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# Current Status of Clinical High-Intensity Focused Ultrasound

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*Abstract*— **High-intensity focused ultrasound (HIFU) is being promoted as a noninvasive method to treat certain primary solid tumors, metastatic disease, and enhance drug delivery. The field of medicine is evolving towards increasing use of noninvasive and minimally invasive therapies such as HIFU. This article provides an overview of current clinical applications of HIFU and future requirements to expand the clinical applications of this technique.**

## I. Introduction

The application of high-intensity focused ultrasound (HIFU) for tumor therapy has recently been gaining momentum due to advances in imaging technology such as magnetic resonance thermometry and advanced ultrasound imaging techniques that permit real-time monitoring of HIFU treatment effects. Currently, several commercially available HIFU devices are manufactured worldwide for treatment of a wide variety of both benign and malignant tumors including uterine fibroids, prostate cancer, pancreatic cancer, liver tumors, thyroid tumors and other solid tumors that are accessible to ultrasound energy. Furthermore, there is considerable research activity in transcranial application of HIFU for creating focal lesions in the brain. This article will discuss the current clinical status of HIFU and potential future applications.

## II. Current Clinical Applications: Tumor Ablation

Although there are a variety of embodiments for HIFU devices, this article will primarily focus on extracorporeal applications. Applications that will not be discussed and are either in use clinically or under investigation that are not extracorporeal include transrectal devices for prostate therapy, laparoscopic and endoscopic devices for intra-abdominal or endoluminal therapy, and catheter-based devices for interstitial or ductal applications. Current clinical applications of extracorporeal HIFU include treatment of uterine fibroids, liver tumors, renal tumors, bone metastasis, breast cancer and pancreatic cancer.

### *A. Uterine leiomyomas*

The use of HIFU is gaining acceptance worldwide as a noninvasive method of treating symptomatic uterine leiomyomas. Several clinical extracorporeal HIFU systems for treating uterine leiomyomas exist. They are guided and monitored by either US or MR imaging. The use of MR-guided HIFU is approved in several regions throughout the world including Japan, Korea, the United States, and Europe. MR-guided HIFU treatment of uterine leiomyomas has been demonstrated to provide short-term symptom reduction as assessed by the Uterine Fibroid Symptoms Quality-of Life questionnaire [1]. In this study there was one serious complication reported which was temporary sciatic nerve palsy. The nerve injury was not a result of direct targeting of the nerve, but resulted from heating of the pelvic bones in the far-field of the HIFU beam that subsequently caused indirect thermal injury to the sciatic nerve. In addition 5% of patients experienced mild skin burns. In a separate case report there was a report of a full thickness skin burn resulting from MR-guided HIFU ablation of a uterine fibroid [2].

### *B. Liver tumors*

Most clinical reports of using HIFU for treatment of liver tumors come from China with some preliminary experience in Europe. HIFU has been used for the treatment of both primary hepatocellular carcinoma (HCC) and secondary metastasis [3;4]. More recently HIFU has been investigated as an adjunctive therapy to trans-arterial chemo-embolization [5]. Although this method appears to hold great promise for the treatment of HCC and metastatic liver lesions, the reliable delivery of HIFU through the ribs without causing significant burns remains a major clinical challenge. Furthermore, the excursion of the liver due to respiratory movement also presents a significant challenge to therapy. This is currently addressed by performing selective intubation, using mechanical ventilation to control respiratory movements and injection of saline to create artificial abdominal ascites to distance the liver from the diaphragm. Research in the area of new transducer array configurations and respiratory tracking is being performed to address these issues [6-8].

### *C. Renal cell carcinoma*

The treatment of renal cell carcinoma is also an attractive target for HIFU given the adequate acoustic window to the kidneys. Furthermore, the use of HIFU for advanced renal carcinoma, even in the setting of metastatic disease, is theoretically beneficial since a survival benefit has been demonstrated in patients with metastatic disease

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who undergo surgical debulking followed by immunotherapy. HIFU has the potential advantage of performing tumor debulking without the need for invasive surgery and it also may help to enhance tumor specific immunity in an immune responsive tumor such as renal cell carcinoma. Again, the preliminary clinical data comes from China suggesting that HIFU ablation of renal cell carcinoma is both safe and feasible [9].

### *D. Bone metastases*

Treatment of bone metastases with HIFU has also been evaluated [4;10]. Catane et al. reported a series of 13 patients who had symptomatic bone metastasis that were treated with MR-guided HIFU for purposes of palliation [4;10]. One patient was unable to tolerate HIFU therapy due to treatment-related pain. Of the 12 remaining patients who were successfully treated all patients experienced improvements in visual analog pain scores. The result of this study suggests that HIFU ablation of bone metastases may palliate pain caused by bone metastases.

### *E. Breast cancer*

Ablation of breast tumors has also been performed using both US and MR guided HIFU methods [11-14]. HIFU is a particularly attractive method for breast tumor ablation in patients desiring breast conserving therapy since it is completely non-invasive. However, the challenge will be demonstrating that HIFU ablation is equivalent to local excision in terms of local recurrence and disease free survival since outcomes for early stage breast cancer are excellent with current therapy that includes local surgical resection. Wu et al. reported a series of 23 patients who underwent wide local ablation of their breast tumors with a 1.5-2 cm margin using US-guided HIFU followed by surgical resection of the treated tumor and demonstrated that HIFU ablation of the tumor consistently resulted in complete ablation of the tumor with negative margins [13]. Furusawa et al. reported their results of a phase II clinical study in Japan using an MR-guided HIFU device. In this study they treated 21 patients with HIFU and experienced one case of recurrence with a median follow-up period of 14 months (range 3-26 months) [11]. These early human clinical studies suggest that HIFU may have a role in select patients who wish to have noninvasive local therapy; however, further studies with long-term observation are necessary. In addition, there are theoretical concerns of thermal injury to the chest wall due to the high impedance mismatch interfaces with either the ribs or lung; however, this has not been reported as a complication in early clinical studies.

### *F. Pancreatic cancer*

The application of HIFU in palliating patients who have symptoms of pain related to pancreatic cancer has been reported by several investigators, primarily out of China where patients have been treated clinically since 1999. Results from a recent retrospective study of 89 patients with advanced pancreatic cancer (TNM stage II-IV) suggested that HIFU treatment can reduce pain [15]. The mechanism for pain relief is unclear but may be due to damage of intratumoral nerve fibers or decompression of the tumor. Of note, there have been no reports of severe acute pancreatitis resulting from HIFU ablation.

### *G. Thyroid and parathyroid tumors*

Tumors of the thyroid and parathyroid are common and can either be benign or malignant. Benign tumors can be clinically significant due to release of systemic hormones. Therefore, therapy for both benign and malignant tumors is often necessary. Current therapies include medical management, surgical resection, or minimally invasive methods for ablation (radiofrequency or alcohol injection). Minimally invasive therapies are performed using ultrasound guidance since the thyroid and parathyroid glands are easily visualized using ultrasound imaging. HIFU for treatment of the thyroid has been reported and clinical trials for treatment of primary hyperparathyroidism are being performed in Europe [16].

## III. Future Clinical Applications

### *A. Enhancement of cancer-specific immunity*

A unique aspect of HIFU is its ability to induce cavitation leading to lysis of cells without denaturing the cellular contents. The tumor-cell lysate provides an antigen source that can be amplified by dendritic cells for potentially inducing a T-cell response against the tumor. This method has been used extensively *in vitro* and in animal models to create dendritic cell-based vaccines directed at various tumors [17;18]. Preliminary animal studies have demonstrated that HIFU therapy that mechanically damages tumors (as opposed to thermal ablation) by enhancing cavitation *in vivo* elicits a systemic anti-tumor immune response [19]. An initial clinical investigation evaluating the effect of HIFU on the immune system of patients with osteosarcoma, hepatocellular carcinoma and renal cell carcinoma demonstrated that the $CD4^+/CD8^+$ ratios (a marker of antitumor immunity) increased following HIFU therapy [20]. If enhancement of cancer-specific immunity by HIFU is demonstrated, then the approach to tumor therapy using HIFU in some instances may shift towards increasing cavitation activity to cause cell lysis as opposed to pure thermal ablation.

### *B. Enhanced drug delivery*

Another active area of preclinical investigation is HIFU-enhanced drug delivery. Preliminary animal studies suggest that pulsed HIFU can increase delivery of chemotherapeutic agents to targeted tumors [21-23]. The mechanisms of HIFU-enhanced drug delivery likely include: 1) increasing the permeability of the vascular endothelial cells (most likely due to intravascular cavitation or thermal effects) allowing the chemotherapeutic agent to escape the vascular space into the interstitial space of the tumor; and 2) aiding the distribution of the chemotherapeutic agent into the tumor due to radiation force from the ultrasound field.

### C. Neurologic applications

Neurologic applications of HIFU include disrupting the blood-brain barrier to permit delivery of therapeutic molecules into the brain [24-27], focal ablation of brain lesions for the treatment of hyperkinetic disorders or epilepsy [28], and ablation of brain tumors [29]. Current research is focused on delivering HIFU energy through the skull so that a craniotomy is not necessary [30-33]. Neurologic applications will require MR-guidance and monitoring given the need for precise targeting and monitoring of therapy.

## IV. Future requirements

### A. Treatment monitoring

An essential component of HIFU therapy is the ability to target and monitor therapy. Currently the two imaging modalities used to target and monitor HIFU therapy are ultrasonography (US) and magnetic resonance (MR) imaging. The benefit of using US to target and monitor therapy is that the energy modality is the same for both imaging and therapy; therefore, if the target cannot be imaged (suggesting high attenuation or reflective interfaces between the transducer and the target) then the energy from the HIFU transducer will also be attenuated or reflected leading to ineffective therapy. US imaging will clearly identify areas of high impedance mismatch such as tissue-gas and tissue-bone interfaces, which are to be avoided when delivering HIFU therapy. However, US imaging currently has limited capability in monitoring temperature or tissue changes unless boiling occurs at the focus, where the temperature exceeds 100 ºC, and a hyperecho can be visualized on US imaging. It is important to note that the hyperecho visualized on US imaging represents gas bubble formation and does not precisely correlate with lesion formation [34]. The other imaging modality used for guiding and monitoring HIFU therapy is MR imaging. MR-guided HIFU has the benefit of being able to provide temperature information within seconds after HIFU treatment. This method is extremely reliable in *ex vivo* situations where the tissue is stable; however, motion artifact and spatial resolution can limit its accuracy in the clinical setting. The selection of a given method of guidance and monitoring will depend on the equipment available and the goal of the ablation procedure. For example, neurologic applications where targeting and monitoring of the ablation are critical, the use of MR would be necessary despite it being expensive and labor intensive; whereas, oncologic applications for palliation of tumors in the abdomen, pelvis and extremities could be more easily performed using US guidance once US monitoring is further developed.

Advances in treatment monitoring will be essential for HIFU therapy to become a clinically viable modality for treatment of tumors with curative intent. Currently, US monitoring does not permit accurate assessment of the treated tumor. Therefore, its use is limited to palliation of symptoms at this time. However, with advances in ultrasound imaging techniques such as thermometry [35] and elastography [36] as well as other advanced imaging techniques [37;38], it may be possible to provide real-time monitoring of HIFU treatments with US imaging that will give the clinician confidence that the entire tumor has been treated.

### B. Transducer developments

New transducers continue to be developed to address current problems of HIFU therapy which include targeting challenging areas due to the lack of an acoustic window and/or respiratory motion, and to improve the speed at which HIFU is delivered. These issues are primarily being addressed by designing electronically phased array transducers that will allow focusing through the intercostal spaces to treat lesions in the liver [6;8] and to scan the focus rapidly permitting more rapid treatment of large tumor volumes [39].

## V. CONCLUSION

The unique nature of HIFU allows for noninvasive therapy to ablate tumors. In addition, mechanical effects of HIFU are being actively investigated as potential mechanisms for unique therapeutic interventions such as HIFU-enhanced drug delivery and enhancement of tumor-specific immunity. Although HIFU technology has been used clinically since the 1950's it remains a new therapeutic technology requiring further critical laboratory and clinical evaluation. Development of imaging techniques to monitor HIFU therapy will be essential for advancing clinical HIFU.

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