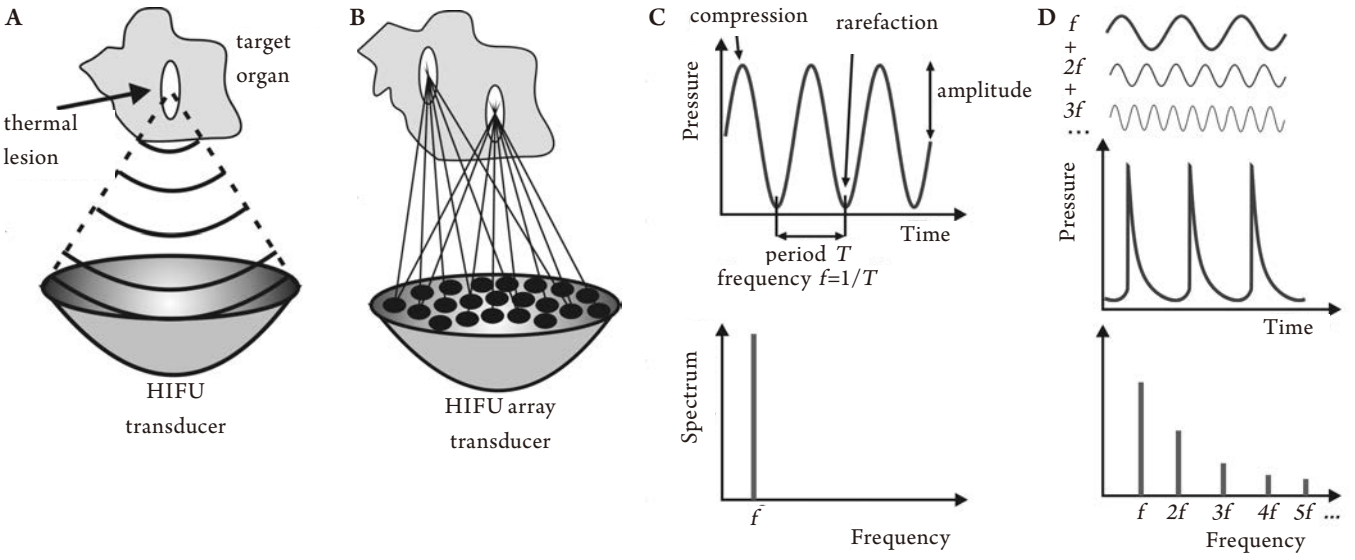

Figure 2 (A) A single-element HIFU transducer has a spherically curved surface to focus ultrasound energy into a small focal region in which ablation takes place, leaving the surrounding tissue unaffected. (B) In a phased-array HIFU transducer the position of the focus can be steered electronically by shifting the phases of the ultrasound waves radiated by each element without moving the transducer. (C) An example of a linear (sine) ultrasound wave; its frequency spectrum contains a single frequency *f*. (D) A nonlinear ultrasound wave is formed by the energy transfer from the linear wave with the fundamental frequency *f* into the waves with higher frequencies (also known as harmonics): 2*f*, 3*f*, etc., and superimposition of these waves. Therefore, the frequency spectrum contains the fundamental frequency *f* as well as higher harmonics: 2*f*, 3*f*, etc.

$$TD(t) = \int_0^t R^{43-T(t')} dt' \qquad (1)$$

where t is treatment time, and R = 0.25 if $T(t)$ < 43 °C and 0.5 otherwise (17). The thermal dose required to create a thermal lesion is equivalent to the thermal dose of a 240-min exposure at 43°C, hence the common representation of thermal dose in "equivalent minutes". This definition originated from the hyperthermia protocol, when the tissue was heated to a temperature of 43–45°C during a long exposure of several hours. However, it has been shown that this model gives good estimations of the thermal lesion dose for the higher temperatures caused by HIFU. For example, thermal lesion forms in 10 s at 53°C and 0.1 s at 60°C. In HIFU treatments, the temperature commonly exceeds 70°C in about 1–4 s. Thus, tissue necrosis occurs almost immediately. Figure 3A shows an example of a lesion with coagulation necrosis after a single treatment with a 1 MHz HIFU device in *ex vivo* bovine liver.

It is worth mentioning here that ultrasound absorption in tissue increases nearly linearly with ultrasound frequency; hence, more heating occurs at higher frequencies. However, the focus becomes smaller with higher frequency (18), and penetration depth is also limited by the higher absorption. Therefore, HIFU frequency should be chosen appropriately for smaller and shallower targets or larger targets located deeper within the body.

In most applications that utilize the thermal effect of HIFU the goal is to induce cell necrosis in tissue from thermal injury. However, several studies have reported that HIFU can also induce cell apoptosis through hyperthermia, i.e. sub-lethal thermal injury (19). In apoptotic cells, the nucleus of the cell self-destructs, with rapid degradation of DNA by endonucleases. This effect may be desirable in some cases, but may also present a limitation for HIFU ablation accuracy. Since cell death due to apoptosis occurs at lower thermal dose than thermal necrosis, the tissue adjacent to the HIFU target might be at risk from this effect (20).

Acoustic cavitation

Acoustic cavitation can be defined as any observable activity involving a gas bubble(s) stimulated into motion by an exposure to an acoustic field. The motion occurs in response to the alternating compression and rarefaction of the surrounding liquid as the acoustic wave propagates through it. Although live tissue does not initially contain gas bubbles, tiny gas bodies dispersed in cells may serve as cavitation nuclei that grow into bubbles when subjected to sufficiently large rarefactional pressure that "tears" the tissue apart at the site of a nucleus. Thus, cavitation activity

in tissue may occur if the amplitude of the rarefactional pressure exceeds a certain threshold, which in turn depends on ultrasound frequency with lower frequencies having lower rarefactional pressure thresholds. Cavitation threshold has been measured in different tissues in a number of studies, but there is still no agreement (21-23,28). For example, cavitation threshold in blood is estimated to be 6.5 MPa (23) at 1.2 MHz.

Once formed, the bubble can interact with the incident ultrasound wave in two ways: stably or inertially. When the bubble is exposed to a low-amplitude ultrasound field, the oscillation of its size follows the pressure changes in the sound wave and the bubble remains spherical. Bubbles that have a resonant size with respect to the acoustic wavelength will be driven into oscillation much more efficiently than others; for ultrasound frequencies commonly used in HIFU the resonant bubble diameter range is 1-5 microns (24). Inertial cavitation is a more violent phenomenon, in which the bubble grows during the rarefaction phase and then rapidly collapses which leads to its destruction. The collapse is often accompanied by the loss of bubble sphericity and formation of high velocity liquid jets. If the bubble collapse occurs next to a cell, the jets may be powerful enough to cause disruption of the cell membrane (25,26).

In blood vessels, violently collapsing bubbles can damage the lining of the vessel wall or even disrupt the vessel altogether. One may assume that the disruption occurs due to bubble growth and corresponding distension of the vessel wall. However, it was shown that most damage occurs as the bubble rapidly collapses and the vessel wall is bent inward or invaginated, causing high amplitude shear stress (27).

Stable cavitation may lead to a phenomenon called "microstreaming" (rapid movement of fluid near the bubble due to its oscillating motion). Microstreaming can produce high shear forces close to the bubble that can disrupt cell membranes and may play a role in ultrasound-enhanced drug or gene delivery when damage to the cell membrane is transient (28).

Cavitation activity is the major mechanism that is utilized when mechanical damage to tissue is a goal. At its extreme, when very high rarefactional pressures (> 20 MPa) are used, a cloud of cavitating bubbles can cause complete tissue lysis at the focus (29). In such treatments the thermal effect is usually to be avoided, therefore, short bursts of very high amplitude ultrasound of low frequency (usually below 2 MHz) are used. The time-averaged intensity remains low, and the thermal dose delivered to the tissue is not sufficient to cause thermal damage. Cavitation can also promote heating if longer HIFU pulses or continuous ultrasound is used (30-32). The energy of the incident ultrasound wave is transferred very efficiently into stable oscillation of resonant-size bubbles. This oscillatory motion causes microstreaming around the bubbles and that, in turn, leads to additional tissue heating through viscous friction, which can lead to coagulative necrosis.

Nonlinear ultrasound propagation effects

Nonlinear effects of ultrasound propagation are observed at high acoustic intensities and manifest themselves as distortion of the pressure waveform: a sinusoidal wave initially generated by an ultrasound transducer becomes sawtooth-shaped as it propagates through water or tissue (Figure 2D). This distortion represents the conversion of energy contained in the fundamental frequency to higher harmonics that are more rapidly absorbed in tissue since ultrasound absorption coefficient increases with frequency. As a result, tissue is heated much faster than it would if nonlinear effects did not occur. Therefore, it is critical to account for nonlinear effects when estimating a thermal dose that a certain HIFU exposure would deliver. For most clinically relevant HIFU transducers, nonlinear effects start to be noticeable if the intensity exceeds 4000 W/cm^2, and at 9000 W/cm^2 it dominates over linear propagation (33).

Probably, the most important consequence of nonlinear propagation effects is that the boiling temperature of water, 100°C, can be achieved as rapidly as several milliseconds, which leads to the formation of a millimeter-sized boiling bubble at the focus of the transducer (34). This changes the course of treatment dramatically: the incident ultrasound wave is now reflected from the bubble and heat deposition pattern is distorted in unpredictable manner. The lesion shape becomes irregular, generally resembling a tadpole, as illustrated in Figure 3B. Moreover, the motion of the boiling bubble may cause tissue lysis that can be seen as a vaporized cavity in the middle of the thermal lesion. Sometimes this effect may be desirable and can be enhanced by using HIFU pulses powerful enough to induce boiling in several milliseconds, and with duration only slightly exceeding the time to reach boiling temperature (35). In that case the temperature rise is too rapid for protein denaturation to occur, but the interaction of the large boiling bubble with ultrasound field leads to complete tissue lysis, as illustrated in Figure 3C (36).

Radiation force and streaming

Radiation force is exerted on an object when a wave is either absorbed or reflected from that object. Complete reflection produces twice the force that complete absorption does. In both cases the force acts in direction of ultrasound propagation and is constant if the amplitude of a wave is steady. If the reflecting or absorbing medium is tissue or other solid material, the force presses against the medium,

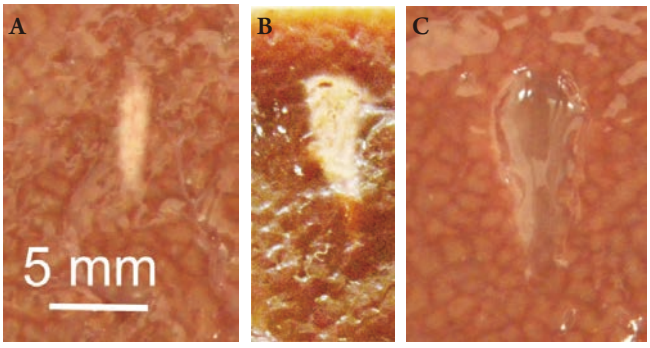

Figure 3 Examples of HIFU lesions produced in ex vivo bovine liver tissue with different sonication reigimes. (A) Absorption of linear ultrasound waves results in predictable cigar-shaped thermal lesion. (B) Irregularly-shaped thermal lesion with evaporated core results from boiling which is induced in tissue by rapid absorption of continuous nonlinear HIFU waves. (C) A lesion containing liquefied tissue may be produced by very short, high-amplitude nonlinear HIFU pulses.

producing a pressure termed "radiation pressure." For most clinically relevant devices and exposures this effect is not very pronounced: radiation pressure does not exceed a few pascals (14). However, if the medium is liquid (i.e., blood) and can move under pressure, then such pressure can induce streaming with speeds of up to 6 m/s (37). This effect has important implications in sonotrombolysis, in which a clot-dissolving agent is driven by streaming towards and inside the clot blocking a vessel (38).

Image guidance and monitoring of HIFU therapy

There are currently two imaging methods employed in commercially available HIFU devices: magnetic resonance imaging (MRI) and diagnostic ultrasound. The role of these methods in treatment is three-fold: visualization of the target, monitoring tissue changes during treatment and assesment of the treatment outcome. In terms of tumor visualization, both MRI and sonography can provide satisfactory images; MRI is sometimes superior in obese patients (39), but is more expensive and labor-intensive.

Unfortunately, to date none of the monitoring methods can provide the image of the thermal lesion directly and in real time as it forms in tissue. The biggest advantage of MRI is that, unlike ultrasound-based methods, it can provide tissue temperature maps overlying the MR image of the target almost in real time. The distribution of sufficient thermal dose is then calculated and assumed to correspond to thermally ablated tissue. The temporal resolution of MR thermometry is 1-4 seconds per image, and the spatial resolution is determined by the size of the image voxel which is typically about 2mm x 2mm x 6mm (40). Therefore, MR-guided HIFU is only suitable for treatments in which the heating occurs slowly, on the order of tens of seconds for a single lesion. Motion artifact due to breathing and heartbeat is also a concern in clinical setting. The only US FDA-approved HIFU device available for clinical therapy utilizes MR thermometry during treatment of uterine fibroids (39,41).

Ultrasound imaging used in current clinical devices does not have the capability of performing thermometry, but it provides real-time imaging using the same energy modality as HIFU. This is a significant benefit, because adequate ultrasound imaging of the target suggests that there is no obstruction (e.g., bowel gas or bone) to ultrasound energy reaching the target, and the risk of causing thermal injury to unintended tissue is minimized. One method that is sometimes used for confirmation of general targeting accuracy is the appearance of a hyperechoic region on the ultrasound image during treatment. This region has been shown to correspond to the formation of a large boiling bubble at the focus when tissue temperature reaches 100°C, and underestimates the actual size of the thermal lesion since thermal lesions develop at temperatures below 100°C (42).

Imaging methods to assess HIFU treatment are similar to those used to assess the response to other methods of ablation such as radiofrequency ablation and include contrast enhanced CT and MRI (43). In addition, the use of microbubble contrast-enhanced sonography is also being examined as a method to evaluate the treatment effect of HIFU (44). These methods all examine the change in vascularity of the treated volume.

HIFU of pancreatic tumors

Devices

Currently, HIFU treatment of pancreatic cancer is widely available in China, with limited availability in South Korea and Europe. There are two US-guided HIFU devices that are commercially available outside of China for treatment of pancreatic tumors, both manufactured in China: The FEP-BY™ HIFU tumor therapy device (Yuande Biomedical Engineering Limited Corporation, Beijing, China, Figure 4) and HAIFU (Chongqing Haifu Technology Co.,) (45). Both devices operate at similar ultrasound frequencies – 0.8 and 1 MHz respectively; both are capable of putting out total acoustic power of about 300 W (corresponding intensity up to 20 000W/cm^2). B-mode ultrasound is also used in both machines for targeting and image guidance. In addition, a patient with pancreatic tumor was recently treated in Italy

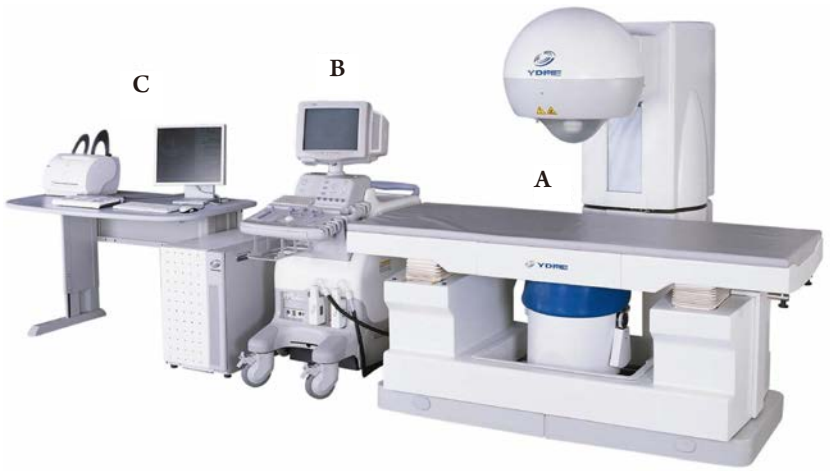

Figure 4 FEP-BY high intensity focused ultrasound device for tumor therapy. Components include a treatment table with upper and lower high intensity focused ultrasound transducers (A), B-mode ultrasound imaging system (B), and computer control system (C). In addition, there is an electrical power system and water treatment system (not pictured). Reproduced with permission (Yuande Biomedical Engineering Corp. Ltd., Beijing, China).

using the MR-guided ExAblate™ system (InSightec, Israel) for palliation of pain.

Animal studies

All the preclinical *in vivo* studies of HIFU ablation of the pancreas utilized the swine model because of its size and anatomy relevance to humans (46-48). The animals were not bearing tumors in the pancreas, therefore, it was not possible to evaluate survival benefits of HIFU therapy; however, the main goal of these studies was to systematically evaluate the safety and efficacy of HIFU ablation of the pancreas. In the earliest study the pancreata of 12 common swine were successfully treated *in vivo* using the FEP-BY02 device, without any significant adverse effects such as skin burns or evidence for pancreatitis during the 7-day post-treatment observation period (46). A subsequent study by another group utilizing the HAIFU device used both light microscopy and electron microscopy to confirm that complete necrosis is confined to the target regions with clear boundaries and no damage to adjacent tissues (47). Pancreatitis was an important safety concern because the mechanical effects of HIFU can cause cell lysis and release of pancreatic enzymes. Although the cavitation or boiling bubble activity during HIFU was confirmed by electron microscopic examination (intercellular space widening and numerous vacuoles of different sizes in the cytoplasm), pancreatitis was not observed thus confirming the safety of treatment protocol. Another preclinical study showed that a combined treatment of HIFU ablation followed by radiation therapy may be a promising method. The injury to the targeted pancreas was increased compared to either modality alone, without additional injury outside of the targeted region (48).

Clinical studies

As mentioned above, most patients diagnosed with pancreatic cancer are considered inoperable and systemic chemotherapy has only modest effect. Development of effective local therapies and strategies for pain relief are both important aspect of managing these patients. HIFU has been first used for the palliative treatment of pancreatic cancer in an open-label study in China in 251 patients with advanced pancreatic cancer (TNM stages II–IV) (49). HIFU therapy resulted in significant pain relief in 84% of the patients. In some cases significant reduction of tumor volume was achieved without any significant adverse effects or pancreatitis, which appears to have prolonged survival. Multiple nonrandomized studies that followed, mostly from China, provided additional evidence to show that HIFU does provide palliation of tumor-related pain and does not cause adverse effects (12-14, 50-56). The mechanism of pain relief in these patients is still unclear, but is hypothesized to result from thermal damage to the nerve fibers in the tumor. In two studies HIFU was used in combination with systemic chemotherapy (gemcitabine), and similar findings were reported in terms of pain relief and safety, even suggesting a survival benefit (14,51). Figure 5 shows representative CT images of a pancreatic tumor before and after HIFU therapy.

In a small study from Europe (55) 6 patients with pancreatic tumors in difficult locations were treated with HIFU, the difficult location being defined as a tumor adjacent to major blood vessels, gallbladder and bile ducts, bowel, or stomach. This study was performed under general anesthesia, after 3-days of bowel preparation to avoid the presence of bowel gas in the acoustic pathway. Symptoms were clearly palliated within 24 hours after treatment in all patients, and the amylase level showed no statistically significant elevation

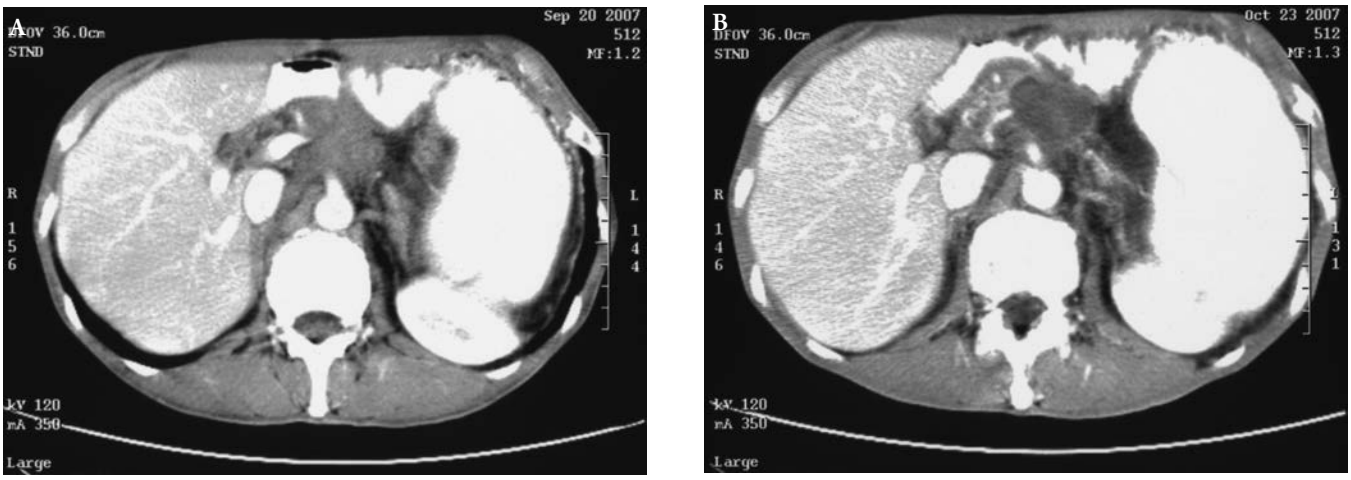

Figure 5 Contrast enhanced-CT scan of a 52-year-old male demonstrating a tumor in the body of the pancreas (A) prior to high intensity focused ultrasound therapy; (B) with evidence of ablation and necrosis following high intensity focused ultrasound therapy. Reproduced with permission from Xiong et al. 2009 (13).

Table 1 Clinical studies of HIFU for palliative therapy of pancreatic cancer (Adapted from Jang HJ et al. (11))

Author	Year	No. of patients	Treatment	Pain relief	Adverse effects
Xiong et.al.	2001	21	HIFU	15/17 (88%)	None
Wang et.al.	2002	13	HIFU	8/10 (80%)	Mild pancreatitis (2)
Xie et.al.	2003	41	HIFU alone vs. HIFU+gemcitabine	66.7% 76.6%	None
Xu et.al.	2003	37	HIFU	24/30 (80%)	None
Yuan et.al.	2003	40	HIFU	32/40 (80%)	None
Wu et.al.	2005	8	HIFU	8/8 (100%)	None
Xiong et.al.	2009	89	HIFU	54/67 (80.6%)	2nd degree skin burns (3) Subcutaneous sclerosis (6) Pancreatic pseudocyst (1)
Zhao et.al.	2010	39	HIFU+gemcitabine	22/28 (78.6%)	None
Orsi et.al.	2010	6	HIFU	6/6 (100%)	Portal vein trombosis (1)
Wang et.al.	2011	40	HIFU	35/40 (87.5%)	None

over baseline 3 days after treatment. According to PET/CT and MDCT scans, the entire tumor volume was successfully ablated in all cases. A major complication – portal vein thrombosis – was observed in one patient, who was hospitalized for 7 days.

The results of the studies are summarized in Table 1, and, as seen, pain relief was achieved consistently in all studies. However, no randomized, controlled trials have been performed to date to confirm these findings or to determine if HIFU can improve overall survival by inducing local tumor response.

Challenges and future directions

The major factors that complicate HIFU ablation of pancreatic tumors are the presence of bowel gas, respiratory motion and the absence of ultrasound-based temperature monitoring methods. Bowel gas may obstruct the acoustic window for transmission of HIFU energy, which may lead to not only incomplete ablation of the target, but also thermal damage to the bowel or colon due to rapid heat deposition at the gas-tissue interface. Therefore, it is critical to evacuate the gas in the stomach and colon, which can be achieved by having the patient fast the night before treatment. Applying

slight abdominal pressure to the target area also helps to displace gas and clear the acoustic window.

Respiratory motion of the tumor during the treatment leads to redistribution of acoustic energy over the area larger than the focal region and may result in incomplete treatment of the target and damage to adjacent tissues. Respiratory motion tracking techniques that would allow for rapid focal adjustment in sync with the target position are currently in development (57). An approach that would avoid both the problem of bowel gas and respiratory motion altogether is the use of a miniature HIFU transducer integrated with an endoscopic ultrasound probe. This approach would be particularly beneficial in obese patients. Such miniature endoscopic systems are not yet available commercially, but are currently in development.

Another problem that is inherent to any HIFU system with ultrasound guidance is the absence of direct operator control over the thermal dose that the target tissue received. In order to estimate thermal dose, one needs to know the output acoustic energy of the device, the absorption coefficient of the target tissue and the attenuation by the intervening tissue (primarily abdominal wall and viscera). Therefore, careful calibration of HIFU fields and studies on in-vivo measurement of acoustic attenuation and absorption in different tissues are of great importance (46).

Summary

HIFU ablation has been shown a promising method for palliative treatment of pancreatic tumors. A number of preliminary studies suggest that this technique is safe and can be used alone or in combination with systemic chemotherapy or radiation therapy. Further clinical trials are currently being planned and will help to define the future role of HIFU in the treatment of patients with pancreas cancer.

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