

## Review Article

# High intensity focused ultrasound ablation: A new therapeutic option for solid tumors

### ABSTRACT

Surgery has been the standard of care in selected cases with solid tumors. However, a majority of patients are unable to undergo surgical resection because of the tumor sites, advanced stages, or poor general condition. High intensity focused ultrasound (HIFU) is a novel non-invasive technique that is capable of producing coagulative necrosis at a precise focal point within the body, without harming overlying and adjacent structures even within the path of the beam. Diagnostic ultrasound was the first imaging modality used for guiding HIFU ablation in the 1990s. Over the last decade, thousands of patients with uterine fibroids, liver cancer, breast cancer, pancreatic cancer, bone tumors, renal cancer have been treated with ultrasound imaging-guided HIFU (USgHIFU) worldwide. This USgHIFU system [Chongqing Haifu (HIFU) Tech Co., Ltd., Chongqing, China] was first equipped in Asia, now in Europe. Several research groups have demonstrated that HIFU is safe and effective in treating human solid tumors. In 2004, the magnetic resonance guided focused ultrasound surgery (MRgFUS) was approved by the United States Food and Drug Administration (FDA) for clinical treatments of uterine fibroids. We conclude that HIFU offers patients another choice when no other treatment available or when patients refused surgical operation. This technique may play a key role in future clinical practice.

**KEY WORDS:** High intensity focused ultrasound, cancer, treatment

### INTRODUCTION

Surgery has been the standard of care in selected patients with solid tumors, offering the chance of complete cure by tumor removal.<sup>[1,2]</sup> However, a majority of patients are unable to undergo surgical resection because of the tumor sites, advanced stage of tumors, or poor general condition. Clinicians have been trying to find out novel treatment techniques, such as radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), cryoablation, microwave coagulation, laser-induced interstitial thermotherapy, and HIFU, to treat those patients. Among these techniques, HIFU is the only non-invasive technique. HIFU ablation is also known as focused ultrasound ablation, focused ultrasound surgery (FUS). The possibility that focused ultrasound ablation might be developed as a result of controlling local heating phenomena was introduced by Lynn *et al.* in the 1940s,<sup>[3]</sup> but the technique was not developed at that time because of inadequate targeting methods. In the 1980s, HIFU has received considerable attention. Chongqing group began HIFU project in China in 1988. After 10 years of basic research, Wang *et al.*<sup>[4]</sup> proposed a new conception of the 'biological focal field' in 1997. In the last decade, several clinical HIFU projects have been conducted by various research groups and significant results indicated that HIFU ablation would be safe, effective, and feasible in clinical application.<sup>[5-7]</sup>

HIFU is a non-invasive technique and thus may be of particular value for patients at risk for surgical operation. In addition to the potential for curative treatment and the extension of life expectancy, HIFU has been demonstrated to reduce or eliminate tumor-related pain and thus improve quality of life for patients with advanced disease. Currently, both ultrasound imaging-guided HIFU (USgHIFU) [Figure 1] and magnetic resonance imaging guided HIFU (MRgHIFU) devices have been developed in Chongqing, China. Insightech has also developed MRI-guided focused ultrasound surgery (MRgFUS). MRgHIFU or MRgFUS is mainly used to treat uterine fibroids. In contrast, USgHIFU is not only used to treat uterine fibroids, but also to treat liver cancer, pancreatic cancer, breast cancer, bone cancer and renal cancer.<sup>[5]</sup> This article reviews the clinical use of MRgHIFU and USgHIFU.

### MRgHIFU OR MRgFUS

For guiding and monitoring HIFU ablation, MRI offers excellent anatomic resolution and temperature sensitivity for real-time treatment monitoring.<sup>[8,9]</sup> Early work by Huber and Hynynen confirmed the feasibility of MR guided focused ultrasound treatment in the breast. Huber *et al.*<sup>[10]</sup> treated one patient with HIFU followed by lumpectomy five days later. MR imaging following treatment and histological examination following

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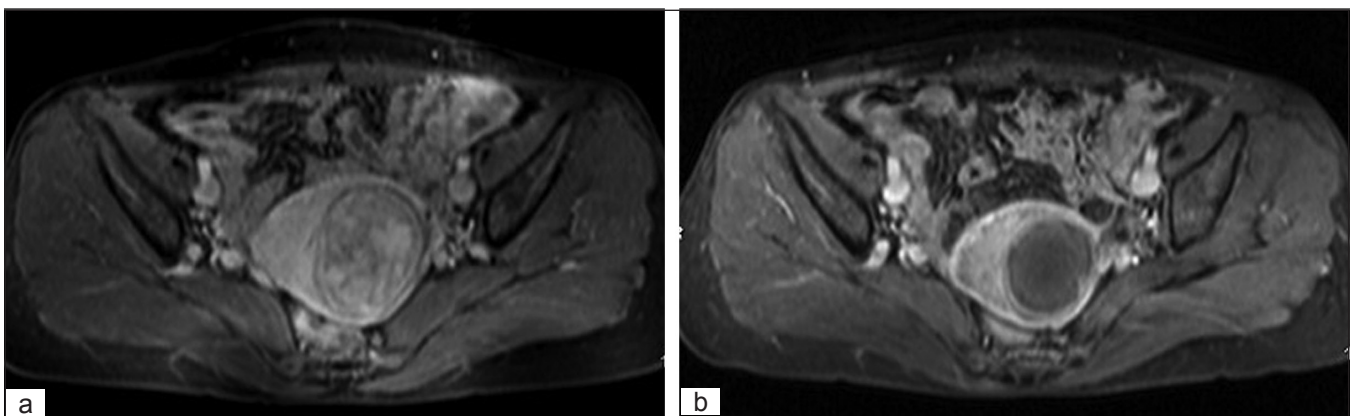
**Figure 1:** Model JC focused ultrasound tumor therapeutic system manufactured by Chongqing Haifu Technology Co., Ltd. (Chongqing, China)

excision revealed lethal and sub lethal damage to the tumor. Hynynen *et al.*<sup>[11]</sup> then treated 11 fibroadenomas in nine patients under local anesthesia using MR guided ultrasound. Fibroadenomas were confirmed by biopsy pre-treatment and the effects of the treatment were evaluated by contrast MR imaging pre- and post-treatment at 2 days, 10 days and 6 months follow-up. Contrast agent uptake was reduced or eliminated in 8 of the 11 lesions after HIFU treatment, which indicates tissue devascularization and necrosis. The treated fibroadenomas were softer and MR imaging showed the mean volume was smaller at six after HIFU ablation.

The feasibility and effectiveness of MRgFUS are being tested in several other clinical applications, which include the ablation of benign and malignant tumors and palliative therapy of bone pain due to metastasis.<sup>[12,13]</sup> However, up until now, the main indication for MRgHIFU or MRgFUS is uterine fibroids.

Stewart *et al.*<sup>[14]</sup> and Tempany *et al.*<sup>[15]</sup> have shown that MRgFUS for uterine fibroids is feasible and safe. Although the ablation volume is only around 30% of the targeted fibroids, patients reported either significant or partial improvement in symptoms. Treated fibroids decreased in volume by 12% and 15% at one and six months, respectively.<sup>[16]</sup> The long-term follow-up also demonstrated that patients undergoing MRgFUS for smaller fibroid volume ablation have sustained symptom relief.<sup>[17]</sup> However, based on the mean non-perfused volume (NPV) ratio immediately after treatment, subjects with higher NPV ratio have significantly greater improvement, with higher probability of intervention-free survival.<sup>[17,18]</sup> Therefore, ablating a large fraction of the volume of uterine fibroids may be important for long-term success.

In earlier studies, a clear pathway from the anterior abdominal wall to the fibroid without passing through the bladder or the bowel was required; many patients were excluded from MRgFUS because of bowel presence in acoustic pathway.<sup>[14,19]</sup> Recently, Zhang *et al.*<sup>[20]</sup> have demonstrated that after the bowel was compressed with a degassed water balloon, MR imaging-guided high intensity focused ultrasound treatment is safe and feasible in ablating uterine fibroids in patients whose bowel lies anterior to uterus [Figure 2]. In this study, Zhang *et al.* have treated 21 patients with 23 fibroids, the mean fibroid volume was  $97.0 \pm 78.3$  (range, 12.7-318.3) cm<sup>3</sup>. According to the treatment plan, an average  $75.0 \pm 11.4\%$  (range, 37.8%-92.4%) of the fibroid volume was treated. The average non-perfused volume was  $83.3 \pm 71.7$  (range, 7.7-282.9) cm<sup>3</sup>, the average fractional ablation, which was defined as non-perfused volume divided by the fibroid volume immediately after HIFU treatment, was  $76.9 \pm 18.7\%$  (range, 21.0%-97.0%). There were no statistically significant differences between the treatment volume and the non-perfused volume. Follow-up magnetic resonance imaging (MRI) at three months obtained in 12 patients; the fibroid volume decreased by  $31.4 \pm 29.3\%$  (range, -1.9% to 60.0%) in average, with paired t-test showing a



**Figure 2:** Contrast agent enhanced MRI from a patient with uterine fibroids. (a) Pre-treatment image shows the fibroid with enhancement. (b) One month post-treatment, MRI shows the fibroid shrank with no enhancement. This patient was treated with Haifu<sup>®</sup> JM focused ultrasound tumor therapeutic system (JM2.5C, Chongqing Haifu Technology Co., Ltd., China), in combination with a 1.5-Tesla MRI system (Symphony, Siemens, Germany), which provides real-time guidance and control

statistically significant reduction ( $P=0.002$ ). The mean treatment time for ablating the average  $83.3 \pm 71.7$  (range, 7.7-282.9)  $\text{cm}^3$  of fibroid volume was  $2.5 \pm 1.4$  h (range, 27-390 min) in this study, which was relatively short and acceptable to patient and therapist. Four patients experienced mild skin burn (two with skin redness, two with blisters); the skin burn subsided within  $\sim 2$  days. No other adverse events were observed.

### USgHIFU

For guiding and monitoring HIFU ablation, ultrasound (US) has its own advantages over other imaging modalities. First, MRI could offer excellent anatomic resolution. However, it has no ability to offer real-time anatomic background imaging for temperature mapping. In contrast, ultrasound provides clear real-time monitoring anatomic imaging without making noise or emitting ionizing particles and radiation. Second, MRI is the only currently available technique with proven capabilities to create quantitative temperature maps. However, it will be very difficult to monitor the temperature changes of the tissue when the movement occurs during HIFU, this may limit application of HIFU technology. *In contrast, ultrasound has not this limitation, and many studies have demonstrated that US grey-scale change is reliable for monitoring the response to HIFU treatment.*<sup>[30,31]</sup> Third, since the bore size of MRI is relatively small, it is difficult to position patient, for example, when tumor locates at right lobe of the liver. There is no such limit for USgHIFU. Therefore, USgHIFU has a relatively wide application area.

### Bone

There has been a general consensus that US energy cannot enter bone at sufficient intensity for therapeutic ablation because of ultrasound energy attenuation by bone. However, it has been demonstrated that thermal lesions can be achieved even transcranially in animals using focused ultrasound: where the tumor results in partial or complete cortical destruction, HIFU can penetrate into the medullary space and achieve complete necrosis.<sup>[21]</sup>

Chen *et al.*<sup>[22,23]</sup> first treated five patients with osteosarcoma who were not candidates for limb salvage surgery in a pilot study. After HIFU ablation, blood supply to the tumor was reduced and  $^{99\text{m}}\text{Tc-MDP}$  bone scan demonstrated reduction in osteogenesis in the treated area. All patients experienced reduction or elimination of pain related to the tumor and an improvement to the range of motion of afflicted joints. Histopathology confirmed that the treatment had reached the target area. Complete necrosis was achieved in 103 of 120 samples.

Following this early success, Chen *et al.*<sup>[24]</sup> continued treatment in another 30 patients who had refused surgery. Complete regression was achieved in 10 patients with partial regression achieved in another 13 patients.

Recently, Chen *et al.*<sup>[25]</sup> evaluated long-term follow-up results of USgHIFU ablation for patients with primary bone malignancies. From December 1997 to November 2004, 80 patients with primary bone malignancy were treated with USgHIFU, including 60 in Stage IIb and 20 in Stage III (Enneking staging). HIFU combined with chemotherapy was performed in 62 patients with osteosarcoma, 1 with periosteal osteosarcoma and 3 with Ewing's sarcoma. The remaining 14 patients with chondrosarcoma, malignant giant cell tumor of bone, sarcoma of the periosteum or unknown histology, received HIFU alone. Magnetic resonance (MR) imaging or computed tomography (CT), and single photon emission CT (SPECT) were used to assess tumor response. Follow-up images demonstrated completely ablated malignant bone tumors in 69 patients and greater than 50% tumor ablation in the remaining 11 patients. Overall survival rates at 1, 2, 3, 4, and 5 years were 89.8%, 72.3%, 60.5%, 50.5%, and 50.5%, respectively. Survival rates at 1, 2, 3, 4, and 5 years were 93.3%, 82.4%, 75.0%, 63.7%, and 63.7%, respectively, in the patients with stage IIb cancer and 79.2%, 42.2%, 21.1%, 15.8%, and 15.8%, respectively, in those with stage III disease. Among the patients with stage IIb disease, long-term survival rates were substantially improved in the 30 patients who received the full treatment—that is, complete high-intensity focused ultrasound and full cycles of chemotherapy—compared with the survival rates for the 24 patients who did not finish the chemotherapy cycles and the six patients who underwent partial ablation only. Only five (7%) of the 69 patients who underwent complete ablation had local cancer recurrence during the follow-up period.

The most frequently observed complication was mild skin burn, usually resolving by one-two weeks after HIFU, even without any medication. At the beginning of this study in 1997, skin burn was mainly due to lack of experience in performing HIFU as most occurred during the years of 1997-1999. Another observed complication was nerve injury, it occurred in 10 of 80 patients. The following factors may be pertinent to nerve injury: (1) Nerves can not be visualized by ultrasound imaging, and are thus difficult to avoid in the beam path if the anatomical location of nerves has changed; (2) Nerves are sensitive to ultrasonic energy; and (3) Tumors were often adjacent to nerves. Bone fracture, ligamentous laxity, epiphysiolysis, and secondary infection were also observed; however, all of these patients recovered after surgical intervention.

Certainly, USgHIFU therapeutic ablation of malignant bone tumors is feasible and effective, and may eventually become part of a regimen of limb-sparing techniques in patients with malignant bone tumors. The patients with bone metastases could also benefit from USgHIFU and have better quality of life.

### Liver

The liver has been a target for HIFU since the early days of animal experimentation.<sup>[26]</sup> In the past ten years, several groups started to use USgHIFU to treat liver cancer. In 2001, Wu

et al.<sup>[27]</sup> has reported the pathological changes of hepatocellular carcinoma (HCC) after extracorporeal ablation with high-intensity focused ultrasound (HIFU).

From November 1998 to May 2000, 50 consecutive patients with stage IVa HCC were enrolled in a clinical study to evaluate the response to USgHIFU ablation combined with transcatheter arterial chemoembolization (TACE).<sup>[28]</sup> These patients were divided into two groups: TACE alone was performed in group 1 ( $n = 26$ ), and HIFU combined with TACE was performed in group 2 ( $n = 24$ ). Tumors ranged from 4 to 14 cm in diameter (mean, 10.5 cm). Follow-up images showed absence or reduction of blood supply in the lesions after focused ultrasound ablation when compared with those after TACE alone. The median survival time was 11.3 months in group 2 and 4.0 months in group 1 ( $P = 0.004$ ). The one-year survival rate was 42.9% and 0% in group 1 and group 2, respectively ( $P < 0.01$ ).

In Oxford, UK, a total of 22 patients with liver metastases were treated with USgHIFU. Using either radiological images such as MRI and contrast ultrasound, or histological examinations, 20 of 22 patients were assessed. The results revealed that the adverse event profile was favorable when compared to open or minimally invasive techniques.<sup>[29]</sup>

Recently, Zhang et al.<sup>[30]</sup> reported that HIFU can achieve complete tumor necrosis even when the lesion is located adjacent to the major hepatic blood vessels. Indeed, there is no discernible damage to the major vessels, even though the adjacent tumor has been completely ablated.

From November 2007 to April 2009, Orsi et al.<sup>[31]</sup> treated 17 patients with 24 liver metastases at difficult locations [Figure 3]. The difficult locations were defined as tumor adjacent to main blood vessels, the heart, the gallbladder and bile duct, bowel or the stomach. After one session of HIFU

treatment, PET-CT and/or MDCT at day 1 showed complete response in 22/24 liver metastases. No side effects were observed during a median of 12 months of follow-up.

We conclude that USgHIFU ablation can be considered as a safe and feasible approach for treating liver tumors at difficult locations.

### Pancreas

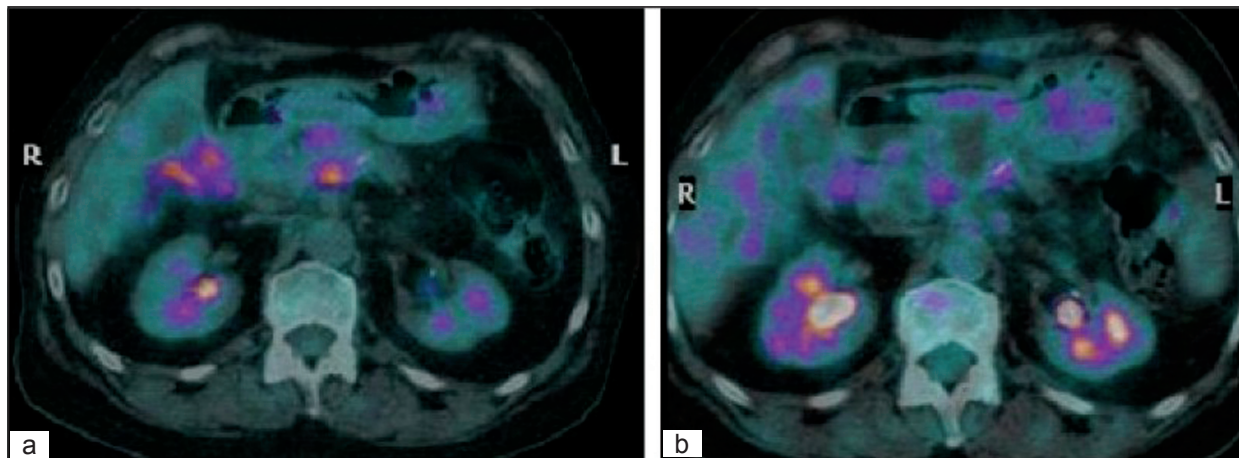
At present, surgery provides the best results for patients with pancreatic cancer. However, most of the patients are not suitable for surgery when the diagnosis is made. For patients who can not undergo surgical operation, HIFU may extend the life expectancy and improve the quality of life.

Between December 2000 and September 2002,<sup>[32]</sup> Chongqing group conducted a prospective trial on eight patients with advanced pancreatic cancer. Patients were enrolled if they were considered unsuitable for surgical operation and had constant localized pain. Three patients had stage III and five patients had stage IV disease. They performed one session of HIFU treatment in six patients and two sessions of treatment in two patients either under general or epidural anesthesia. The pain associated with the pancreatic lesion relieved in all patients during the follow up period. Reduction of tumor volume was observed in all patients, ranging from 20% to 70%. The median survival time was 11.25 months. Serum amylase and bilirubin remained at normal levels and no complications were reported.

More recently, Orsi et al.<sup>[31]</sup> treated seven patients with USgHIFU between November 2007 and June 2009. All of the seven patients were almost completely palliated in symptoms by 24 h after treatment. The median survival time was 11 months. MDCT or MRI at 24 h after treatment did not detect any injury of the surrounding structures. PET-CT at one month after HIFU showed good response to HIFU [Figure 4]. At the beginning of



**Figure 3:** MDCT images obtained from a patient with liver metastasis from breast cancer. (a). Pre-HIFU treatment contrast-agent enhanced CT image shows a lesion at segment I. (b). One day after HIFU treatment, MDCT shows the treated area was larger than the tumor. There was no enhancement in the treated region. (c). Three months post-treatment, CT image shows the treated area was getting smaller. This patient was treated in European institute of oncology, Milan, Italy and she is disease free for two years after HIFU treatment



**Figure 4:** PET-CT images from a woman with pancreatic cancer. (a) Pre-treatment PET-CT image shows positive for tumor. (b) One month post-treatment, PET-CT image shows negative for the treated tumor. This patient was treated in European institute of oncology, Milan

this study, all patients were cautiously observed in hospital for at least three days. Portal vein thrombosis was observed in one patient who was discharged seven days later. The amylase level showed no elevation over baseline in the three days after treatment.

We conclude that HIFU is an alternative treatment option for patients with pancreatic cancer.

#### Breast

Breast cancer is the most common cancer in women and a leading cause of mortality. In the recent years, the progressive reduction of local treatment, that achieve the same result as standard treatment but with less morbidity and better quality of life, has opened up new horizons toward minimally invasive technology.

In this scenario, we believe that HIFU should be investigated deeply, as a non-invasive new treatment option for highly selected patients suffering from early breast cancer.

The first randomized controlled clinical trial was conducted by the group in Chongqing.<sup>[33]</sup> In this study, patients were treated with either modified radical mastectomy ( $n=25$ ) or HIFU followed by modified radical mastectomy within one-two weeks ( $n=23$ ). The HIFU procedure was performed under general anesthesia in 19 patients and under conscious sedation in four patients. The HIFU-treated area included the tumor and 1.5-2.0 cm of surrounding normal tissue. Pathological results showed that coagulative necrosis occurred in the cancerous tissue and the safety margin. They also noted that the expression of PCNA, CD44v6 and MMP-9 was significantly higher in the untreated cancerous tissue than that in the untreated normal breast tissue. However, there was no expression in the HIFU-treated area. Additional histological analysis using NADH staining confirmed complete necrosis.<sup>[34]</sup>

Wu *et al.*<sup>[35,36]</sup> evaluated the long-term clinical results of HIFU in another study. They treated twenty two patients with biopsy-confirmed breast cancer. These patients were enrolled if they were deemed unsuitable for surgery ( $n=6$ ) or refused surgical resection ( $n=16$ ). Among them, four patients at stage I, nine patients at stage II A, eight at stage III B and one at stage IV. All patients received six cycles of adjuvant chemotherapy and radiotherapy after HIFU ablation. On completion of the chemotherapy, two years hormone therapy (tamoxifen) followed.

The absence of blood flow was reported in 19 of 22 patients after HIFU treatment. Tumor shrank in 14 patients and disappeared in eight patients. As anticipated, all patients experienced a palpable breast lump following HIFU which extended to the whole treatment area (tumor and margin) and was therefore greater than the original tumor. Although patients were advised of this in advance, it did give rise to anxiety, and 2 of the 21 patients elected to have mastectomy as a result. Local recurrence occurred in two patients at 18 and 22 months after HIFU ablation. Five years disease-free survival and recurrence-free survival were reported as 95% and 85%, respectively. It demonstrated that HIFU is a safe and effective treatment for patients with breast cancer.

Currently, another clinical trial is underway at the European Institute of Oncology (Milan, Italy). Twelve patients with small breast cancers (<1.5 cm) have been treated with USgHIFU in a single session. After HIFU, all the patients underwent conservative surgery in order to obtain the standard breast cancer surgical treatment and an accurate histo-pathological assessment to confirm the correct HIFU treatment. The pathologic results have shown that the tumors have been ablated without side effects.

#### Kidney

Renal cancer may also be treated with this non-invasive

approach. Wu *et al.*<sup>[37]</sup> described a series of 13 patients with renal cell carcinoma. All the 13 patients received HIFU treatment safely, including 10 who had partial ablation and three who had complete tumor ablation. After HIFU, hematuria disappeared in seven of eight patients and flank pain of presumed malignant origin disappeared in 9 of 10 patients. 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.

Illing *et al.*<sup>[29]</sup> treated eight patients with renal cancer in Oxford. After a single therapeutic HIFU session under general anesthesia, the results were evaluated with either radiological images such as MRI or contrast ultrasound, or histological examinations. The results revealed that the adverse event profile was favorable when compared to open or minimally invasive techniques.

A number of other patients in Oxford have been treated outside any trials. A patient with a 5 cm biopsy proven renal cell carcinoma in a transplant kidney was treated twice with 90% ablation of the tumor (confirmed histologically after a subsequent partial nephrectomy). A transplant kidney would seem to be ideally suited to HIFU treatment as it is sited in the groin area and thus ribs do not pose a problem. Furthermore, perinephric fat, which on occasions seems to impair treatment, has been removed.

### Uterus

In China, Wang *et al.*<sup>[38]</sup> have reported their preliminary results of HIFU treatment for symptomatic uterine fibroids in 2002. Between July 2001 and January 2003, He *et al.*<sup>[39]</sup> treated 23 patients with HIFU at one center. Patients were enrolled if they refused hysterectomy. The fibroids were between 4 and 8 cm in diameter and located at the anterior wall of uterus. The average volume of menstruation and uterine volume decreased throughout the follow-up period and the average size of uterine fibroids reduced in 17 patients with a mean reduction of 78.9%. The fibroid in one patient was resected because of the persistent menorrhagia. Histopathological results from this patient showed that normal tissues around the treated area were undamaged. Unfortunately, four patients had temporary numbness on the lower limbs because of damage to the sciatic nerve which is now avoided by changing the treatment protocol.

In 2004, Wu *et al.*<sup>[7]</sup> reported the use of HIFU in treatment of 85 patients between 1997 and 2001 with uterine fibroids at centers in China. Over the last three years, this JC model HIFU system has been modified and thus led to a very low level of adverse effects. Currently, this technique has been clinically considered as an alternative treatment for patients with uterine fibroids in China.

In Spain, a total of 54 patients with uterine fibroids less than

13 cm in diameter were treated in Hospital Mutua de Terrassa (HUMT) from January to Dec 2009. The post-operative pain score was 0 (at 4 h after HIFU) and all patients returned to their normal life within 24 to 48 h after the treatment. The treated volume covered more than 80% of the fibroid in most cases. The data showed a significant improvement in uterine fibroid symptom and quality of life (UFS-QOL) scores. In the Medical Center of Central Bank, Moscow, Russian, Khitrova treated 61 patients with 143 fibroids (1-7 lesions per patient), there was no complication after treatment, only two patients with submucous fibroids had two-day temperature elevation (under 38.5°C). No skin burns or nerve injury occurred. All clinic signs later disappeared, and two pregnancies subsequently occurred in two patients.

### Others

HIFU has been successfully used in China for the treatment of soft tissue sarcoma.<sup>[7]</sup> It has been used as an organ preserving treatment in patients with uterine adenomyosis.<sup>[40]</sup> Wang *et al.* also reported that US-guided HIFU ablation appears to be safe and effective for the treatment of abdominal wall endometriosis. The cyclic pain disappeared in all patients during a mean follow-up of 18.7 months.<sup>[41]</sup>

### CONCLUSIONS

These results from different groups are encouraging. HIFU ablation can achieve complete response without significant adverse effects; therefore, it is a safe, effective and feasible modality for the destruction of benign and malignant solid tumors. On the basis of the results from clinical trials and studies, we conclude that HIFU seems to be a new therapeutic option for solid tumors.

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