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REVIEW

High-intensity focused ultrasound tumor ablation: Review of ten years of clinical experience

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Abstract High-intensity focused ultrasound (HIFU) is a technique to destroy tissue at depth within the body, selectively and without harming overlying and adjacent structures within the path of the beam because the ultrasonic intensity at the beam focus is much higher than that outside of the focus. Diagnostic ultrasound is the first imaging modality used for guiding HIFU ablation. In 1997, a patient with osteosarcoma was first successfully treated with ultrasound imaging-guided HIFU in Chongqing, China. Over the last decade, thousands of patients with uterine fibroids, liver cancer, breast cancer, pancreatic cancer, bone tumors, and renal cancer have been treated with ultrasound imaging-guided HIFU. Based on several research groups' reports, as well as our ten-year clinical experience, we conclude that this technique is safe and effective in treating human solid tumors. HIFU is a promising technique. Most importantly, HIFU offers patients another alternative when those patients have no other treatment available.

Keywords high-intensity focused ultrasound (HIFU); ultrasound imaging-guided HIFU (USgHIFU); magnetic resonance imaging-guided HIFU (MRgHIFU)

1 Introduction

High-intensity focused ultrasound (HIFU) is a new technique that bears great potential for tumor ablation. The possibility that focused ultrasound therapy might be developed as a result of controlling local heating phenomena was introduced by Lynn *et al*. in the 1940s [1], but the technique was not developed at that time because of inadequate targeting methods. With the progress in diagnostic imaging, the HIFU technique has received considerable international attention. In the 1980s, our group began a HIFU project in Chongqing, China. After ten years of basic research, we proposed a new conception of the "biological focal field" in 1997 [2]. In the same year, we successfully treated the first patient with osteosarcoma by this technique in Chongqing. Since then, several clinical HIFU projects have been conducted by various research groups, indicating that HIFU ablation is safe, effective, and feasible in clinical application [3–5].

HIFU is a nonsurgical technique and thus may be of particular value for patients at risk for operative procedures. It may also provide more cosmetically acceptable results in the treatment of benign and malignant tumors of the breast. 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) (Fig. 1) and magnetic resonance imaging-guided HIFU (MRgHIFU) devices have been developed in Chongqing, China. MRgHIFU is mainly used to treat uterine fibroids [6]. In contrast, USgHIFU can also treat liver cancer, pancreatic cancer, breast cancer, bone cancer, and renal cancer [5]. This article reviews the clinical use of this innovative and potentially revolutionary technology in China.

2 HIFU ablation for bone cancer

Primary bone malignancies are relatively uncommon, occurring most frequently in children and young adults. Amputation has been traditionally used in the treatment of primary bone malignancies [7]. Over the past decades, a shift in practice toward limb salvage with intact local function has gradually evolved, leading recently to its use

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

as a standard procedure for primary bone malignancy. However, the procedure requires a tailor-made surgical plan for each patient and has high complication rates [8,9]. Allograft implantation is technically easier but carries the risks of disease transmission (e.g., hepatitis), immune rejection, nonunion, and bone resorption [10,11].

Up to the present, there has been a general consensus that ultrasound energy cannot enter bone at sufficient intensity for therapeutic ablation, because of energy attenuation by bone. However, thermal lesions can be achieved even transcranially in animals using focused ultrasound: where tumor receives partial or complete cortical destruction, HIFU can penetrate into the medullary space and achieve complete necrosis [12].

Chen *et al*. [13,14] first treated five patients with osteosarcoma who were not candidates for limb salvage surgery. After ultrasound treatment, blood supply to the tumor was reduced, and ^{99m}Tc-MDP bone scan demonstrated reduction in osteogenesis. All patients experienced reduction or elimination of pain related to the tumor and an improvement of range of motion in the affected 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*. [15] continued HIFU treatment in another 30 patients who had refused surgery. Complete regression was achieved in ten patients, and partial regression achieved in another 13.

After that, HIFU combined with chemotherapy was studied in 44 patients with a variety of primary bone tumors from December 1997 to May 2000 [13,16]. Among these patients, 34 were at stage IIb, with the remaining ten at stage IIIb. After an average of 23 (range 10–39) months of follow-up, a survival rate of 85% was reported.

Recently, Chen *et al*. [17] 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 on 62 patients with osteosarcoma, one with periosteal osteosarcoma and three 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 complete ablation of malignant bone tumors in 69 patients, with greater than 50% tumor ablation in the remaining 11 patients. Overall survival rates of one, two, three, four, and five years were 89.8%, 72.3%, 60.5%, 50.5%, and 50.5%, respectively. Survival rates of one, two, three, four, and five 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 HIFU 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 in one to two weeks after HIFU, even without 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, occurring in 10 of 80 patients or less. The following factors may be pertinent to nerve injury: (1) Nerves cannot be visualized by ultrasound imaging and are thus difficult to avoid in the beam path if the anatomical location of nerves has changed in the face of tumor; (2) Nerves are sensitive to ultrasonic energy; and (3) Tumors are often adjacent to nerves. Bone fracture, ligamentous laxity, epiphysiolysis, and secondary infection were also observed; however, all such patients recovered after surgical intervention.

Up to date, no prospective comparative trials have yet been published to evaluate the efficacy of HIFU compared to other therapies. However, a retrospective analysis has been conducted [18]. The results of conventional surgical treatment with chemotherapy carried out since 1993 in 67 patients in Korea have been compared with 71 patients treated with HIFU and chemotherapy in China since 1997. Average follow-up time was 46 months in Korea and 32 months in China. The overall survival rates were comparable: 78.5% in Korea and 76.1% in China. The five-year survival rates for stage II patients were 87.5% in Korea, 98.1% in China (full treatment protocol) and 56.6% in China (part protocol). Three-year survival rates in stage III patients were 20% (1/5 patients) in Korea and 7.1% (1/14 patients) in China.

HIFU is also effective for bone metastases. In Milan, Orsi *et al*. have treated some patients with bone metastases (Fig. 2). The pain score decreased from 10 out of 10 to 0–1 out of 10.

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.

3 HIFU ablation for liver cancer

Liver cancer is a comparatively frequent life-threatening malignancy. Surgery is the current standard of care in selected cases, offering a chance of cure by complete tumor removal. Radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), cryoablation, microwave coagulation, and laser-induced interstitial thermotherapy also offer potential local tumor control and occasionally achieve long-term disease-free survival. However, using these techniques remains difficult in treating tumors at problematic locations or advanced stages.

Over ten years ago, our group started to use USgHIFU to treat liver cancer. In 2001, Wu *et al*. [19] reported pathological changes in hepatocellular carcinoma (HCC) after extracorporeal ablation with 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 trans-catheter arterial chemo-embolization (TACE) [20]. 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 4–14 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

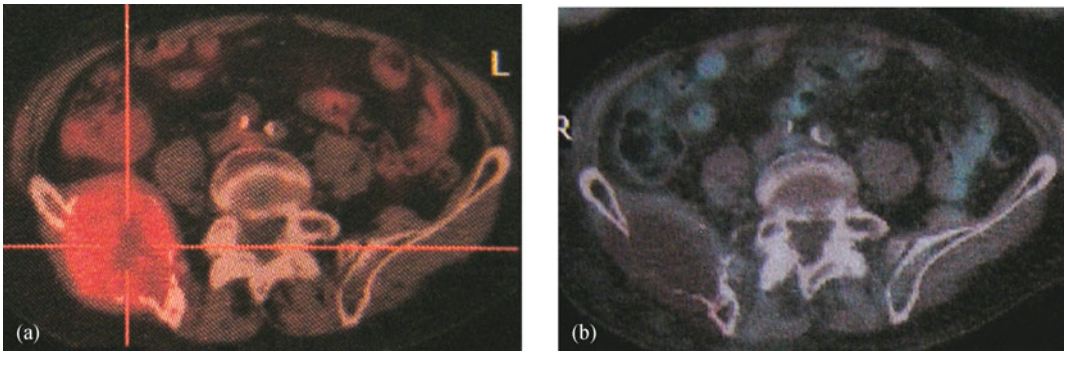

Fig. 2 PET-CT from a patient with iliac metastasis from multiple myeloma. (a) Pretreatment PET-CT image showing positive of the tumor; (b) one month posttreatment, PET-CT image showing negative of the tumor. Courtesy of Dr. Franco Orsi from the European Institute of Oncology, Milan, Italy. PET: positron emission tomography; CT: computed tomography.

42.9% and 0 in groups 1 and 2, respectively ($P < 0.01$).

In another study [21], patients received either HIFU plus supportive treatment (HIFU group, $n = 151$) or supportive treatment only (control group, $n = 30$), according to their willingness. A complete or a partial response was achieved in 28.5% ($n = 43$) or 60.3% ($n = 91$) of cases in the HIFU group. In contrast, the response rates were 0 and 16.7%, respectively, in the control group. In addition, the one- and two-year survival rates were 50.0% and 30.9% in the HIFU group, which were significantly higher than those in the control group (both $P < 0.01$).

In Oxford, UK, 22 patients with liver metastases were treated with USgHIFU. Twenty out of 22 patients were assessed by using either radiological images, such as MRI and contrast ultrasound, or histological examinations. The images revealed that the adverse event profile was favorable when compared to open or minimally invasive techniques [22].

Recently, Zhang *et al*. [23] reported that HIFU could achieve complete tumor necrosis even when the lesion was located adjacent to the major hepatic blood vessels. Indeed, there was no discernible damage to the major vessels, even though the adjacent tumor had been completely ablated. From November 2007 to April 2009, Orsi *et al*. [24] treated 17 patients with 24 liver metastases at difficult locations. 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 solid liver tumors at difficult locations.

4 HIFU ablation for pancreatic cancer

Pancreatic cancer is among the eight most common cancers. At present, surgery provides the best results; however, only less than 20% of patients are suitable for surgery when the diagnosis is made. For patients who cannot undergo operation, chemotherapy and radiotherapy can be alternative choices, but the role in local tumor control is limited. Thus, we attempted to find alternative treatment for these patients.

A prospective trial was first conducted on eight patients with advanced pancreatic cancer between December 2000 and September 2002 [25]. Patients with biopsy-confirmed cancer and a Karnofsy Performance Status of at least 70 were enrolled if they were considered unsuitable for surgical operation. Three patients had stage III disease, and five patients had stage IV disease. Five of the eight patients had liver metastases, and one had bone metastasis. All of the patients had constant localized pain.

Six patients underwent one HIFU session, and two patients underwent two sessions of treatment either under general or epidural anesthesia. After HIFU treatment, the pain associated with the pancreatic lesion was relieved in all patients during the follow-up period. In those patients who underwent contrast MRI, there was no enhancement in the treated region (Fig. 3). Reduction of tumor volume was observed in all patients, ranging from 20% to 70%. The median survival time was 11.25 months. Follow-up images were obtained every three to six months after HIFU ablation. Serum amylase and bilirubin remained at normal levels, and no complications were reported.

Wang *et al*. [26] reported on an extended population of 15 patients that included seven patients with lesions in the head of the pancreas. Thirteen of the 15 patients had pain associated with the cancer prior to treatment. Pain was fully alleviated in 11 patients and partly alleviated in the other two. Amylase levels rose slightly in one patient but returned to normal levels within two days after HIFU treatment, and two patients were treated with insulin for raised blood glucose levels. No serious complications occurred.

More recently, Orsi *et al*. [4] treated seven patients with USgHIFU between November 2007 and June 2009. All of the seven patients were almost completely palliated in symptoms in 24 h after treatment. The median survival time was 11 months. MDCT or MRI performed 24 h after treatment did not detect any injury of the surrounding organs, and all patients but one were as a precaution observed in hospital for three days. Portal vein thrombosis was observed in one patient who was discharged 20 days later. The amylase level showed no elevation over baseline in three days after treatment.

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

5 HIFU ablation for breast cancer

Breast cancer is the most common cancer in women and a leading cause of mortality. A variety of treatments may currently be used depending on tumor size, location, intraductal spread, and risk of recurrence. We hypothesized that HIFU could be a potential choice of treatment for breast cancer in the future.

The first randomized controlled clinical trial was conducted by our group in Chongqing [27]. In this study, patients were treated with either modified radical mastectomy ($n = 25$) or HIFU followed by modified radical mastectomy within one to 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 documented that coagulative necrosis occurred in the cancerous tissue and the safety margin. We also noted that the expression of cell nuclear antigen (PCNA), CD44v6, and metalloproteinase (MMP)-9 was significantly higher in the untreated cancerous tissue than that in the untreated normal

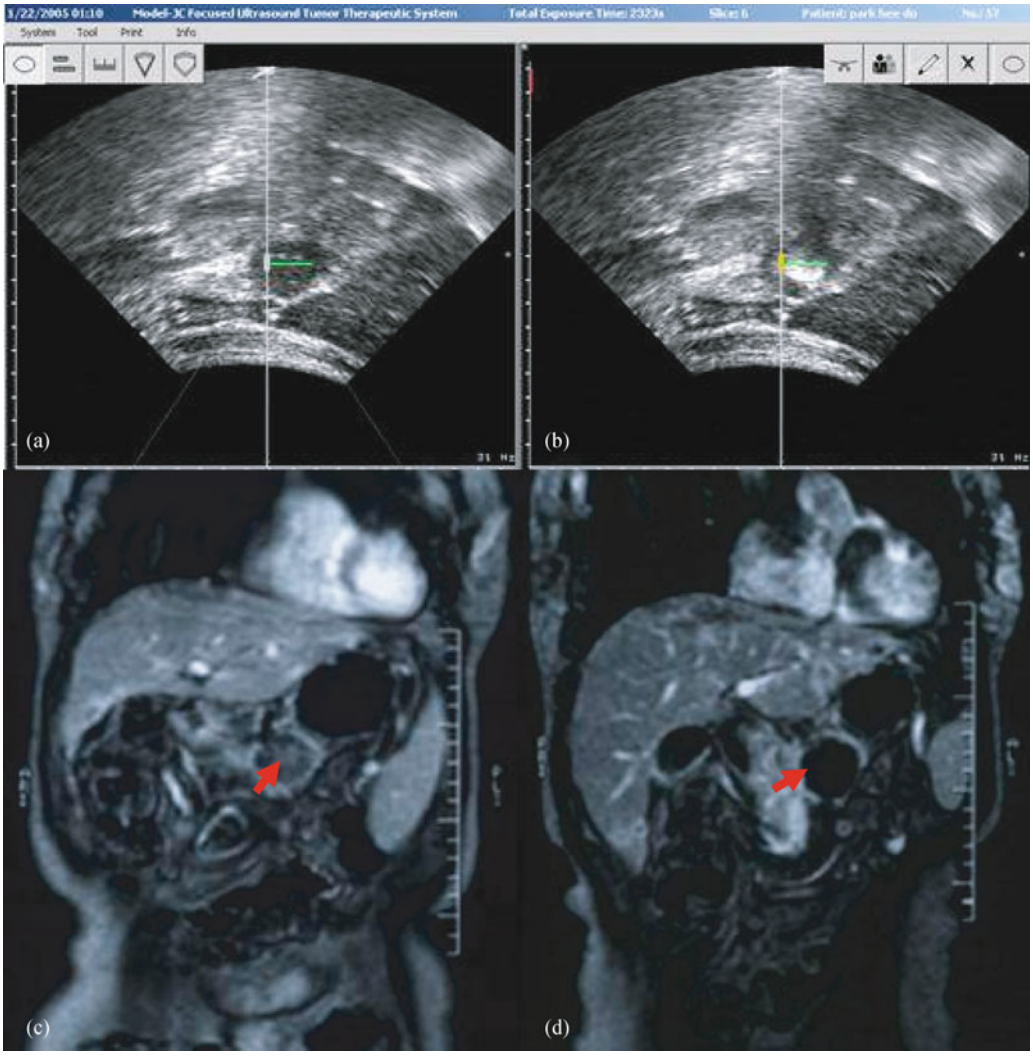

Fig. 3 Real-time ultrasonography and contrast-enhanced MR images from a patient with pancreatic cancer. (a) Real-time ultrasound image before HIFU treatment reveals a hypoechoic lesion; (b) real-time ultrasound image during HIFU treatment shows massive gray-scale change in the tumor; (c) pretreatment contrast-enhanced MRI shows perfusion in the tumor (arrow); (d) one month after HIFU treatment, contrast-enhanced MRI shows the treated tumor with no enhancement (arrow). MRI: magnetic resonance imaging; HIFU: high-intensity focused ultrasound.

breast tissue, while there was no expression in the HIFU-treated area. Additional histological analysis using NADH staining [28] confirmed complete necrosis.

In a nonrandomized prospective study [29,30], we evaluated the long-term clinical effects of HIFU. Twenty two patients with biopsy-confirmed breast cancer were enrolled if they were deemed either unsuitable for surgery ($n = 6$) or had refused surgical resection ($n = 16$). Using the tumor node metastasis (TNM) staging, four patients were at stage I, nine at stage IIA, eight at stage IIB, and one at stage IV. The tumor and surrounding margins of 1.5–2.0 cm were treated. Axillary lymph node dissection was performed on patients with stage IIB disease 4–8 weeks following ablation (except in three patients who refused the surgery). All patients received six cycles of adjuvant chemotherapy and radiotherapy after HIFU ablation. On the completion of the chemotherapy, two years of hormone therapy (tamoxifen) followed.

Absence of tumor blood flow was reported in 19 of 22 patients after HIFU treatment. Tumor decreased 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 two of the 21 patients were elected to have mastectomy as a result. It is noted that in the Chinese patient population, breast cancer is often

diagnosed at the advanced stage and that the average tumor size was larger than that which would typically be treated conservatively in the West (the typical size for conservative resection in China versus in the West is 4 cm *versus* 2 cm in diameter).

During the follow-up period, two patients with stage IIB disease developed local recurrence at the 18th and 22nd months. Modified radical mastectomy was performed, followed by chemotherapy in these two patients.

Five-year disease-free survival and recurrence-free survival were reported as 95% and 85%, respectively. Thus, HIFU seems to be a safe and effective treatment for patients with breast cancer.

Currently, another clinical trial is underway at the European Institute of Oncology (Milan, Italy), wherein 12 patients with small breast cancers (< 1.5 cm) have been treated with USgHIFU. All tumors were resected for pathologic evaluation after HIFU. The pathologic results showed that all the tumors were completely ablated. Even though local edema was observed in 30% of the patients, the edema usually subsided in one day. No other side effects were observed.

6 HIFU ablation for renal cancer

Renal cancer may also be treated with this noninvasive approach. Wu *et al*. [31] performed HIFU treatment in 12 patients with advanced stage renal cell carcinoma and one patient with colon cancer metastasized to kidney. All the 13 patients received HIFU treatment safely, including ten who had partial ablation and three who had complete tumor ablation. After HIFU, hematuria disappeared in seven of eight patients, and the flank pain of presumed malignant origin disappeared in nine of ten 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 either cure or palliation.

In Oxford, UK, the extracorporeal, ultrasound-guided Model-JC Tumor Therapy System (Haifu Tech Co. Ltd., China) has been used to treat patients with renal cancer. After a single therapeutic HIFU session under general anesthesia, the results were evaluated with either radiological images, such as MRI, contrast ultrasound, or histological examinations. The results revealed that the adverse event profile was favorable when compared to open or minimally invasive techniques [22].

A number of other patients in Oxford were also treated outside any trials. A patient with a 5-cm biopsy-proven renal cell carcinoma in a transplanted 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 situated in the groin area, and thus, ribs do not pose a problem for beam penetration. Furthermore, perinephric fat, which on occasion seems to impair treatment, is no longer present. This patient was obese and suffered 1° skin burns, but these healed with conservative treatment.

A new kidney trial is currently underway in Oxford, UK. Fifteen patients have been screened and, to date, four treated with HIFU. The protocol allows suitable patients with renal tumors under 4 cm to enter into the study. The renal tumor is biopsied under CT guidance. The result of this trial should be available in 2011.

7 HIFU ablation for uterine fibroids

Uterine fibroid tumors (or leiomyomas) are the most common benign tumors in the female genital tract. The frequency of uterine fibroids is different across races and generally reported as 20% to 40% among reproductive age women [32]. Depending on their location and size, they may lead to heavy bleeding, pain, and miscarriage. Hysterectomy is the definitive treatment for uterine fibroids, since such benign tumors cannot recur after total uterus removal. However, this operation is unsuitable for patients wishing to remain fertile. Myomectomy can be performed on patients who wish to retain their uterus, but cumulative uterine fibroid recurrence rates of 12 and 24 months after abdominal myomectomy were 12.4% and 46.0%, respectively [33]. The requirement for further surgery is high, and these surgical procedures are associated with morbidity in about 17% to 23% of cases [34]. As a noninvasive technique, HIFU is a potential treatment of choice for benign tumors, because these tumors do not require complete excision.

In October 2004, MRgFUS has received US Food and Drug Administration (FDA) approval for treatment of uterine fibroids. In China, Wang *et al*. [35] reported their preliminary results of HIFU treatment of symptomatic uterine fibroids in 2002. This was the first clinical study on HIFU ablation for uterine fibroids. Between July 2001 and January 2003, He *et al*. [36] treated 23 patients with HIFU at one center. Patients were enrolled if they did not wish to have hysterectomy and if the fibroids were between 4 and 8 cm in diameter and located at the anterior wall of uterus. The results showed that the average volume of menstruation and uterine volume decreased throughout the follow-up period. The average size of uterine fibroids was reduced in 17 patients, and a mean reduction of 78.9% was achieved. The fibroid in one patient was resected because of persistent menorrhagia. The histopathological results demonstrated that tissues around the treated area were undamaged. Unfortunately, four patients had temporary numbness on the lower limbs because of the damage to the sciatic nerve, which is now avoided by changing the treatment protocol.

In 2004, Wu *et al*. [5] reported the use of HIFU in treatment of 85 patients with uterine fibroids between 1997

and 2001 at some centers in China.

Currently, this technique has been clinically considered as an alternative treatment for patients with uterine fibroids in China. MRI images are presented in this review (Fig. 4).

In Spain, 54 patients with uterine fibroids less than 13 cm in diameter were treated in the Hospital Mutua de Terrassa from January to December 2009. All treatments were performed with an average power of 370 W. The operating time was from two to five hours. No patient complained postoperative pain at 4 h after HIFU, and all patients resumed to normal functional status within 24 to 48 h after 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. Notable were the concomitant reduction in symptom severity with an increase in quality of life, which persisted for 6–12 months. Such clinical improvement was correlated to fibroid size reduction. In early 2010, the first baby conceived after treating a fibroid with HIFU therapy was born in Mútua (Hospital Mutua de Terrassa). On Saturday, he was born in the University Hospital Mútua de Terrassa. His weight was 3.230 kg. This baby could be one of the more than two thousand babies born each year in this hospital. However, the circumstances have made this event a milestone in the Department of Obstetrics and Gynecology run by Dr. Antoni Pessarrodona.

In the Medical Center of Central Bank, Moscow, Russia, Khitrova wrote us that she treated 61 patients with 143 fibroids (1–7 lesions per patient) by HIFU. There were no major complications after treatment; only two patients with submucous fibroids experienced two-day temperature elevation (to 38.5°C). No skin burns or nerve damage occurred. All clinical signs later disappeared, and two pregnancies subsequently occurred in two patients.

8 Other applications

HIFU has been used successfully for the treatment of soft tissue sarcoma in China [5]. It has been used as an organ preserving treatment in patients with uterine adenomyosis [37]. The cyclic pain disappeared in all patients during a mean follow-up of 18.7 months.

9 Conclusions

These results from different groups are consistently encouraging. Based on the results from clinical trials and studies, we conclude that ultrasound-guided HIFU ablation can achieve substantial tumor responses with only minimal and transient adverse effects. Thus, HIFU seems to be emerging as a safe, effective, and feasible modality for the destruction of both benign and malignant solid tumors.

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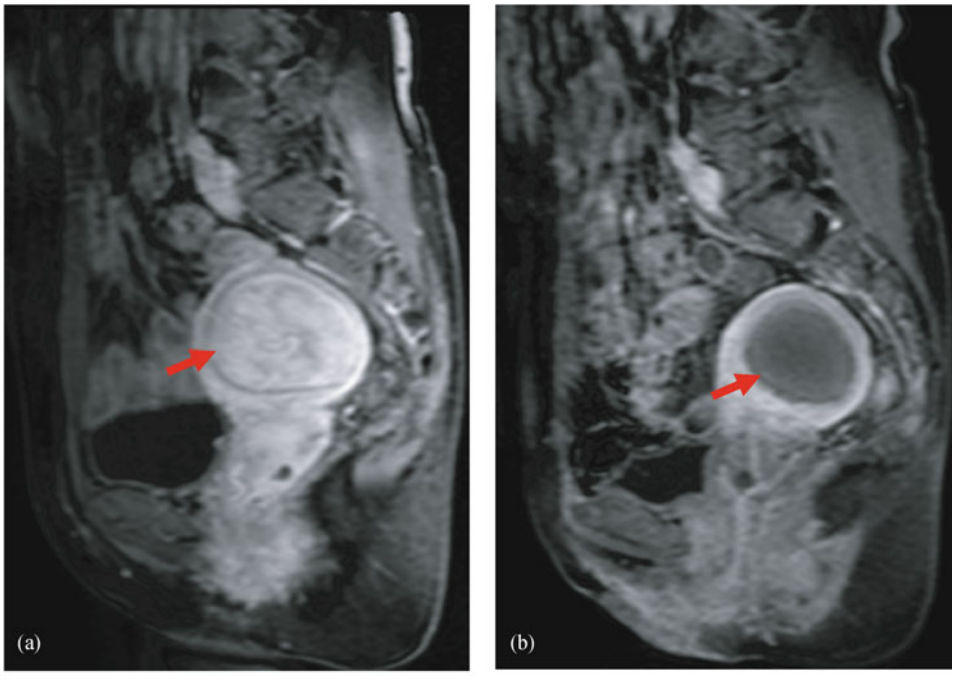

Fig. 4 Contrast-agent-enhanced MRI from a patient with uterine fibroids. (a) Pretreatment image showing the fibroid with enhancement (arrow). (b) One month posttreatment, MRI showing the fibroid shrunk with no enhancement (arrow). MRI: magnetic resonance imaging.

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