

High-Intensity Focused Ultrasound Ablation: Effective and Safe Therapy for Solid Tumors in Difficult Locations

Franco Orsi¹
Lian Zhang²
Paolo Arnone³
Gianluigi Orgera¹
Guido Bonomo¹
Paolo Della Vigna¹
Lorenzo Monfardini¹
Kun Zhou²
Wenzhi Chen²
Zhibiao Wang^{2,4}
Umberto Veronesi³

Keywords: difficult locations, high-intensity focused ultrasound, solid tumors

DOI:10.2214/AJR.09.3321

Received July 6, 2009; accepted after revision February 22, 2010.

Lian Zhang is a consultant to Chongqing Haifu. Wenzhi Chen and Zhibiao Wang are shareholders of Chongqing Haifu.

¹Interventional Radiology Unit, European Institute of Oncology, 435 Via Ripamonti, 20141 Milan, Italy. Address correspondence to F. Orsi (franco.orsi@ieo.it).

²Clinical Center for Tumor Therapy, 2nd Hospital, Chongqing University of Medical Sciences, 74 Linjiang Rd., Chongqing 400010, China. Address correspondence to L. Zhang (lianwzhang@yahoo.com).

³Division of Senology, European Institute of Oncology, Milan, Italy.

⁴National Engineering and Research Center for Ultrasound Medicine, Chongqing Medical University, Chongqing, China

WEB

This is a Web exclusive article.

AJR 2010; 195:W245–W252

0361–803X/10/1953–W245

© American Roentgen Ray Society

OBJECTIVE. The aim of this study was to evaluate the safety and efficacy of ultrasound-guided high-intensity focused ultrasound therapeutic ablation of solid tumors in difficult locations.

SUBJECTS AND METHODS. A procedure was performed with a focused ultrasound tumor therapeutic system which provides real-time ultrasound guidance. All patients underwent MDCT or MRI, and some patients underwent PET/CT. From November 2007 through April 2009, 31 patients with 38 lesions of the liver and pancreas in difficult locations were treated. Six patients had hepatocellular carcinoma, 13 patients had hepatic metastasis from colorectal cancer, two had hepatic metastases of breast cancer, two had hepatic metastasis of neuroendocrine tumors, one patient had lymph node metastasis of breast cancer at the hepatic hilum, six patients had pancreatic cancer, and one patient had a neuroendocrine tumor. Difficult location was defined as tumor adjacent to a main blood vessel, the heart, the gallbladder and bile ducts, the bowel, or the stomach.

RESULTS. The mean diameter of tumors was 2.7 ± 1.4 cm. PET/CT, MDCT, or both on the day after one session of high-intensity focused ultrasound treatment showed complete response in all six patients with hepatocellular carcinoma, the patient with lymph node metastasis, and 22 of 24 patients with hepatic metastasis. The symptoms of all seven patients with pancreatic cancer or neuroendocrine tumors were palliated, and PET/CT or MRI showed complete response of six of seven lesions. Portal vein thrombosis occurred after high-intensity focused ultrasound ablation in one patient with pancreatic cancer. No other side effects were detected in a median follow-up period of 12 months.

CONCLUSION. According to our short- and long-term follow-up results, ultrasound-guided high-intensity focused ultrasound ablation can be considered a safe and feasible approach to the management of solid tumors in difficult locations.

Surgery is the current standard of care of selected patients with solid tumors, offering the chance of complete cure by tumor removal [1, 2]. Most patients, however, cannot undergo surgical resection because of the tumor site, advanced stage of the tumor, or poor general condition. Radiofrequency ablation (RFA), percutaneous ethanol injection, cryoablation, microwave coagulation, and laser-induced interstitial thermotherapy also can result in local tumor control, and use of these treatments occasionally leads to long-term disease-free survival [3–5]. It remains difficult, however, to use these techniques to manage tumors in difficult locations, such as close to the heart, diaphragm, a main blood vessel, the stomach, bowel, and bile ducts and gallbladder, because of the substantial risk of injury to these structures, pneumothorax and hemothorax, and tumor seeding [6–9].

High-intensity focused ultrasound is a relatively new technique that has great potential for further development. The possibility that focused ultrasound therapy might be developed through control of local heating phenomena was introduced by Lynn et al. in the 1940s [10], but the 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 high-intensity focused ultrasound. Currently, both ultrasound-guided high-intensity focused ultrasound and MRI-guided high-intensity focused ultrasound devices are available.

High-intensity focused ultrasound has received considerable attention for the management of solid tumors [11]. Several clinical high-intensity focused ultrasound projects have been conducted by various research groups, and results have shown the technique is safe, effective, and feasible in clinical application [12–15].

Experience in China has included use of ultrasound-guided high-intensity focused ultrasound in the management of solid malignant tumors, including primary and metastatic liver cancer, malignant bone tumors, breast cancer, soft-tissue sarcoma, renal cancer, pancreatic cancer, and metastatic bone tumors [16–19]. In the largest series of clinical application of high-intensity focused ultrasound to date [16], 1,038 patients were treated with ultrasound-guided high-intensity focused ultrasound in 10 centers for both curative and palliative purposes, and the results were promising.

The Chinese experience may not be applicable to Western countries. In the United States, an MRI-guided high-intensity focused ultrasound device has been approved by the Food and Drug Administration for management of uterine fibroids. The results showed MRI-guided focused ultrasound ablation feasible and safe for that purpose [20, 21]. In Oxford, England, a total of 22 patients with liver metastasis were treated with ultrasound-guided high-intensity focused ultrasound [14], and 20 of the 22 underwent imaging (MRI or contrast ultrasound) or histologic assessment. The results revealed that the adverse event profile was favorable compared with that for open and minimally invasive techniques. To our knowledge, however, no report of high-intensity focused ultrasound management of solid malignant tumors from a member of the European Comprehensive Cancer Centre Alliance has defined the clinical and technical indications for this technique, although advances have been made in developing and improving ultrasound-guided high-intensity focused ultrasound technique. The aim of our study was to evaluate the efficacy and safety of this technique in the management of different types of solid malignant tumors in difficult locations.

Subjects and Methods

This study was performed in accordance with institutional guidelines on minimally invasive management of solid tumors according to the European Institute of Oncology. Every patient was selected by a multidisciplinary task force that included surgeons, medical oncologists, radiotherapists, interventional radiologists, pathologists, and endoscopists. Every patient signed a specific written informed consent document before being selected and treated.

Patients

From November 2007 through April 2009, a total of 31 patients (14 men, 17 women; age range, 37–77 years; mean age, 64.3 ± 8.5 [SD] years)

with 38 lesions were treated with high-intensity focused ultrasound. Twenty-six patients had a solitary malignant tumor; three, two tumors; and two, three tumors (Table 1). The tumor diameter ranged from 1.0 to 6.9 cm (mean, 2.7 ± 1.4 cm). All patients included in this study were deemed not candidates for surgery, RFA, or transcatheter arterial chemoembolization or embolization or were unwilling to undergo any of those treatments. Among the 31 patients, six had hepatocellular carcinoma (HCC), 13 had hepatic metastasis of colorectal cancer, two had hepatic metastasis of breast cancer, two had hepatic metastasis of neuroendocrine tumors, one patient had lymph node metastasis from breast cancer at the hepatic hilum, one had a neuroendocrine tumor, and six patients had pancreatic cancer (Table 2). All lesions were adjacent to main hepatic blood vessels or the heart, stomach, bowel, bile ducts, or gallbladder. Table 3 shows the number of tumors at each difficult location. Among the 30 liver lesions in 23 patients, three lesions were located at segment I, three lesions at segment II, five lesions at segment III, three lesions at segment IV, two lesions at segment V, three lesions at segment VI, seven lesions at segment VII, and four lesions at segment VIII.

Six patients with pancreatic cancer and one patient with a neuroendocrine tumor underwent palliation treatment. Six of these patients had disease

TABLE 1: Characteristics of 31 Patients Treated With High-Intensity Focused Ultrasound

Characteristic	Value
No. of patients	31
Male-to-female ratio	14/17
Age (y)	64.3 ± 8.5 (37–77)
Tumor diameter (cm)	2.7 ± 1.4 (1.0–6.9)
No. of tumors	
1	26
2	3
3	2

Note—Values in parentheses are ranges.

in an advanced stage and no indication for surgical resection, and the other patient had local relapse after surgery. All of the patients with pancreatic cancer underwent chemotherapy and radiotherapy and had progressive local disease at the time of high-intensity focused ultrasound treatment. They all reported severe back pain before treatment. The number and dimension (defined as the largest diameter) of target lesions were defined with CT or MRI.

TABLE 2: Types of 38 Tumors Managed With High-Intensity Focused Ultrasound

Tumor	No. of Tumors	No. of patients
Hepatic metastasis from colorectal cancer	20	13
Hepatic metastasis from breast cancer	2	2
Hepatic metastasis from neuroendocrine tumor	2	2
Hepatocellular carcinoma	6	6
Pancreatic cancer	6	6
Neuroendocrine tumor	1	1
Lymph node metastasis at hepatic hilum	1	1
Total	38	31

Note—Among the 23 patients with liver tumors, two patients had three lesions, and three patients had two lesions.

TABLE 3: Difficult Locations in 31 Patients Treated With High-Intensity Focused Ultrasound

Location	No. of Tumors at Each Location	Distance Between Tumor and Organ at Risk (cm)
Main blood vessel	27	< 1
Heart	3	< 1
Stomach	10	< 1
Bowel	12	< 1
Bile duct	4	< 1
Gallbladder	2	< 1

Note—Difficult location was defined as < 1 cm distance between the tumor and the structure. Some tumors involved several difficult locations.

High-Intensity Focused Ultrasound Ablation of Solid Tumors

Pretreatment Preparation

Routine examinations and preprocedure preparations were conducted according to the principles for surgery. Conventional liver biochemical tests, prothrombin time, and complete blood cell counts, chest radiography, abdominal sonography, ECG, and lung function were evaluated before treatment. MDCT, PET/CT, MRI, or a combination of these techniques were performed as baseline imaging.

Specific bowel preparation was required for patients with pancreatic cancer and patients with hepatic metastatic lesions and HCC close to the stomach and bowel. Careful bowel preparation was performed for 3 days and consisted of liquid food, no milk, fasting for 12 hours before treatment, and an enema in the early morning on the day of treatment. Degassed water balloons were used for all patients with pancreatic tumors to compress the bowel and push it away from the acoustic pathway during treatment.

High-Intensity Focused Ultrasound Therapeutic Procedure

High-intensity focused ultrasound ablation was performed with a system (JC HIFU, Chongqing Haifu Technology) equipped with an ultrasound device for real-time guidance of the treatment. Therapeutic focused ultrasound energy was produced with a 20-cm-diameter transducer with a focal length of 15 cm operated at a frequency of 0.8 MHz. An ultrasound imaging device (MyLab70, Esaote) coupled with the high-intensity focused ultrasound machine was used as the real-time imaging unit. This 1.0- to 8.0-MHz imaging probe is situated in the center of the high-intensity focused ultrasound transducer and allows real-time sonographic monitoring during treatment.

The skin surface overlying the lesion was shaved in all cases to avoid the presence of hairs in the acoustic pathway. The same skin surface also was degassed with a vacuum cup aspiration device

and degassed with 95% alcohol. A urinary catheter was inserted before every treatment.

For this study, high-intensity focused ultrasound therapy was performed under general anesthesia. General anesthesia was necessary to prevent pain and discomfort and to ensure immobilization during treatment. General anesthesia with endotracheal intubation and mechanical ventilation also had the supplementary benefit of allowing provisional suspension of breath with controlled pulmonary inflation, as needed for ablating hepatic lesions behind the rib cage, through the intercostal space. After suitable anesthesia was induced, patients were carefully positioned over the treatment bed for correct placement of the skin surface so that the lesion to be treated was in contact with the degassed water. All patients were monitored for respiration and heart rate, blood pressure, and oxygen and carbon dioxide saturation during the procedure.

The sagittal ultrasound scanning mode was chosen for both pretreatment planning and sonication. Both point and line-scan energy delivery were used during treatments. The distance between treated slices was 5 mm. Treatment power was increased stepwise after the start of the procedure, and ablation was terminated after the increased gray scale covered the tumor margin (Fig. 1). Treatment power of 200–400 W was used for different types and sites of tumors.

Follow-Up

All patients underwent unenhanced and contrast-enhanced MDCT or MRI. The patients with hepatic metastasis, pancreatic cancer, and lymph node metastasis of breast cancer at the hepatic hilum underwent PET/CT for verification of the resultant necrosis. To exclude major complications and evaluate treatment efficacy, MDCT was performed within the first 24 hours after treatment. All patients then underwent ¹⁸F-FDG PET/CT or abdominal MDCT or MRI 3–4 weeks after treatment and every 3 months thereafter. Adverse events and

complications were recorded. The follow-up period of this study ended on October 31, 2009.

PET/CT Scan Interpretation

Baseline and follow-up FDG PET/CT scans were read by one experienced nuclear medicine physician blinded to clinical status and physical examination findings, other imaging findings, and histopathologic results. Assessment of residual disease was based on focal uptake of FDG at the site of high-intensity focused ultrasound ablation.

MDCT Scan Interpretation

Follow-up MDCT scans were read by experienced radiologists blinded to other imaging findings and histopathologic results. When an irregular area of high attenuation was found around the site of the ablated lesion or increased size of the treated area was observed, the MDCT finding was considered positive. Detection of an area of low attenuation at the ablation site without contrast enhancement at the edges was considered absence of lesion, and the MDCT finding was interpreted as negative.

Statistical Analysis

All data are reported as mean $\pm$ SD. Local tumor recurrence and overall survival rate were estimated with the Kaplan–Meier method, and differences were determined with the log-rank test. A value of $p < 0.05$ was considered statistically significant. The follow-up period was defined as follows: for local tumor progression rate, the time from the beginning of high-intensity focused ultrasound ablation to local tumor progression or death; for overall survival rate, the time to last follow-up visit or death.

Results

Changes in Gray-Scale Values

Massive gray-scale changes (Fig. 1) interpreted as tissue necrosis with high-intensity

Fig. 1—57-year-old woman with liver metastasis from colon cancer.

A, Real-time ultrasound image obtained before high-intensity focused ultrasound treatment shows small lesion (arrow) close to inferior vena cava.

B, Ultrasound image obtained at end of high-intensity focused ultrasound ablation shows hyperechoic region in treated area (arrow).

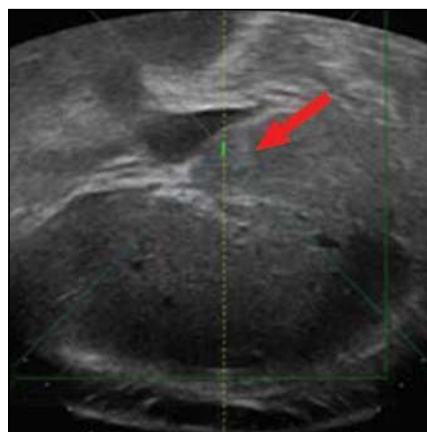
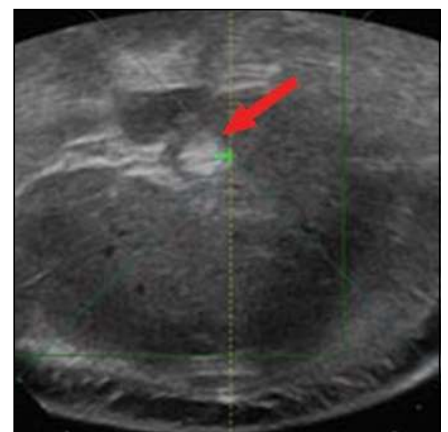


TABLE 4: High-Intensity Focused Ultrasound Treatment of 31 Patients With Solid Tumors

Tumor Site	No. of Lesions	Size (cm)	Treatment Time (min)	Sonication Time (min)	Total Average Energy (J)
All organs	38	2.7 ± 1.4	105.3 ± 56.6	28.5 ± 17.8	612,674 ± 537,958
Liver	30	2.2 ± 1.0	99.1 ± 55.0	28.2 ± 19.1	570,558 ± 496,776
Pancreas	7	4.6 ± 1.4	142.5 ± 58.5	29.7 ± 12.2	793,168 ± 704,778

focused ultrasound sonication were found in 35 of 38 lesions (92.1%). Gray-scale changes were not found in one pancreatic tumor and two hepatic metastatic lesions in segments I and VII. The average energy used for hepatic metastatic lesions (2.2 ± 1.0 cm in diameter) was $570,558 \pm 496,776$ J and for pancreatic tumors (4.6 ± 1.4 cm) was $793,168 \pm 704,778$ J (Table 4).

Immediately Postprocedure Evaluation and Short-Term Follow-Up

MDCT or MRI performed 1 day after high-intensity focused ultrasound treatment showed complete response in the patient with lymph node metastasis of breast cancer at the hepatic hilum, six of seven patients with pancreatic lesions, all six patients with hepatocellular carcinoma, and 22 of 24

patients with hepatic metastasis. PET/CT, MDCT, or MRI performed 3–4 weeks after treatment also depicted coagulative necrosis of these lesions (Figs. 2–5). Symptoms were clearly palliated within 24 hours after treatment in six of seven patients with pancreatic tumors. One patient with pancreatic cancer did not have a good response to high-intensity focused ultrasound treatment because

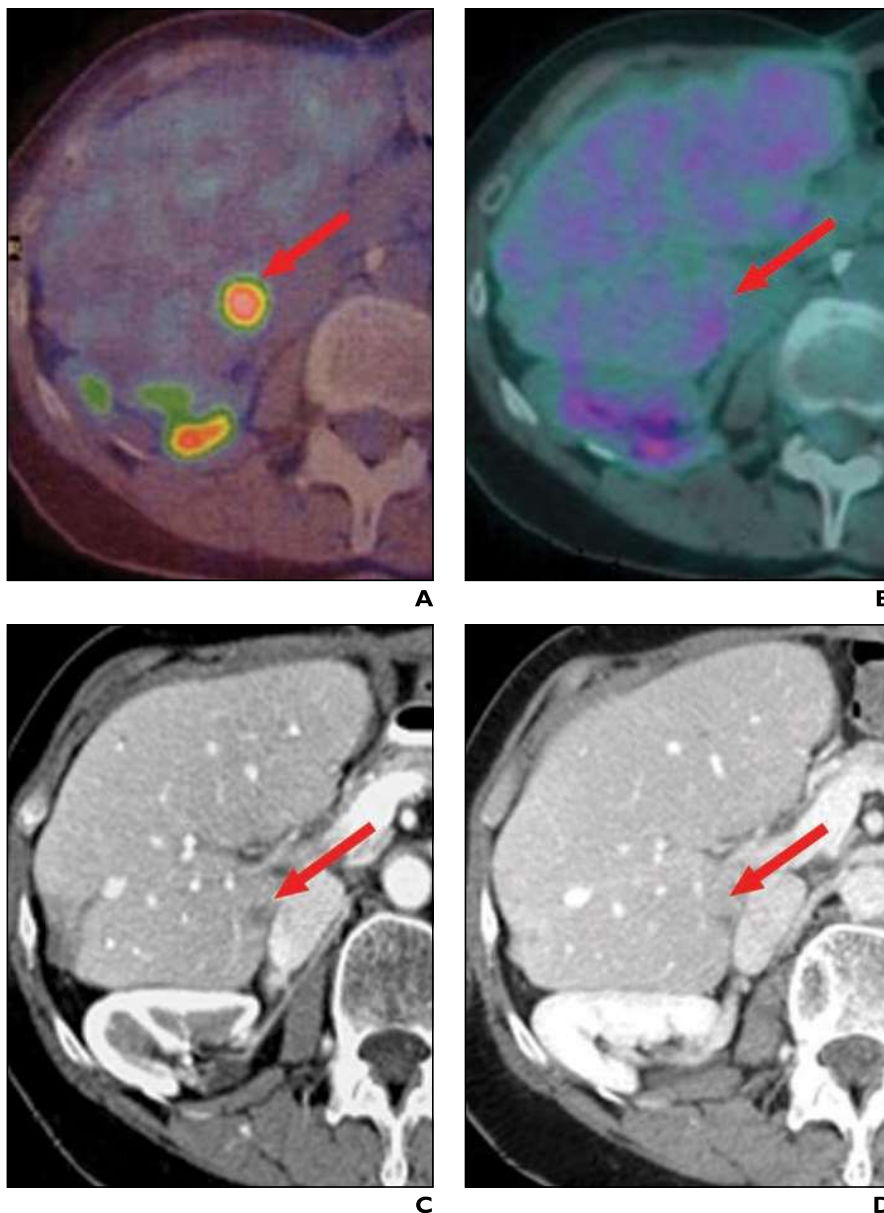


Fig. 2—61-year-old woman with liver metastasis from colon cancer.

A, Transverse pretreatment PET/CT image shows hypermetabolic lesion (arrow).

B, Transverse PET/CT image obtained 1 month after high-intensity focused ultrasound treatment shows negative finding (arrow).

C, Transverse pretreatment contrast-enhanced MDCT image shows lesion (arrow) close to inferior vena cava.

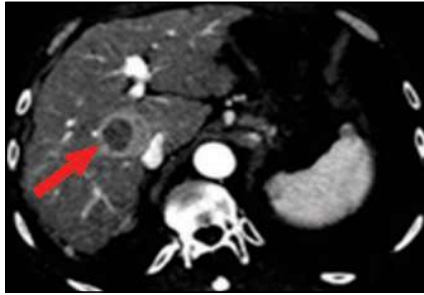
D, Transverse contrast-enhanced MDCT image obtained 1 month after high-intensity focused ultrasound treatment shows size of lesion (arrow) has decreased.

High-Intensity Focused Ultrasound Ablation of Solid Tumors

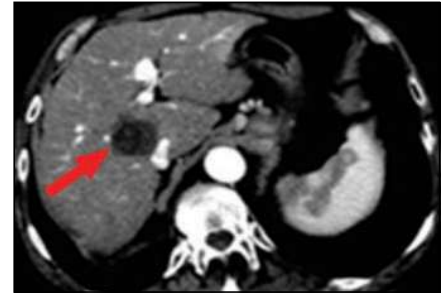
Fig. 3—52-year-old man with hepatocellular carcinoma treated with radiofrequency ablation and then high-intensity focused ultrasound.

A, Contrast-enhanced CT scan obtained in arterial phase after radiofrequency ablation shows residual hepatocellular carcinoma (*arrow*) close to inferior vena cava.

B, Contrast-enhanced CT obtained 4 weeks after high-intensity focused ultrasound treatment shows uniform low attenuation (*arrow*) and absence of contrast enhancement, which are evidence of successful treatment. Inferior vena cava is well perfused.



A



B

we observed a large number of gas bubbles in the stomach and duodenum during treatment. We treated this patient with relatively low power in the safe region. MDCT and MRI 24 hours after treatment depicted portal vein thrombosis in one patient with pancreatic cancer but did not depict injury to the surrounding organs. All patients with pancreatic tumors underwent precautionary observation in the hospital for 3 days. The amylase level showed no statistically significant elevation over baseline in the 3 days after treatment.

Local Tumor Progression

For the patients with hepatic metastasis or HCC, after a median of 12 months (range, 1–18

months) of follow-up, local (within 2 cm of the main tumor) tumor progression occurred in six of 17 patients with hepatic metastasis. No local tumor recurrence was found in patients with HCC. Figure 6 shows the cumulative local tumor recurrence rate of hepatic metastasis after high-intensity focused ultrasound ablation.

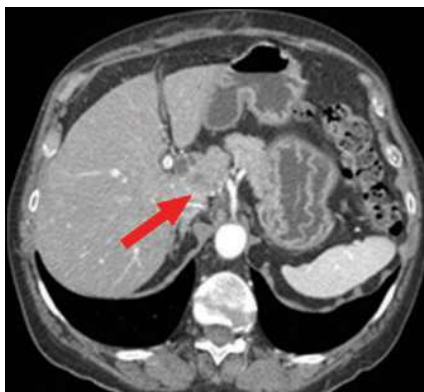
Overall Survival Rate

The 1- and 2-year survival rates among the patients with hepatic metastasis were 88.2% and 88.2% (Fig. 7). Two of 17 patients died during a median follow-up period of 12 months (range, 1–18 months). The causes of death included hemorrhagic stroke and other causes. The six patients with small HCC were

still alive at the end of the study. The survival rates at different intervals were higher among patients with HCC than those with liver metastasis, but the difference was not statistically significant ($p = 0.3936$, log-rank test). The 1- and 2-year survival rates among the patients with pancreatic cancer were 42.9% and 21.4%. The median survival time was 7 months after treatment (Fig. 8).

Timing

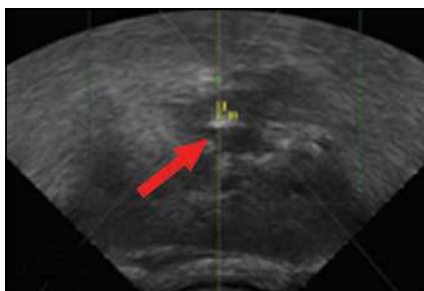
Details on the length of the procedure were as follows. Room time, including preparation time and treatment time, defined as the time from patient entrance to the high-intensity focused ultrasound unit to patient



A



B



C



D

Fig. 4—69-year-old woman with lymph node metastasis of breast cancer in hepatic hilum; patient also has colon cancer.

A, Pretreatment MDCT image shows 4-cm lymph node (*arrow*) at hepatic hilum.

B, Pretreatment real-time ultrasound image shows hypoechoic lesion (*arrow*).

C, Real-time ultrasound image shows massive gray-scale changes (*arrow*).

D, MDCT obtained 1 day after high-intensity focused ultrasound treatment shows lesion has been completely ablated (*arrow*).

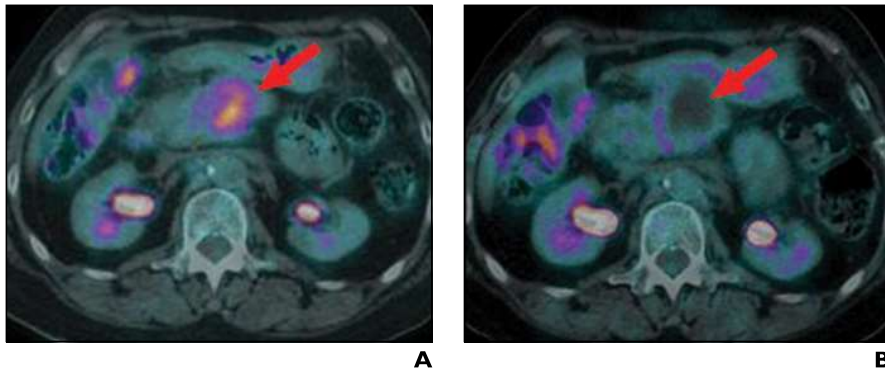


Fig. 5—60-year-old woman with pancreatic cancer. **A**, Transverse pretreatment PET/CT image shows positive findings for tumor (arrow). **B**, PET/CT image obtained 1 month after treatment shows negative findings for tumor (arrow).

exit from the room, ranged from 2 hours 30 minutes to 5 hours 25 minutes. The overall treatment time, defined as the time from the beginning of localization to the last sonication, ranged from 59 minutes to 180 minutes (mean, 105.3 ± 56.6 minutes). The calculated the sonication time—defined as the exposure time and related to tumor size, site, and blood supply—ranged from 6 minutes 47 seconds to 87 minutes 10 seconds (mean, 28.5 ± 17.8 minutes) (Table 3).

Adverse Events

The adverse events and complications were categorized according to the Society of Interventional Radiology classification system for complications by outcome [22]. Portal vein thrombosis was detected in one patient with pancreatic cancer and was defined as a major complication. This patient was hospitalized for 7 days. All the other patients were observed in the hospital for 1–3 days after high-intensity fo-

cused ultrasound treatment. Local edema and skin burn were not detected in any of these patients after treatment. No patient in this study reported local pain after treatment.

Discussion

Minimally invasive therapies, such as RFA, transcatheter arterial chemoembolization, percutaneous ethanol injection, cryoablation, microwave coagulation, laser-induced interstitial thermotherapy, and high-intensity focused ultrasound, have been used to ablate solid tumors. High-intensity focused ultrasound, however, is the only technique to be completely extracorporeal, through the use of nonionizing energy. As a noninvasive technique, high-intensity focused ultrasound is receiving increasing interest in the management of hepatic tumors. Wu et al. [23] reported achieving large areas of coagulation necrosis with this technique in the management of HCC. Zhang et al. [24] reported that high-in-

tensity focused ultrasound can achieve complete tumor necrosis even when the lesion is located adjacent to the major hepatic blood vessels. There is no discernible damage to the major vessels, even though the adjacent tumor has been completely ablated. Surgery is considered the only potentially curative treatment even of patients with pancreatic cancer. However, because of the frequent delay in diagnosis, approximately 80% of patients have unresectable disease at presentation [2]. Local treatment may benefit patients with advanced pancreatic cancer who are not candidates for surgical treatment. A study with a small number of patients [13] showed that high-intensity focused ultrasound is safe and feasible in the management of pancreatic cancer.

At our comprehensive cancer center, we are daily involved in the care of patients with advanced disease who have no other options for cure or palliation of cancer. Minimally invasive treatment may be indicated most often for

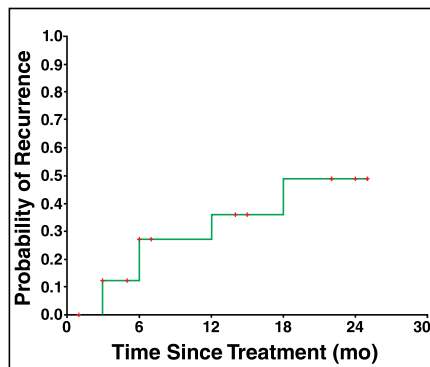


Fig. 6—Graph shows cumulative recurrence rate calculated with Kaplan-Meier method for 17 patients with hepatic metastasis treated with high-intensity focused ultrasound. Cumulative recurrence rates at 1 and 2 years were 36.2% and 49.0%.

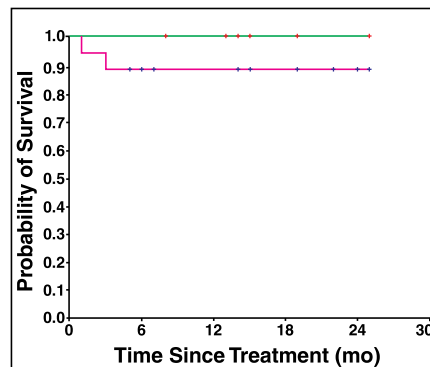


Fig. 7—Graph shows survival rates of patients with hepatocellular carcinoma (HCC) (green line) ($n = 6$) and those with hepatic metastasis (magenta line) ($n = 17$) 1 and 2 years after high-intensity focused ultrasound treatment. Survival rates for HCC were 100% and 100%, and those for hepatic metastasis rates were 88.2% and 88.2%. Survival rates at different intervals were not significantly different between patients with HCC and those with hepatic metastasis ($p = 0.3936$, log-rank test).

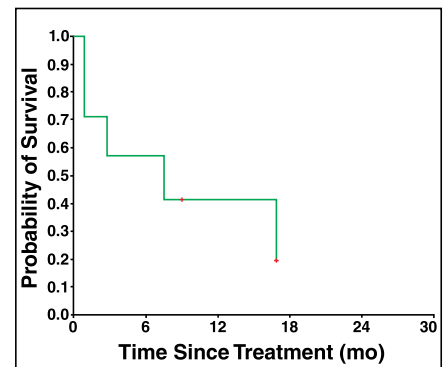


Fig. 8—Graph shows cumulative survival curve calculated with Kaplan-Meier method for seven patients with pancreatic tumors managed with high-intensity focused ultrasound. Median survival time was 7 months. Overall 1- and 2-year survival rates based on inclusion of all patients (one with neuroendocrine tumor, six with pancreatic cancer) are 42.9% and 21.4%.

High-Intensity Focused Ultrasound Ablation of Solid Tumors

these patients, for whom an aggressive approach would not be justified because of the clinical status. Minimally invasive treatment can be troublesome when the tumor is in a difficult location. As a so-called noninvasive technology, high-intensity focused ultrasound may play a key role in this field. For this reason, we decided to study the application of this technology to patient care.

Our results suggest that high-intensity focused ultrasound can safely achieve almost complete necrosis of tumors in difficult locations without damage to the structures at risk (Figs. 2–5). Complete ablation was achieved in more than 90% of the tumors in this study. Two hepatic lesions did not have gray-scale changes during treatment, and PET/CT and MDCT showed no response after high-intensity focused ultrasound treatment. These two lesions were very deep and adjacent to major blood vessels; one was in segment I and the other in segment VII of the liver. These two lesions were the first at difficult sites to be treated in this study. Treatment failed because we delivered only the regular power in a short time (350 W for 2 seconds for each sonication). Because of the ultrasound attenuation with irradiation depth and the cooling effects of great vessels, higher power and more energy are needed for ablating tumors that are very deep or close to major blood vessels [24, 25]. With more experience, we achieved better results. We later treated other lesions in segments I and VII (Fig. 2) with higher power and longer exposure time (400 W, 5 seconds for each sonication) than we used during the learning period, and those lesions were completely ablated.

Until now, most patients with unresectable hepatic metastatic lesions of colorectal carcinoma have undergone either systemic or locoregional chemotherapy. The mean and median survival times reported for these patients ranged between 12.7 and 18.7 months [26]. In contrast, for the patients in this study who had hepatic metastasis, use of high-intensity focused ultrasound was associated with an overall mean survival period longer than 24 months. A large volume of results have shown that the survival rates at 1, 3, and 5 years have been 78–96%, 54–70%, and 33–45% after RFA, laser-induced interstitial thermotherapy, and surgical resection of hepatic metastatic lesions [27–30]. Our results showed that the 2-year survival rate among patients with hepatic metastasis was 88.2%, superior to that after systemic and locoregional chemotherapy and similar to that after

RFA, laser-induced interstitial thermotherapy, and surgery. The survival rate among patients with HCC and pancreatic cancer in this study also is better than or equal to that after RFA, surgery, and systemic and locoregional chemotherapy. Thus our results suggest that patients' completion of the local treatment protocol is pivotal to survival.

Our results of high-intensity focused ultrasound treatment show a higher local tumor recurrence rate than in investigations [28–30] in which different techniques were used (RFA, laser-induced interstitial thermotherapy, and surgical resection of hepatic metastatic lesions). Although the difficulty of the locations may explain the high local recurrence rate, it appears that ablation volume also is related to local control. No local recurrence was detected in patients with small HCCs. Although already effective, high-intensity focused ultrasound ablation may continue to improve as the technique and operator experience evolve.

Our results show that we had fewer complications and adverse effects than in previous studies. In earlier studies [14, 31] mild discomfort or local pain was found in 54–80% of treated patients. In our study, no patient reported discomfort or local pain the day after high-intensity focused ultrasound treatment. A low-grade fever was another often experienced adverse effect in earlier studies [14], but none of our patients had low-grade fever. We do not precisely understand why our patients had fewer complications and adverse effects than those in other studies. Selection of patients (lower weight, smaller tumor size), device development, and different levels of experience may explain the difference because the previous studies were performed more than 5 years before ours. The other possible complications of high-intensity focused ultrasound treatment include damage to adjacent viscera, such as bowel and gallbladder, but none of our patients had these side effects.

Portal vein thrombosis occurred in one patient with pancreatic cancer. We carefully reviewed the pretreatment images and found that the portal vein was compressed by the tumor. We surmise that the portal vein was further compressed by the edematous tumor after high-intensity focused ultrasound ablation, and the compression caused inappropriate blood clotting. After being treated with low-molecular-weight heparin for 1 week, the patient was discharged from the hospital and died of infection 1 month later. All the other patients felt well. The other five patients with

pancreatic cancer and the one with a neuroendocrine tumor were observed in the hospital for 3 days according to protocol. All of the patients with HCC, hepatic metastasis, and lymph node metastasis in the hepatic hilum were discharged from the hospital the day after high-intensity focused ultrasound treatment. No treatment-related adverse effects were detected during a median follow-up period of 12 months (range, 1–18 months).

Our results show ultrasound gray-scale values are reliable for defining coagulation necrosis. Massive gray-scale values increased in 35 of 38 lesions. In these 35 lesions, the gray-scale changes were consistent with the MDCT, PET/CT, or MRI findings. In the three lesions in which we did not find the massive changes in gray-scale values, PET/CT and MDCT showed no changes after treatment.

Treatment time is another practical issue on which we focused. We calculated the room time and treatment time and found 51% of room time was spent preparing the patient for treatment. The mean overall treatment time for ablating the average 2.7 ± 1.4 cm (range, 1.0–6.9 cm) tumor ranged from 59 minutes to 180 minutes (mean, 105.3 ± 56.6 minutes), which was longer than desirable. Our results also showed that sonication time (28.5 ± 17.8 minutes) was much shorter than the overall treatment time. We were just beginning to perform high-intensity focused ultrasound treatment at our institution and believe that the room time and overall treatment time may be further reduced by optimization of workflow and avoiding repetitious steps. Improvement in lesion targeting with ultrasound also may shorten treatment time.

Our study was limited in that the difficult locations were diverse and the number of patients was small. Another limitation was that the follow-up time was short because the aim of the study was to evaluate the feasibility of the new technique. Future studies with larger numbers of patients with lesions at difficult locations are needed to define whether these patients will benefit from high-intensity focused ultrasound treatment. Additional studies comparing high-intensity focused ultrasound treatment with other available techniques, such as transarterial embolization and RFA, will be important to select among therapies in the care of individual patients.

The results of this study show that ultrasound imaging-guided focused ultrasound ablation of lesions in difficult locations can achieve complete response without serious side effects. Further studies, such as randomized

control studies, are needed to ascertain the patient group for whom this noninvasive treatment is best suited. On the basis of results with this small number of patients with solid malignant tumors, ultrasound-guided focused ultrasound treatment appears to be feasible and safe for ablation of primary and metastatic liver tumors, lymph node metastasis in difficult locations, and pancreatic cancer and can have a role in the multiple-technique care of patients with tumors.

Acknowledgments

We thank Adriana Barioli, Marco Tullii, Antonella Tosoni, Gianfranco Manfredi, Giuseppe Bonfitto, Ubaldo Piccololongo, Lorenza Ambrosino, Claudio Acerbi, Anna Zubani, and Nicola Sciancalepore for contributions to this work.

References

1. Livraghi T, Makuuchi M, Buscarini L. *Diagnosis and treatment of hepatocellular carcinoma*. London, England: Greenwich Medical Media, 1997
2. DeVita VT, Hellman S, Rosenberg SA. *Cancer: principles and practice of oncology*. Philadelphia, PA: Lippincott Williams & Wilkins, 2001
3. Llovet JM, Real MI, Montana X. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359:1734–1739
4. Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G, Gandini G. Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). *Eur Radiol* 2006; 16:661–669
5. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. *Gastroenterology* 2004; 127[suppl 1]:S179–S188
6. Koda M, Ueki M, Maeda N, Murawaki Y. Diaphragmatic perforation and hernia after hepatic radiofrequency ablation. *AJR* 2003; 180:1561–1562
7. Kim YS, Rhim H, Sung JH, et al. Bronchobiliary fistula after radiofrequency thermal ablation of hepatic tumor. *J Vasc Interv Radiol* 2005; 16:407–410
8. Ishiko T, Beppu T, Sugiyama S, et al. Radiofrequency ablation with hand-assisted laparoscopic surgery for the treatment of hepatocellular carcinoma in the caudate lobe. *Surg Laparosc Endosc Percutan Tech* 2008; 18:272–276
9. Akahane M, Koga H, Kato N, et al. Complications of percutaneous radiofrequency ablation for hepatocellular carcinoma: imaging spectrum and management. *RadioGraphics* 2005; 25[suppl 1]:S57–S68
10. Lynn JG, Zwemer RL, Chick AJ. A new method for the generation and use of focused ultrasound in experiment biology. *J Gen Physiol* 1942; 26:179–193
11. Kennedy JE. High intensity focused ultrasound in the treatment of solid tumours. *Nat Rev Cancer* 2005; 5:321–327
12. Tempany CM, Stewart EA, McDannold N, Quade BJ, Jolesz FA, Hynynen K. MR imaging-guided focused ultrasound surgery of uterine leiomyomas: a feasibility study. *Radiology* 2003; 226:897–905
13. Wu F, Wang ZB, Zhu H, et al. Feasibility of US-guided high-intensity focused ultrasound treatment in patients with advanced pancreatic cancer: initial experience. *Radiology* 2005; 236:1034–1040
14. Illing RO, Kennedy JE, Wu F, et al. The safety and feasibility of extracorporeal high-intensity focused ultrasound (HIFU) for the treatment of liver and kidney tumours in a Western population. *Br J Cancer* 2005; 93:890–895
15. Morita Y, Ito N, Hikida H, Takeuchi S, Nakamura K, Ohashi H. Non-invasive magnetic resonance imaging-guided focused ultrasound treatment for uterine fibroids: early experience. *Eur J Obstet Gynecol Reprod Biol* 2008; 139:199–203
16. Wu F, Wang ZB, Chen WZ, et al. Extracorporeal high intensity focused ultrasound ablation in the treatment of 1038 patients with solid carcinomas in China: an overview. *Ultrason Sonochem* 2004; 11:149–154
17. Wu F, Wang ZB, Cao YD, et al. Wide local ablation of localized breast cancer using high intensity focused ultrasound. *J Surg Oncol* 2007; 96:130–136
18. Li YY, Sha WH, Zhou YJ, Nie YQ. Short and long term efficacy of high intensity focused ultrasound therapy for advanced hepatocellular carcinoma. *J Gastroenterol Hepatol* 2007; 22:2148–2154
19. Zhu H, Zhou K, Zhang L, et al. High intensity focused ultrasound (HIFU) therapy for local treatment of hepatocellular carcinoma: role of partial rib resection. *Eur J Radiol* 2009; 72:160–166
20. Stewart EA, Gedroyc WM, Tempany CM. Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique. *Am J Obstet Gynecol* 2003; 189:48–54
21. Stewart EA, Gostout B, Rabinovici J, Kim HS, Regan L, Tempany CM. Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. *Obstet Gynecol* 2007; 110:279–287
22. Sacks D, McClenny TE, Cardella JF, Lewis CA. Society of Interventional Radiology clinical practice guidelines. *J Vasc Interv Radiol* 2003; 14(9 Pt2):S199–S202
23. Wu F, Wang ZB, Chen WZ, et al. Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma. *Ann Surg Oncol* 2004; 11:1061–1069
24. Zhang L, Zhu H, Jin CB, et al. High intensity focused ultrasound (HIFU): effective and safe therapy for hepatocellular carcinoma adjacent to major hepatic veins. *Eur Radiol* 2009; 19:437–445
25. Wang Z, Bai J, Li F, et al. Study of a “biological focal region” of high-intensity focused ultrasound. *Ultrasound Med Biol* 2003; 29:749–754
26. Lorenz M, Muller HH. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2000; 18:243–254
27. Veltri A, Sacchetto P, Tosetti I, Pagano E, Fava C, Gandini G. Radiofrequency ablation of colorectal liver metastases: small size favorably predicts technique effectiveness and survival. *Cardiovasc Intervent Radiol* 2008; 31:948–956
28. Hänsler J, Frieser M, Tietz V, et al. Percutaneous radiofrequency ablation of liver tumors using multiple saline-perfused electrodes. *J Vasc Interv Radiol* 2007; 18:405–410
29. Mack MG, Straub R, Eichler K, Söllner O, Lehnert T, Vogl TJ. Breast cancer metastases in liver: laser-induced interstitial thermotherapy—local tumor control rate and survival data. *Radiology* 2004; 233:400–409
30. Slupski M, Włodarczyk Z, Jasinski M, Masztalerz M, Tujakowski J. Outcomes of simultaneous and delayed resections of synchronous colorectal liver metastases. *Can J Surg* 2009; 52:E241–E244
31. Kennedy JE, Wu F, ter Haar GR, et al. High-intensity focused ultrasound for the treatment of liver tumours. *Ultrasonics* 2004; 42:931–935