Treatment with high intensity focused ultrasound: Secrets revealed

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Abstract

For many decades open surgery remained the only way available for local control of body tumors. In order to decrease the patients' morbidity and mortality several image guided minimally invasive procedures have been adopted. High intensity focused ultrasound (HIFU) is an extracorporeal non invasive method for tumor ablation. High intensity ultrasonic waves can be focused to a focal point resulting in lethal elevation of the temperature at the target site with consequent damage of the tumoral cells. The advances in HIFU technology during the past two decades expanded the HIFU applications to include ablation of both benign and malignant tumors with different treatment strategies being implemented for each type. The aim of this review is to introduce the reader to the details of the treatment process including pretreatment preparation, treatment planning, different ablation strategies, patients' after care as well as the follow up regimens for the most common HIFU applications.

1. Introduction

High intensity focused ultrasound (HIFU) is an extracorporeal non invasive method for tumor ablation. High intensity ultrasonic beams can be focused with high accuracy using an extracorporeal transducer to thermally ablate tumors without the need to introduce needles or probes into the tumor [1]. The delivery of such high acoustic energy to a focal point results in formation of essentially cigar shaped areas of coagulative necrosis known as the Biological Focal Region (BFR). The dimensions of the BFR depends on the acoustic pressure, exposure time and tissue characteristics. Nowadays, HIFU is used for ablation of both benign and malignant tumors. The most common applications of HIFU are the treatment of uterine fibroids, liver tumors and prostate cancer. Other applications include ablation of the pancreas, breast, kidney, bone and soft tissue tumors.

2. HIFU effects

The main lethal effect of HIFU is the thermal effect. The high intensity acoustic energy is absorbed and converted to heat at the focal point (Fig. 1). The heat raises the temperature rapidly to 60 °C or higher causing local coagulative necrosis [2]. Other mechanical phenomena include acoustic cavitation and radiation forces which also contribute to the lethal effect at the focal point. Acoustic cavitation can be defined as the interaction of a sound field with microscopic gas bodies [3]. In order for cavitation to occur in tissues, the presence of gaseous nuclei which probably exist in mammalian tissues is required [4–10]. Two types of acoustic cavitation are identified: stable cavitation and inertial cavitation. Stable cavitation occurs when a bubble oscillates steadily in an ultrasonic field, thus intercepting and radiating energy to the surrounding tissues resulting in micro streaming of fluid around the bubble. This highly localized shear stress causes cell damage [3]. Above a certain pressure amplitude threshold, the bubble oscillation becomes non-linear and the bubbles expand and collapse vigorously resulting in localized high acoustic pressure of several thousands atmospheres that causes damage of the exposed tissues, this is known as inertial cavitation [11] (Fig. 2).

The non linear propagation of ultrasound waves through tissues causes the particles within the focal region to be under mechanical forces resulting in appreciable tissue movement causing bioeffects (Fig. 3). This is called radiation force [3,12]. Radiation torque is another mechanical phenomena associated with ultrasound propagation through tissues. Radiation torque causes rotary motion on the cellular level resulting in spinning of the intracellular organelles causing lethal cellular bioeffects [13].

3. The HIFU device

The device reviewed in this article is the model JC focused ultrasound tumor therapeutic system produced by Chongqing Haifu Technology Co., Ltd. (Fig. 4). The device has been described in detail elsewhere [14,15]. The system is guided by real time ultrasound (US) imaging. It has the following main elements: a real time diagnostic ultrasound device, integrated therapeutic transducers, a six direction movement system that allows movement of the integrated transducer along X, Y and Z planes, moving table that allows...
moving the patient body over the therapeutic transducer for better tumor localization and targeting, computer units for automated control, an ultrasound generator for producing the high intensity ultrasound and a degassed water circulation unit. The focused ultrasound is produced by therapeutic transducers of different frequencies. The integrated transducer is placed within a reservoir of degassed water and is directed upwards towards the body of the patient. The degassed water provides acoustic coupling between the transducer and the patient allowing the ultrasonic beam to pass directly towards the patient body without any deflection [1].

The operating console for the device has three monitors. The first monitor is used to control the therapeutic process. All the information regarding the ongoing treatment process is displayed on this monitor including the slice being treated, the focal point, the treatment mode (dot or linear mode), the acoustic intensity and exposure time. The control keys of the therapeutic transducer are also displayed on this monitor through which the position of the focal point could be adjusted to the treatment site. The second monitor is a diagnostic ultrasound monitor that monitors the echogenic changes associated with the treatment process. It has Doppler that allows real time assessment of the vascularity of the treated area. The last monitor displays information regarding the circulation of the degassed water allowing control of the level and temperature of the degassed water in the water reservoir.

The system can be operated by one of several transducers with focal lengths varying from 90 to 160 mm. The choice of the transducer depends on the depth of the target tumor. A transducer with a focal length of 135 mm and operating frequency of 0.8 MHz is the most commonly used one [1]. The position of the focal point could be adjusted to the tumor region through the control system as long as the deepest layer of the target tumor lies within the focal length of the therapeutic transducer, otherwise, different therapeutic transducers should be used.
4. Pre treatment simulation

Once the patient is a candidate for HIFU treatment, pre treatment simulation is done to assess the feasibility of the treatment. The patient is placed on the HIFU machine in the same position that would be used during the treatment process. Several items are to be evaluated. The most important item is to assess whether the lesion could be seen by the integrated transducer or not. If the lesion cannot be clearly visualized due to overlying bowel gas or ribs so the patient is unsuitable for HIFU treatment as the factors that hindered visualization of the tumor will likely hinder the passage of the therapeutic US during treatment. This point is an important advantage of the ultrasound guided systems over the MRI guided ones because if the lesion can not be seen by diagnostic US clearly so the therapeutic ultrasound will not be able to target the lesion.

The acoustic path is also assessed during the simulation process. The typical path is the shortest one through which an US beam can be safely directed towards the target region. This path should be away from any obstructing agents like the ribs or any organs that could be injured like the bowel loops.

The focal length of the therapeutic transducer should also be evaluated. The operating doctor must be sure that the therapeutic ultrasound can reach to the deepest layer of the tumor plus a safety margin which is of great importance during the treatment of malignant tumors. The ideal focal length of the transducer should be equal to the distance from the deepest layer of the tumor to the skin surface plus 1 cm safety margin.

Other items to be assessed include the need for auxiliary methods for HIFU therapy. For example, for lesions at the hepatic dome an artificial hydrothorax may be induced to provide a window for the ultrasonic beams to reach the target. For uterine fibroids, water bags may be used to displace the bowel loops away from the acoustic pathway. For tumors with unclear margins like breast or bone cancer chemotherapy sessions may be needed prior to HIFU treatment to get more clear margins.

5. Patient preparation

Preoperative assessment of the patients differs according to the target lesion, yet the following items are required: history taking, hematological evaluation (hematocrite, platelets count and prothrombin time), liver and kidney functions and assessment of tumor markers. Chest X ray and electrocardiogram are needed to assess whether the patient is suitable for HIFU treatment as the factors that hindered visualization of the tumor will likely hinder the passage of the therapeutic US during treatment. This point is an important advantage of the ultrasound guided systems over the MRI guided ones because if the lesion can not be seen by diagnostic US clearly so the therapeutic ultrasound will not be able to target the lesion.

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Skin preparation is a crucial step for successful HIFU treatment. Any hair, dirt or topical creams on the skin surface overlying the target tumor can cause deflection of the ultrasonic beams resulting in accidental skin burn. The skin covering the presumed course of the therapeutic ultrasound beams should be shaved and clean [17,18]. The skin is cleaned by cotton soaked by alcohol. Suction is done in order to remove any dermal micro bubbles. This must be done gently to avoid any skin injury. The range of skin preparation is determined by location and volume of the tumor which should extend at least 8 cm beyond the tumor margins.

Patient position depends on the site of the tumor. Hepatic tumors usually require the patient to be in a prone or right lateral position [18]. Prone position is used for uterine fibroids, breast cancer and pancreatic cancer ablation. The body is fixed in the desired position by cushioned straps (Fig. 5).

Treatment of uterine fibroids is done under conscious sedation. This allows continuous feed back from the patient. If the patient feels pain during the treatment then the acoustic path and therapeutic parameters should be rechecked. For hepatic, breast and soft tissue tumors, ablation is usually done under general anesthesia. General anesthesia allows complete patient immobilization and satisfactory respiratory control which is important for ablation of the hepatic tumors particularly those at the dome [18]. Intermittent breath holding at sustained airway pressure is usually needed to move the lesions at the hepatic dome downwards away from the ribs allowing better targeting and ablation [19]. Epidural anesthesia may be also used; however this is less common than general anesthesia.

7. Treatment process and monitoring

After anesthesia and proper positioning, patient is placed over the integrated transducer. Moving the treatment bed helps to adjust the patient body over the integrated transducer. Treatment planning is then started. The computer control allows obtaining both axial and sagittal images of the tumor. The treatment planning should consider the full extension of the tumor plus 1–3 cm safety margins all around the lesion for malignant tumors. The first and last slices are identified by the operating doctor and their coordinates are entered to the planning software of the device together
with the desired spacing in between the slices (usually 5 mm). The integrated transducer then moves automatically to obtain contiguous slices of the treatment region according to the data entered. The slices are displayed over the therapeutic monitor. The operating doctor selects the slice to start with and moves the transducer along the different planes to place the focal point at the desired part of the tumor. The treatment always starts at the deepest part of the tumor to avoid obscuring bubbles that will arise if the treatment is started at the superficial layer of the tumor. Such bubbles will not allow the therapeutic beam to reach the deepest layers of the tumor if the treatment is started first superficially.

Two treatment modes are used. The “dot” mode and “linear” mode. The operating doctor can choose to go by anyone of them according to the treatment strategy and type of the tumor to be ablated. In “linear” mode the therapeutic ultrasonic beam is shoted continuously along a line without gaps or stops (Fig. 6). The direction and length of the line is determined by the operating doctor. The “dot” mode allows giving interrupted therapeutic doses to produce cigar shaped areas of coagulative necrosis. The therapeutic parameters of each dot could be determined through the system. Dots can be repeated by the desirable spacing or gaps to create a row then a slice (Fig. 7). Differences between the “linear” and “dot” modes are listed in Table 1. Whatever the scanning mode used, the focused high intensity ultrasound is scanned in successive sweeps from deep to superficial layers of the tumor. The process is repeated section by section to achieve complete tumor ablation.

After each shoot, the ultrasound images are compared to those before the treatment to determine whether the echogenic changes which indicate the extent of coagulation necrosis had covered the desired treatment area or not [19]. Special attention should be paid to the skin overlying the tumor region. If there are considerable skin changes like edema or blistering the therapeutic parameters should be readjusted, the therapeutic power and exposure time could be decreased and the scanning speed may be increased.

8. After care

After finishing the treatment and ensuring recovery from general anesthesia patients are transmitted to the aftercare room, kept at a semi recumbent position and monitored for the vital signs. Patients may feel some pain after recovery from anesthesia. Short

Table 1

<table>
<thead>
<tr>
<th>“Linear” mode</th>
<th>“Dot” mode</th>
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<tr>
<td>Therapeutic ultrasound shoted continuously without interruption</td>
<td>Therapeutic ultrasound shoted in the form of interrupted dots</td>
</tr>
<tr>
<td>No spacing within the same line</td>
<td>Dots may be spaced or be completely overlapping</td>
</tr>
<tr>
<td>The therapeutic lines have the same acoustic power</td>
<td>Each dot may have different acoustic powers according to the treatment preferences</td>
</tr>
<tr>
<td>Used with malignant tumors so as not to miss any point without ablation</td>
<td>Used more with benign tumors e.g.: uterine fibroids</td>
</tr>
<tr>
<td>Less controlled</td>
<td>More controlled</td>
</tr>
<tr>
<td>More risk of skin injury</td>
<td>Less risk of skin injury</td>
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acting pain killers may be used to control pain. Non steroidal anti-inflammatory drugs should be avoided for patients with platelet dysfunction, renal impairment or esophageal varices [18]. The use of paracetamol within the recommended maximum daily dose is safe for hepatic patients [20–22]. Skin monitoring is very important. If the skin is edematous or shows local redness or blistering cold fomentations (10–20 °C) could be applied for 24–48 h till the temperature reaches normal.

Grade I skin toxicity (blister or burn <1 cm in diameter) generally resolves by day 12 without additional measures. Grade II toxicity (partial thickness blister or burn >1 cm in diameter) required longer time to resolve [23].

For patients with hepatic carcinoma the gastric tube is drawn out after recovery from anesthesia except for those with tumors close to the gastrointestinal tract, in this case the tube is kept for 24 h and removed only when normal bowel sounds are heard and patient passes flatus.

For patients with pancreatic cancer, the gastric tube is kept for 72 h with no oral feeding. Changes of blood sugar and amylase are monitored. When these indices are normal the tube could be removed and patients recover normal diet gradually.

As regards uterine fibroids, patients usually experience peri procedural pelvic cramps but can be discharged on the same day with oral analgesics. Fever, urinary tract infection, hematuria and back pain have been reported [24,25]. Patients can have some solid food two hours after the treatment. Up to two weeks after the treatment, the patient is advised to drink plenty of water with vegetable and fruits constituting about 50% of the meals to avoid any constipation. Some laxatives may also be given to prevent constipation. Some patients may experience increased vaginal discharge or bloody discharge which may last for one week. Local vaginal disinfectant douches may be used to prevent secondary infection. If pain is experienced, short acting analgesics may be used. Sexual intercourse is strictly not allowed until after the first menstruation after the treatment.

9. Follow up

Follow up of the patients is crucial to assess the efficacy of the treatment. Follow up usually entails assessment of the improvement in the clinical condition of the patients as well as monitoring the changes in the imaging and laboratory parameters.

Herein, in this article we are concerned about reviewing the most important and common applications for extracorporeal HIFU, namely liver cancers, uterine fibroids and pancreatic cancer. Other information regarding the follow up of the other applications like breast cancer, prostatic cancer and renal cancer are beyond the scope of this article and can be found elsewhere [26–30].

10. Liver cancer

Follow up is usually done at month 1, 2, 3 and then at an interval of 3–6 months after HIFU [1,16]. At each time, physical examination of the patients is done and symptom scores are recorded. Blood samples are taken to assess the liver functions as well as to estimate the Alpha-Feto Protein (AFP). Imaging is done (US and CT/MRI) and images are archived and compared with the previous imaging findings (Fig. 8).

Symptom scoring systems are usually used to monitor the improvement of the clinical condition. Usually Karnofsky Performance Status (KPS) scales for general health and Numerical Rating Scales (NRS) for pain are assessed at month 0, 1, 3, 6 and 12. In addition, Quality of life (QOL) scores are assessed at month 0, 3 and 12 [16].

KPS scales (scores from 0 to 100) are assessed according to the severity of the symptoms as rated by the patients them selves, activities of daily life and levels of nursing as evaluated by the medical staff. High KPS scores suggest good health [31]. NRS for evaluation of abdominal pain is rated on a score from 0 to 10 as reported by the patients them selves [32]. QOL scales are estimated with a questionnaire form of QOL for liver cancer (QOL–LC) issued by Sun Yat-Sen University of Medical Sciences, China [33]. The form includes 22 questions and patients answer each question by self rating. A total score (from 0 to 100) is obtained by summarizing all the ratings [33].

As regards the laboratory findings, monitoring of AFP is crucial during the follow up period. The change of AFP level coincides with the tumor response to HIFU treatment as seen radiologically, thus reduction of AFP levels indicates good response to the treatment [1]. Follow up imaging includes Doppler Ultrasound, CT and MRI. Two main parameters are assessed (I) the absence or obvious reduction in the tumor vascularity and (II) the shrinkage of the treated lesions [1].

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In a study performed by Wu et al. [1] two important observations were reported. For patients who had previous Trans Arterial Chemo Embolization (TACE), the retained hyper dense iodized oil made the CT assessment of the tumor vascularity more difficult. Thus dynamic contrast-enhanced MR imaging would be more sensitive in assessment of such patients [34–36]. It was also reported that contrast enhanced MRI was more accurate than either Doppler ultrasound or CT scan in demonstrating changes in tumor vascular perfusion and in distinguishing the difference between non viable and residual tumor. In a recent study done by Zhang et al. the superiority of contrast-enhanced MRI for evaluation of short term response after HIFU ablation was confirmed. In addition, it was shown that Diffusion Weighted Images (DWI) would give additional valuable information regarding the evaluation of the treatment efficacy and prediction of possible recurrence [37].

An important advantage of HIFU is that it can be combined with other already available treatment options for hepatic tumors like chemo-embolization, this is important specially for treating large hepatic tumors. Chemo-embolization sessions prior to HIFU reduce the vascularity of the tumor thus making it more vulnerable to coagulative necrosis when HIFU is done afterwards. Also, the deposited lipiodol increases the heat deposition of HIFU within the tumors allowing for more effective thermal ablation. In a study performed by Wu et al. it was obvious that patients who received chemo-embolization followed by HIFU achieved more reduction of their tumor size and better survival rates than those who received chemo-embolization alone [19]. These results were confirmed by another more recent study carried by Jin et al. [38].

11. Uterine fibroids

In a study performed by Ren et al. [39] follow up of the patients was done at month 1, 3, 6 and 12 after treatment. This included monitoring of the clinical symptoms and imaging changes as well as assessment of the histo-pathological changes of the ablated fibroids.

As for the clinical assessment, all the patients were asked to fill out a questionnaire about fibroid related symptoms and to rank the severity of symptoms onto a scale from 1 to 10 where 10 meant maximum severity of the symptoms. The symptoms of concern were menometrorrhagia, dysmenorrhea, dyspareunia, pelvic pain, dysuria and bulk related symptoms. Each woman is asked to answer the same questionnaire in each visit without seeing her previous answers [39].

Doppler ultrasound, contrast enhanced CT and MRI were used for radiological assessment of tumor response. Assessment criteria included reduction of both tumor blood supply and size. The most striking changes were seen on post-HIFU enhanced MRI and CT in which it was common to observe the absence of contrast enhancement in the treated region and a thin peripheral rim of enhancement surrounding the coagulative necrosis [39] (Fig. 9).

Macroscopic examination showed that the treated areas presented pale coagulation necrosis after one week of the treatment. Microscopic examination showed homogenous coagulative necrosis with distorted cells. However, biopsy does not provide histological results from the whole treated fibroid and it is impossible to perform biopsies for all the patients. Thus, diagnostic imaging methods are considered the most feasible and reliable methods for assessment of the therapeutic response [39].

Regression of the tumor size is expected to begin 1 month after the treatment and becomes obvious usually after 3 months of the treatment. It was also found that the changes in the vascularity of the treated tumor correlate with the volume change. Tumors in which blood supply decreased immediately after HIFU session decreased in size on follow up, however tumors that did not show significant change in vascularity immediately after the treatment increased in size during the follow up period [39].

12. Pancreatic cancer

Most of the patients who underwent HIFU ablation for pancreatic cancers were at the late stage of the disease. In a study...
performed by Wu et al. [40] the most striking change in the patients' clinical condition was that there was an immediate relieve of pain immediately after HIFU treatment. In this study it was found that there were no significant gray scale changes observed after HIFU although there was obvious regression of the tumor size during the follow up periods, thus it was concluded that Doppler US was not sufficiently sensitive for assessment of the treatment response. Thin cuts contrast-enhanced CT and MRI were more sensitive during the follow up either to assess the tumor viability or to monitor the regression in size of the tumor [40] (Fig. 10).

In this study [37] no bile or pancreatic duct injury was reported during the follow up period as most treated cancers were located in the body or the tail of the pancreas. However, for pancreatic head cancers an endobiliary stent should be routinely placed before HIFU to avoid any possible strictures.

Laboratory assessment includes assessment of the serum amylase and bilirubin levels. This could be done daily in the first 7 days after the treatment to check for any developing pancreatitis or obstructive jaundice.

13. Discussion

HIFU is a non invasive method for treatment of body tumors. It allows treatment of body tumors without even the need to insert any probes or needles within the tumor like the other minimally invasive methods. In addition to its local ablative nature, HIFU can also activate the body immunity and decrease the tumor growth rate, thus allowing for better control of the malignant tumors [41,42].

HIFU has many advantages. It is a non invasive safe treatment option that carries less risk of injury to the healthy tissues surrounding the tumor specially the blood vessels. However, HIFU procedures are still considered lengthy when compared to the other minimal invasive procedures. We believe that with the advances in HIFU technology and development of clinical experience the time of the HIFU treatment will decrease significantly.

HIFU has attracted the attention of many physicians from different specialties. Today, HIFU is practiced by interventional radiologists, clinical oncologists, surgical oncologists, gynecologists and urologists. We do believe that with the expansion of HIFU applications and the spread of HIFU devices in the coming few years specialized “HIFU doctors” will be needed. HIFU doctors should have experience regarding the different interventional procedures available for the patients to select the suitable patients for HIFU.

This will also need a “HIFU team” that can discuss and design the HIFU treatment regimen to achieve the best outcome.

HIFU applications are not limited to tumor ablation. Nowadays extensive research is concerned with the use of HIFU for acoustic hemostasis, gene therapy and drug delivery with promising preliminary results [43–49]. It is also being investigated for lysis of blood clots and opening the blood brain barrier, the latter application would facilitate targeted drug delivery to the brain [50–53].

HIFU is a technology that was born to grow. We believe that with the current interest in HIFU and the ongoing extensive research in this field, HIFU will likely be an important treatment tool in the coming few years.

References
