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# CLINICAL USE OF HIGH-INTENSITY FOCUSED ULTRASOUND IN THE MANAGEMENT OF DIFFERENT SOLID TUMORS

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**Absract:** *High-Intensity Focused Ultrasound (HIFU) is a new non invasive technique that induce the ablation of tumors without damaging overlying and adjacent structures. This technique can be used clinically to treat solid tumours (both malignant and benign), including those of the prostate, liver, breast, kidney, bone and pancreas and may represent a valid alternative technique for the palliative treatment of this advanced cancer. The nonsurgical ablation methods are thought to be psychologically and cosmetically more satisfactory and more easily accepted by patients. HIFU therefore may play a key role in future clinical practice and may offer patients another choice when no other treatment available or when patient refused surgical operation.*

**Key words:** *Ultrasound, Non-invasive technique, Ablation, Cancer treatment, Palliative care.*

## INTRODUCTION

High-Intensity Focused Ultrasound (HIFU) is a novel non invasive technique that is capable of inducing coagulative necrosis of target lesion within the body, without requiring surgical exposure or insertion of applicators. This technique can induce the ablation of tumors without damaging overlying and adjacent structures. The therapeutic capacity of high focused ultrasound was introduced in 1940s by Lynn et al[1]. Technique was not developed at that time because of inadequate targeting methods. The advent of more sophisticated imaging has led to a resurgence of interest in HIFU. Currently, both B-mode ultrasonography (US) and magnetic resonance imaging (MRI) have been incorporated into HIFU devices[2].

HIFU devices for clinical use fall into three main categories: extracorporeal, transrectal, and interstitial. Extracorporeal transducers are used for targeting organs that are readily accessible through an acoustic window on the skin, whereas transrectal devices are used for the treatment of the prostate and interstitial probes are being developed for the treatment of biliary duct and esophageal tumors[3].

In several centers worldwide, HIFU is now being used clinically to treat solid tumours (both malignant and benign), including those of the prostate, liver, breast, kidney, bone and pancreas.

HIFU may also be a useful modality for palliation of cancer-related pain[4] (Table 1).

The aim of this article is to review the clinical use of this technology in the management of different types of solid malignant and benign tumors.

## HIFU PRINCIPLES

The typical diagnostic US (B-mode, pulsed or continuous Doppler) uses frequencies in the range of 1-20 MHz, the time-averaged intensities can be up

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**Table 1.**

| Site | Authors | Treatment | Patients | Outcomes |
|---|---|---|---|---|
| Prostate | Chaussy C et al [13] | Curative | 184 | 80% of patients were cancer free. tumor mass was reduced more than 90%. nadir PSA <4 ng/mL in 97%, 61% < 0.5 ng/mL |
| | Blana et al [14] | Curative | 146 | 87% PSA level < 1 ng/mL; 93.4% patients had negative control biopsies. |
| | Blana et al [19] | Curative | 163 | 92.7% had negative post-treatment biopsy findings. 86.4% nadir PSA < 1 ng/mL |
| Bone | Chen W et al [23] | Curative | 44 | survival rates were 84.1 |
| | Chen W et al [24] | Curative | 80 | survival rates at 1, 2, 3, 4, and 5 years were 89.8%, 72.3%, 60.5%, 50.5%, and 50.5%, respectively |
| | Liebermen et al [25] | Palliative | 25 | 72% of the patients (18/25) reported significant pain improvement |
| Liver | Wu F et al [28] | Palliative | 50 | 6 mo survival rate was 80.4%: 85.4% in group 2 (HIFU + TACE) and 13.2% in group 1 ($p < 0.002$) (only TACE). 1-year survival rate was 42.9% and 0%, respectively |
| | Li YY et al [29] | Palliative | 151 HIFU group; 30 control group | Response rate: HIFU group 88.8%; control group 16.7% ($p < 0.01$). Survival rates: HIFU group 50.0% (1 y) and 30.9% (2 y); control group 3.4% (1 y) and 0% (2 y) (both $p < 0.01$). QOL score: 83.1 +/- 8.0 at 3 months after HIFU, pre-HIFU score was67.7 ± 5.9; at 3 months after treatment (69.0 ± 8.5) in the control group (both $p < 0.05$). |
| | Zhang L et al [30] | Palliative | 39 pat with 42 lesions | 21/42 complete tumor necrosis; 21/42 ablated than > 50%. survival rates: 75.8% (1 y), 63.6% (2 y), 49.8% (3 y), 31.8% (4 y), 31.8% (5 y) |
| | Illing RO et al [31] | Palliative | 22 | 100 % Ablation |
| | Orsi et al [32] | Palliative | 31 | 29/31 responsive. Survival rates 88.2% 2y |
| Pancreas | Wu F et al [3] | Palliative | 8 | Median survival time was 11.25 months (range, 2-17 months). |
| | Wang X et al [35] | Palliative | 15 | Clinical symptoms such as pain were significantly alleviated. Eating, sleeping and mental status were all markedly improved. |
| Breast | Wu F et al [43] | Curative | 23 | HIFU treatment induced complete coagulative necrosis of the target tissue |
| | Wu F et al [44] | Curative | 22 | Five-year disease-free survival and recurrence-free survival were 95% and 89%, respectively. Cosmetic result was judged as good to excellent in 94% of patients. |
| | Furusawa et al [45] | Curative | 21 | Median period of observation is 14 months (range: 3-26). One case of recurrence |
| Kidney | Wu F [47] | Palliative | 13 | Of the 13 patients 7 died (median survival 14.1 months, range 2 to 27) and 6 were still alive with median followup of 18.5 months (range 10 to 27). |
| | Ritchie RW [48] | Palliative | 17 | Achieves stable lesions in two-thirds of patients, with minimal morbidity, |
| Uterine fibroid | He et al [50] | Curative | 23 | The average size of uterine fibroids was reduced in 17 patients, and a mean reduction of 78.9% was achieved |
| | Ren XL [52] | Curative | 119 | Median reductions in tumor size as a percentage of initial tumor volume at 1, 3, 6, and 12 months after HIFU treatment were 21.2%, 29.6%, 44.8%, and 48.7%, respectively |

to 720 mW/cm$^2$. By contrast, frequencies of 0.8-3.5 MHz are generally used during the clinical applications of HIFU, and the energy levels of HIFU in the focal region is about several orders higher, 100-10 000 W/cm$^2$, with peak compression pressures of up to 70 MPa and peak rarefaction pressures up to 20 Mpa[3].

The energy released can be directed to a small target sparing the surrounding tissue. Mechanisms of tissue destruction are thermal effect and cavitation. The fundamental physical mechanism of HIFU, ultrasound absorption and conversion into heat, was first described in 1972[5]. Both diagnostic ultrasound and HIFU heat tissue, however, since

the heating rate is proportional to the ultrasound intensity, the thermal effect produced by diagnostic ultrasound is negligible. In HIFU tissute temperature within the focal regions instantly elevated to 65-100 °C within 1 second HIFU exposure, and therefore coagulation necrosis is immediately induced in the tumor. Cavitation is the formation and then immediate implosion of cavities in a liquid. Intracellular water may enter the gaseous phases, wich would lead to the development of micro-bubbles. When they reach the size of resonance, these bubbles suddenly collapse and produce high-pressure shock waves, destroing tumor tissue. Small tumor blood vessels, a diameter of less than 2 mm, can be absolutely destroyed by HIFU, resulting in secondary effect of HIFU on the target tumor.

## PALLIATIVE CARE

WHO Definition of Palliative Care is "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"[6]. The aim of Palliative Care, in advanced disease, is to relieve the patients from pain and other distressing symptoms and improve quality of life. Palliative treatment may be surgical, chemotherapy or radiotherapy.For exemple, surgical treatment is made in metastatic colorectal cancer[7]. A palliative surgical resection of the primary tumor can be performed to prevent tumor-related complications, such as obstruction, bleeding and perforation, and thus to minimize cancer-related morbidities. Any chemotherapy regimens may help relieve the symptoms of advanced stage cancer[8,9], such as lessening pain, improving a patient's energy and appetite, and stopping or slowing weight loss. Although painful bone metastasis is the most common reason for the delivery of palliative radiotherapy, approximately 66% of palliative radiotherapy is delivered for the management of other clinical conditions such as brain metastases, the masses mediastinal tumors and advanced tumor lesions very responsible for bleeding disorders[10]. A new valid alternative technique for the palliative treatment of advanced cancer is High-Intensity Focused Ultrasound. The first studies suggest efficacy and safety of HIFU ablation in the treatment of advanced stage malignacy. This technique could be an important alternative to surgery especially for patients with comorbility and show an important effect in the treatment of cancer pain.

## CLINICAL APPLICATION

### *Prostate cancer*

Prostate cancer is the leading malignancy in men and the second most common cause of cancer-related mortality in the Western World. The recommented treatment for patient with T1-2, N0, M0 prostate carcinoma who have a life expectancy exceeding 10 years is radical prostatectomy[11,12] Several alternative treatments have been developed to treat localized prostate carcinoma in patients unfit for surgery or unwilling to experience its side effects. Brachytherapy, cryosurgical ablation of the prostate (CSAP), and (conformal) radiotherapy have all been applied. A new therapeutic option for prostate cancer is HIFU ablation by transrectal device. A number of studies have indicated that transrectal HIFU enables minimally invasive local prostate tissue ablation with high rates of negative biopsies[13], low PSA nadir[14], and low complication rate[15]. Complications reported from prostate HIFU include hematuria, urinary obstruction, urethral stricture and incontinence. HIFU treatment can be repeat but it is associated with much higher complication rates than single treatment[16]. Some studies reported has been evaluated the impact of a combined transurethral resection of the prostate (TURP) and HIFU to mitigate urinary retention associated with concomitant prostate enlargement[17]. In France, from February 1993 and January 2007 a total of 803 patients from six urologic departments were treated using HIFU with curative intent. Local control and disease free survival rate (DFSR) achieved with HIFU were similar to those expected with conformal external-beam radiation therapy (EBRT). The excellent cancer-specific survival rate is also explained by the possibility to repeat HIFU and use salvage EBRT[18]. A study by Blana et al[19] after long-term follow-up have indicated that HIFU is an efficient and safe treatment for patients with localized prostate cancer. Comparative data from four studies[18-21] are listed in Table 2. Studies conducted so far suggest that HIFU is a valid alternative technique for the treatment of prostate cancer. I made a long-term follow-up showed the safety of the technique could be an important alternative to surgery especially for patients with comorbility.

### *Bone cancer*

Primary bone malignancies are relatively uncommon, occurring most frequently in children and young adults. Surgical removal and radiation therapy are commonly used strategies to treat bone tu-

**Table 2.**

| | Crouzet S et al[18] | Blana et al[19] | HM Lee[20] | T. Uchida[21] |
|---|---|---|---|---|
| ***Stage n° patients*** | | | | |
| T1 | 481 | 39 | 32 | 92 |
| T2 | 322 | 124 | 26 | 89 |
| ***Gleason score*** | | | | |
| ≤6 | 510 | 138 | 30 | |
| 7 | 242 | 25 | 17 | |
| ≥8 | 48 | - | 11 | |
| ***Risk group*** | | | | |
| Low | 323 | 84 | 13 | 52 |
| Intermedie | 372 | 79 | 26 | 81 |
| High | 108 | - | 19 | 48 |
| ***Mean age*** | 70,8 | 66 ± 7,1 | 70 ± 5,7 | 70 |
| ***Mean PSA before HIFU ng/ml*** | 9,1 | 7,9 ± 3,7 | 10.9 ± 6.4 | 9,76 |
| ***Mean PSA after HIFU ng/ml*** | 1 ± 2,8 | <0.2 (64%); 0.21-1 (18.5%); >1 (14%) | 0,6 | |
| ***Control biopsies*** | 85 % negative | 92,7 % negative | 50 % negative | |
| ***Follow-up mean*** | 42±33 months | 4,8 ±1,2 y | 14 ± 4 months | 18 months |

mors. First Smith et al[22] found that focused US beams can target bone tissues and induce necrosis of osteocytes in normal rabbits.

Chen et al[23] to develop a new non invasive limb-salvaging method in the treatment of primary malignant bone tumor in the extremities studied the combination of HIFU and chemotherapy in 44 patients. After a mean follow-up time of 17.6 mo, the overall survival rate was 84.1%. For the 34 cases of stage IIb, 30 cases continued to survive disease-free, 2 died of lung and brain metastases, and the other 2 had local recurrence. Among 10 of the stage IIIb cases, 5 survived with tumor, 1 had local recurrence, and 5 died of lung metastases.

In another study Chen et al[24] to evaluate the long-term follow-up results of ultrasonographically USgHIFU ablation in patients with primary bone malignancy were treated 80 patients with a primary bone malignancy – 60 with stage IIb disease and 20 with stage III disease (Enneking staging system) – with US-guided high-intensity focused ultrasound ablation. High-intensity focused ultrasound ablation combined with chemotherapy was performed in 66 patients. The remaining 14 patients were treated with high-intensity focused ultrasound ablation only. 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.

Liberman et al[25] have used HIFU ablation for Pain Palliation in Patients with Bone Metastases. 25 patients underwent the planned treatment and were available for 3 months post treatment follow-up. 72% of the patients (18/25) reported significant pain improvement. Average VAS score was reduced from 5.9 prior to treatment to 1.8 at 3 months post treatment. 67% of patients with recorded medication data reported a reduction in their opioid usage. These studies suggest efficacy and safety of HIFU ablation in the treatment of primary and secondary bone tumors. Data indicate an important effect in the treatment of pain from bone metastases. HIFU ablation may acquire considerable importance as limb-sparing technique.

## *Liver cancer*

Hepatocellular carcinoma (HCC) is one of the most common malignant tumours around the world[26]. Surgery is the current standard of care in selected cases, offering a chance of cure by complete tumor removal. Other techniques such as 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. These patients could be treated by extracorporeal ablation with HIFU.

In 2001, Wu et al[27] treated 56 patients with HCC. Of the 56 patients treated, 6 underwent surgical resection of the tumor 5 to 18 days following HIFU treatment. The resected specimens were examined under light and electron microscope. Light microscope examination showed clear boundary between the treated and untreated area. Outside of the boundary the hepatic parenchyma was almost normal. In the treated area, all tumor cells appeared irreversibly dead in the forms of nuclear pyknosis, debris, and dissolution. The blood sinusoids were collapsing with endothelial cell damage. Granulation tissue was formed with the presence of immature fibroblasts and new capillaries in the boundary region between treated and untreated area. Eighteen days after HIFU treatment, the ultrasound damaged area was partially replaced by the proliferative repair tissue. Electronic microscopic examination showed the distorted tumor cells with severe destruction of cell organelles and nuclei. The cytoplasm was irregularly vesiculated, and the membranes of the organelles were broken. Cell membrane and nuclear membrane disintegration, as well as nucleus disruption were generally observed.

From November 1998 to May 2000 Wu F et al[28] treated by the combination of USgHIFU ablation and transcatheter arterial chemoembolization (TACE) 50 consecutive patients with stage IVA HCC (TNM classification, T4N0-1M0). Patients were alternately enrolled in one of two treatment groups: group 1 (n = 26), in which TACE was performed alone, and group 2 (n = 24), in which transcutaneous ablation of HCC with high-intensity focused ultrasound was performed 2-4 weeks after TACE. The tumors were 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 blood supply 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 6-month survival rate was 80.4%-85.4% in group 2 and 13.2% in group 1 ($p = 0.002$), and the 1-year survival rate was 42.9% and 0%, respectively. Median reductions in tumor size as a percentage of initial tumor volume at 1, 3, 6, and 12 months after treatment, respectively, were 28.6%, 35.0%, 50.0%, and 50.0% in group 2 and 4.8%, 7.7%, 10.0%, and 0% in group 1 ($p < .01$).

Short and long term efficacy of high intensity focused ultrasound therapy (HIFU) in patients with advanced HCC has been studied by Li et al[29]. Patients with surgically unresectable HCC were enrolled in two treatment groups (151in HIFU group, 30 in control group). The response rate (88.8%) was significantly greater in the HIFU group (16.7%) than in the control group ($p < 0.01$). The 1- and 2-year survival rates were 50.0% and 30.9%, respectively, in the HIFU group, which were significantly greater than those (3.4% and 0%, respectively) in the control group (both $p < 0.01$). The QOL score was 83.1 ± 8.0 at 3 months after HIFU, which was significantly greater than the pre-HIFU score (67.7 ± 5.9) and the score at 3 months after treatment (69.0 ± 8.5) in the control group (both $p < 0.05$).

Zhang et al[30] enrolled thirty-nine patients with unresectable HCC (37 patients with 1lesion, one with 2 lesion, one with 2 lesion). The distance between the tumor and major blood vessels (inferior vena cava, main hepatic vein branches, and the portal vein and its main branches) was less than 1 cm. Indeed, there was no discernible damage to the major vessels, even though the adjacent tumor had been completely ablated. Comparative data from two studies [28-30] are listed in Table 3.

HIFU used to treat liver metastases. Illing et al[31] and Orsi et al[32] treated respectively 22 and 17 patients with liver metastases at difficult locations. In both studies ultrasound-guided focused ultrasound treatment appears to be feasible and safe for ablation of primary and metastatic liver tumors, and lymph node metastasis in difficult locations, with a favourable side-effect profile.

**Table 3.**

| *Characteristic* | *Zhang L et al[30]* | *Wu F et al[28]* |
|---|---|---|
| No of patients | 39 | 50 |
| Sex (male/female) | 23/16 | 36/14 |
| Mean age (y) ± DS | 53.2 ± 12.3 | 45.8 ± 10.5 |
| HBV ± | 20/19 | 38/12 |
| No of lesion | 47 | 126 |
| Lesion diameter (cm | | |
| <5 | | 1 |
| 5-10 | | 20 |
| >10 | | 29 |
| Mean | 7.36 +- 4.25 | 10.6 |
| Child-pugh class | | |
| A | 39 | 48 |
| B | 0 | 2 |
| C | 0 | 0 |
| TNM | | |
| I | – | – |
| II | 16 | – |
| III | 12 | – |
| IV | 11 | 50 |

The articles data indicate efficacy of HIFU in HCC or liver metastates. USgHIFU ablation can be considered as a safe and feasible approach for treating solid liver tumor. Interesting is the possibility of using HIFU with other techniques such as TACE in advanced tumors or as a palliative technique in unresectable tumors to improve the quality of life of patients.

### *Pancreatic cancer*

Pancreatic cancer is among the eight most common cancers. At present, only less than 20% of patients have a resectable cancer when the diagnosis is made. For patients with inoperable cancer chemotherapy and radiotherapy can be alternative choices, but the role in local tumor control is limited. The prognosis of patients with pancreatic cancer is one of the worst among all cancers. From the EUROCARE study, based on 31,312 European cases, overall survival at 1, 3 and 5 years was 16%, 5% and 4%, respectively[33]. Several studies have been reported on the use of HIFU treatment in pancreatic cancer (Table 4). These reports, investigated the use of HIFU as monotherapy or as combination therapy with chemotherapy. In general, these reports suggest that HIFU treatment reduce the size of pancreatic tumors without causing pancreatitis. An interesting finding is that over 80% of patients with pain due to pancreatic cancer obtained significant relief of their pain after treatment with HIFU. Furthermore, no significant adverse effects were reported in any of these studies.

Pancreatic cancer in most cases diagnosed when the cancer is advanced, this means that HIFU can be an important tool for the treatment of pancreatic cancer. HIFU can be an important help to improve the quality of life of patients.

### *Breast cancer*

Breast cancer with more than 1 million cases diagnosed worldwide each year, is the most frequent cancer in women. Breast cancer treatment has moved from the radical to conservative surgery. To treat patients with minimally conservative procedures and to safeguard the quality of life and the cosmetic appearance of the breast has been evaluated the efficacy and safety of HIFU in women with breast cancer.

The first randomized controlled clinical trial was conducted by Wu et al[43]. In this study, 48 patients were randomised to two treatment groups: the control group (n=25), in which modified radical mastectomy

**Table 4.**

| *Author* | *Year* | *N° of patients* | *Treatment* | *Pain relief* | *HIFU related adverse effects* | *Stage* | *Median survival time* |
|---|---|---|---|---|---|---|---|
| Xiong [34] | 2001 | 21 | HIFU | 88% | None | – | – |
| Wang X [35] | 2002 | 15 | HIFU | 100% | None | Late stage | – |
| Xie [36] | 2003 | 41 | HIFU vs HIFU + gemcitabine | 66,7% | | | |
| | | | | 76,6% | None | _ | _ |
| Xu [37] | 2003 | 37 | HIFU | 80% | None | _ | _ |
| Yuan [38] | 2003 | 40 | HIFU | 80% | None | _ | _ |
| Wu [3] | 2005 | 8 | HIFU | 100% | None | III (3), IV(5) | 11,25 months |
| Xiong [39] | 2009 | 89 | HIFU | 80,6% | Superficial skin burns (3.4%), subcutaneous fat sclerosis (6.7%), asymptomatic pancreatic pseudocyst (1.1%) | II (4), III (39), IV (46) | 26.0 months for stage II, 11.2 months for stage III, 5.4 months |
| Zhao [40] | 2010 | 39 | HIFU + gemcitabine | 78,6% | Grade 3-4 neutropenia (6). Grade 3 thrombocytopaenia (2). Grade 3 nausea/vomiting(3), and diarrhea (2). Grade 1 or 2 fever (27) | | 12,6 mo |
| Orsi [32] | 2010 | 6 | HIFU | 100% | Portal vein thrombosis (1) | Advanced | 7 mo |
| Sung [41] | 2011 | 46 | HIFU | ? | None | III (18), IV (28) | 7 mo |
| Wang K [42] | 2011 | 40 | HIFU | 87,5% | None | III (13), IV (27) | 8 mo |

was performed without any intervention prior to surgery; or the HIFU group (n=23), in which extracorporeal in situ ablation of the breast cancer with HIFU was followed by modified radical mastectomy within 1-2 weeks. In all cases, the treated area included the tumour and a 1.5-2.0 cm margin of normal breast tissue around the tumour. In all cases, macroscopic examination showed that HIFU treatment induced complete coagulative necrosis of the target tissue, which included the tumour and a normal breast tissue surrounding the tumour. Another study[44], conducted in Chongqing University of Medical Sciences (China), evaluated the long-term clinical results of HIFU. 22 patients received breast conservation treatment with HIFU. After a mean follow-up time of 54.8 mo, 1 patient died, 1 was lost, and 20 were still alive; 2 of 22 patients developed local recurrence; 5-year disease free survival and recurrence-free survival were 95% and 89%, respectively; Furusawa et al[45] treated twenty one cases of invasive/noninvasive ductal carcinoma. After a median period of observation of 14 months (3-26 months) one case of recurrence of pure mucinous carcinoma was experienced. In 2009 HIFU was used in a breast cancer nodal metastasis[46]. The patients was a 69-year-old woman with a past positive oncologic history for a malignant tumor in the left breast which was treated with quadrantectomy and sentinel lymph node excision. During follow-up ultrasound (US) scan a single 30-mm hypoechoic solid mass was detected close to the hepatic hilum and was considered likely to be a metastatic lymphnode. After biopsy of the mass pathology and immunohistochemistry confirmed the presence of metastatic cells from breast cancer. The patient was also not considered suitable for surgery or percutaneous ablation due to her history of cardiac failure, comorbidities and the potential risk of thermal injury of the adjacent structures. TC 24 h after treatment showed lack of enhancement in approximately 90% of the lesion's volume. Follow-up MDCT performed at 5 and at 8 months later showed decreased size of the mass with persistant lack of enhancement, suggesting successful lesion ablation. All studies have demonstrated the safety and effectiveness of HIFU ablation in the treatment of breast cancer. Side effects were infrequent, the most frequent was skin burns. The results of these studies suggest a possible future use of this technique which combines medical care, low psychological impact, and and a good aesthetic appearance of the breast treated.

### *Renal cancer*

Renal cell carcinoma (RCC) is one of the most common urological malignancies. Surgery is the only curative modality in the treatment of RCC. Renal cancer may also be treated with HIFU.

HIFU ablation of renal tumors in humans remains in the early stages of clinical trials.

Wu et al[47] 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 7 of 8 patients and flank pain of presumed malignant origin disappeared in 9 of 10 patients. Postoperative images showed decrease in or absence of tumor blood supply in the treated region and significant shrinkage of the ablated tumor. Of the 13 patients 7 died (median survival 14.1 months, range 2 to 27) and 6 were still alive with median followup of 18.5 months (range 10 to 27).

Ritchie RW et al[48] treated 17 patients (mean tumour size 2.5 cm) with radiologically suspicious renal tumours who underwent extracorporeal HIFU. Of the 17 patients, 15 were treated according to protocol; two procedures were abandoned due to intervening bowel. There were no major complications related to HIFU. Radiological evidence of ablation was apparent at 12 days in seven of the 15 patients. Before the 6-month follow-up one patient had surgery due to persisting central enhancement. Fourteen patients were evaluated at the 6-month follow-up; eight tumours had involuted (mean 12% decrease in tumour area). Four patients had irregular enhancement on imaging and had alternative therapies. Ten patients remain on follow-up at a mean (range) of 36 (14-55) months after HIFU (mean 30% decrease in tumour area). There was central loss of enhancement in all. Renal HIFU could be safe and feasible in the treatment of patients with advanced renal malignancy. Further trials with accurate follow-up are essential to fully evaluate this novel technique.

### *Uterine fibroid*

Uterine fibroid tumors (or leiomyomas) are the most common benign tumors in the female genital tract. Whereas many patients remain asymptomatic, others experience symptoms such as pelvic pain, menorrhagia, dysmenorrhea, dyspareunia, urinary frequency, and infertility. The first clinical study on HIFU ablation of symptomatic uterine fibroids was by Wang et al[49].

Between July 2001 and January 2003, He et al[50] treated 23 patients with HIFU at one center. The results showed that the average volume of menstruation and uterine volume decreased throughout the followup period. The average size of uterine fibroids was reduced in 17 patients, and a mean re-

duction 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[51] 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. 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. The data showed a significant improvement in Uterine Fibroid Symptom and Quality of Life (UFS-QOL) scores.

In a study performed by Ren et al[52] from May 2004 to June 2005, 119 consecutive patients with 187 uterine fibroids were treated with HIFU. Sixty-two fibroids received ultrasonographically guided needle puncture biopsy 1 week before and after HIFU treatment, respectively, to confirm the diagnosis and to assess the early therapeutic efficacy. Hematoxylin-eosin staining and electron microscopy were performed to characterize more subtle phenotypic changes to determine treatment success. Immediate therapeutic effects were assessed at follow-up with Doppler ultrasonography and computed tomography or magnetic resonance imaging. All patients were followed for 6 to 12 months to observe long-term therapeutic effects. Fibroid mean diameters, volumes, and reduction rates 1, 3, 6, and 12 months after HIFU treatment were calculated and compared with 1-way analysis of variance and Student-Newman-Keuls tests. No severe complications were observed after HIFU ablation. Fifty-one (82.3%) of 62 biopsy specimens revealed obvious signs of necrosis under light microscopy, and more subtle changes in cellular structure that indicated nonviability could be found in 60 specimens (96.8%) under electron microscopy. However, viable cells still could be found in 16 specimens (25.8%). Follow-up images showed absence or reduction of blood supply in the lesions after HIFU ablation. Median reductions in tumor size as a percentage of initial tumor volume at 1, 3, 6, and 12 months after HIFU treatment were 21.2%, 29.6%, 44.8%, and 48.7%, respectively. Based on the results from clinical trials and studies HIFU seems to be emerging as a safe and effective modality not only for the treatment of malignancy but also benign disease.

## SIDE EFFECTS

In all studies there were no significant side effects. The most frequent event was a skin burn, it is due to overheating of the target lesion and no by action of HIFU. In 2011 Tinghe Yu et al[53] published an article on side effects of HIFU (Table 5). Of 13,262 cases analyzed, adverse events were fewer in benign lesions than in malignant lesions (11.81% vs. 21.65%, $p < 0.0001$). Skin burn was the most common side effect seen in liver, pancreas and breast cancer. In bone tumors frequent AEs were nerve injury (6.25%), skin burn (4.46%) and fracture (4.46%). In prostate cancer hematuria was present in 17,33% of case. In uterine fibroid the most frequent AEs were nerve injury (3.06%), hematuria (2.88%) and burn (2.44%).

## CONCLUSIONS

Cancer is a disease with a strong psychological impact because for many years has been synonymous with death. The purpose in modern medicine is to develop treatments and techniques that minimize interventions on patients. High-Intensity Focused Ultrasound is a new technique that may play a key role in future clinical practice and may offer patients another choice when no other treatment available or when patient refused surgical operation. The nonsurgical ablation methods are thought to be psychologically and cosmetically more satisfactory and more easily accepted by patients. All preliminary studies suggest that HIFU ablation is a technique completely safe. Side effects are always shown insignificant compared to the benefits for both in curative and palliative treatments. Another important element is the reduced time of hospitalization, in fact the patient was discharged in most cases after only 1 day. This element is very important because this technique could be easily accepted even by those patients who refuse hospitalization, but also for the cost of hospitalization is an important fact with which health must confront daily. HIFU is suitable to be used alone or in combination with other techniques, for example, with TACE in HCC or with TURP in prostate cancer. This allows to have better results. HIFU is not just a technique to induce necrosis of tumors, gene therapy and drug delivery may be other ways to use this technique. New clinical trials are essential to eliminate any doubt on the efficacy and safety of this technique, to establish guidelines on its use in the fight against cancer also to evaluate its use in so called disadvantages patients.

**Table 5.**

| *Disease* | *Case* | *Adverse event* | *Incidence* |
|---|---|---|---|
| ***Malignant*** | | | |
| Liver | 2201 | Skin burn 493<br>ALT/AST elevation 81<br>Hydrothorax 57<br>Severe abdomen pain 39<br>Other 107 | 35.30% (777/2201) |
| Pancreas | 1717 | Burn 51<br>Pancreatitis 32<br>Diabetes 22<br>Steatorrhea 13<br>Gastroenteric dysfunction 13<br>Other 19 | 8.74% (150/1717) |
| Bone | 224 | Nerve injury 14<br>Fracture 10<br>Skin burn 10<br>Other 12 | 20.54% (46/224) |
| Breast | 167 | Skin burn 19 | 11.38% (19/167) |
| Soft tissues | 81 | Skin burn 5<br>Cutaneous necrosis 4<br>Nerve injury 3 | 14,81% (12/81) |
| Prostate | 375 | Hematuria 65<br>Skin burn 27<br>Urinary obstruction 9<br>Other 6 | 28.53% (107/375) |
| ***Benign*** | | | |
| Uterine fibroid | 5526 | Nerve injury 169<br>Hematuria 159<br>Skin burn 112<br>Severe/prolonged abdomen pain 92<br>Other 31 | 10.19% (563/5526) |
| Prostate hyperplasia | 883 | Hematuria 157<br>Urinary irritation 38<br>Urine retention 24 | 24.80% (219/883) |

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