High intensity focused ultrasound: A noninvasive therapy for locally advanced pancreatic cancer

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Abstract

The noninvasive ablation of pancreatic cancer with high intensity focused ultrasound (HIFU) energy is received increasingly widespread interest. With rapidly temperature rise to cytotoxic levels within the focal volume of ultrasound beams, HIFU can selectively ablate a targeted lesion of the pancreas without any damage to surrounding or overlying tissues. Preliminary studies suggest that this approach is safe and feasible, and can be used alone or in combination with systemic chemotherapy for the treatment of patients with locally advanced pancreatic cancer. It can effectively alleviate cancer-related abdominal pain, and may confer an additional survival benefit with few significant complications.

INTRODUCTION

Carcinoma of the exocrine pancreas is the fourth leading cause of cancer-related death in the United States and the Western world. In 2013, 45220 estimated new cases were diagnosed for the United Sates, with 38460 associated deaths[1,2]. Because of the frequent delay in diagnosis, more than 80% of patients have locally advanced or metastatic disease at presentation, and are unsuitable for curative surgical resection[1,2]. Prognosis in pancreatic cancer is generally dismal. Median survival for locally advanced disease is just 6-10 mo, but this falls to 3-6 mo in patients with metastatic disease; overall 5-year survival rate is about 5%[1,2].

Standard options available for treating patients with unresectable pancreatic cancer are limited to chemotherapy, radiotherapy, or a combination of the two. Though few regimens may offer a limited survival benefit, novel treatment strategies are urgently needed. As a noninvasive approach, high intensity focused ultrasound therapy can selectively ablate a targeted lesion of the pancreas. Preliminary studies indicate that this approach is safe and feasible, and can be used alone or in combination with chemotherapy. It can effectively alleviate cancer-related abdominal pain, and may confer an additional survival benefit with few significant complications.

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Ultrasound beam is observed under light microscope only less than the size of 10 cells, which is histologically.

The boundary of the thermally necrosed region, referred to in HIFU as the “lesion” represents the “56°C for 1 s or longer” contour. Higher temperatures will have been reached at its source, and used to set fire to combustible material using a magnifying glass, the power of an ultrasound beam can be focused. If the concentrated energy is sufficient, there may be tissue destruction solely within the focal volume, while cells lying elsewhere remain unharmed.

Ultrasound energy absorption by living tissue can result in measurable temperature rises. For HIFU, the energy is greatest within the focal volume, and thus the temperature is maximal there. The mechanism for cell killing is primarily thermal. The temperature rises rapidly, and is held in excess of 56°C for 1 s or longer. This causes immediate coagulation necrosis of the targeted volume. The extent of cellular thermal damage is determined both by the temperature achieved, and the length of time for which it is maintained, the higher the temperature, the shorter the time required to produce identical effects.

The boundary of the thermally necrosed region, referred to in HIFU as the “lesion” represents the “56°C for 1 s or longer” contour. Higher temperatures will have been reached at its centre, and in reality, the temperature within the focal volume may rise rapidly above 80°C during HIFU treatments. A steep temperature gradient exists at the lesion boundary, and therefore a sharp demarcation between the treated and normal extra-focal tissue is only less than the size of 10 cells, which is histologically observed under light microscope.

DEFINITION OF HIFU ABLATION

Ultrasound is a form of vibrational wave. It can be brought to a tight focus at a distance from its source while an ultrasound beam propagates harmlessly through living tissues. Just as energy in the sun can be concentrated to a point, and used to set fire to combustible material using a magnifying glass, the power of an ultrasound beam can be focused. If the concentrated energy is sufficient, there may be tissue destruction solely within the focal volume, while cells lying elsewhere remain unharmed.

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Figure 1 Schematic diagram demonstrating the principle of high intensity focused ultrasound treatment for pancreatic cancer. Ultrasound beam is focused into a small volume in which ultrasound energy is converted into heat to induce the required coagulation necrosis of a targeted pancreatic tumor. T: HIFU transducer; C: The targeted pancreatic cancer.

At high ultrasound intensity levels, not only thermal effects, but those resulting from mechanical mechanisms become important. The most important non-thermal mechanism for tissue disruption in HIFU fields is acoustic cavitation, which leads to the local destruction of the tissue due to cavitation-induced high pressures and temperatures.

The intention of a HIFU treatment is to deliver ultrasound energy to a well-defined targeted volume at depth, and to induce complete coagulation necrosis of the tumor. A single (1-3 s) HIFU exposure usually produces a very small cigar-shaped lesion of dimensions of 10-20 mm along the beam axis and 1-2 mm in the transverse direction. However, by placing lesions side by side, conformal confluent volumes of ablation of clinically relevant size can be achieved, as shown in Figure 1. It is important that individual lesions overlap in order that no viable tumor cells remains between them. Due to the nature of using a small lesion to cover the large volume of tumor, theoretically there should be no limitation of tumor size, but it will take long and costly treatment times when attempting to ablate a large tumor. For safety reasons, in weaken and old patients HIFU procedure may be divided into two sessions when tumor is too large, and each session ablates the separated part of the targeted tumor. However, as HIFU is guided by either US or MRI, it is unsuitable to treat small tumors (less than 0.5 mm), if they are not clearly detected by both images.
DESTRUCTIVE EFFECTS OF HIFU ABLATION

Direct thermal and non-thermal effects

The effects of thermal ablation on a targeted tumor are determined by increased temperatures due to thermal energy deposition, rate of removal of heat, and the specific thermal sensitivity of the tissue. As the tissue temperature rises, the time required to achieve irreversible cellular damage decreases exponentially. At temperatures between 50 °C and 55 °C, cellular death occurs instantaneously in cell culture. Protein denaturation, membrane rupture, cell shrinkage, pyknosis, and hyperchromasia occur between 60 °C and 100 °C, leading to almost immediate coagulation necrosis. In addition, acoustic cavitation, one of the mechanical effects induced by HIFU ablation, is the most important non-thermal mechanism for tissue disruption. Small gaseous nuclei existing in subcellular organelles and fluid in tissue are the sources of cavitation, which can expand and contract under the influence of the acoustic pressure. During the collapse of bubbles, the acoustic pressure, shear stress, and subsequently high temperature can induce the local destruction of a targeted tissue.

Thermal effects on tumor blood vessels

Structural and functional changes are directly observed in tumor blood vessels after thermal ablation. These changes are not as well described as thermal effects on the tissues, but they rely on varying temperatures. At temperatures between 40 °C and 42 °C, there is no significant change in tumor blood flow after 30-60 min exposure. Beyond 42 °C to 44 °C, there is an irreversible decrease in tumor blood flow, with vascular stasis and thrombosis, resulting in heat trapping and progressive tissue damage. When temperatures exceed 60 °C, immediate destruction of tumor microvasculature occurs. It cuts the blood supply to the tumor directly through the cauterization of the tumor feeder vessels, leading to deprivation of nutrition and oxygen. Thus, tissue destruction can be enhanced by the damage caused by thermal ablation to tumor blood vessels.

CLINICAL OUTCOMES

Up to now, HIFU has been largely reported as a palliation option to treat patients with locally advanced pancreatic cancer. There are mainly two HIFU commercial devices available to clinical application, and the HIFU-treated patients are almost from Asia. Both devices incorporate B-mode ultrasonography to target and monitor the therapeutic procedure. One is Chongqing HIFU system (Model-JC and JC200 HIFU system, Haifu Medical Technology, Chongqing, China). It is an extracorporeal ultrasound-guided HIFU device, and employs continuous HIFU wave with high intensity (5-20 kW/cm²). The therapeutic regime is a typically thermal ablation, and each patient receives HIFU treatment only once. Treatment time is dependent on the size of a targeted tumor, which ranges from 45 min to 3.2 h. During the procedure, acoustic intensity should gradually increase in the focus until a hyperechogenic change is clearly observed within the targeted lesion on ultrasound imaging (Figure 2). This tissue response is not only a good real-time imaging assessment to determine whether coagulation necrosis could occur during each HIFU shot in the targeted tumor, but also a imaging feedback to control energy delivery of HIFU exposures. Chongqing HIFU device got CE approval in 2005 for the treatment of pancreatic cancer, and now it has been increasingly used for clinical applications in Europe. The other is a FEB-BY Serial HIFU System (China Medical Technologies, Beijing, China). It is also an extracorporeal ultrasound-guided HIFU device, but uses pulsed-wave HIFU with low intensity (< 3 kW/cm²). The therapeutic regime is similar to focused ultrasound hyperthermia treatment. Each patient has separately undergone 4-7 sessions over the course of 10-14 d, and every session lasts about 1-1.5 h. During the procedure, acoustic intensity should drop down if a patient feels abdominal pain or discomfort. The clinical outcomes of the both HIFU devices are summarized in Tables 1 and 2.
Continuous-wave HIFU treatment

The first success of HIFU ablation for advanced pancreatic cancer was conducted in Chongqing China in 2000\cite{21}. It was a phase I - II prospective clinical trial, and both survival benefit and pain control were observed during follow-up period. Eight patients with locally advanced pancreatic cancer were treated only once with continuous-wave HIFU alone for palliation. The tumor ranged from 4.5 to 8 cm in diameter (mean 5.89 cm), and was mainly located in the body and tail of the pancreas. The results showed that HIFU treatment was safe and feasible, and no complications were recorded. After HIFU, pre-existing severe back pain of presumed malignant origin disappeared in each patient. Follow-up images showed reduction or absence of tumor blood supply in the treated region with significant shrinkage of the ablated tumor, as shown in Figure 3. Of them, 4 patients died (median survival time 11.25 mo, range 2-17 mo), and the remaining 4 patients were still alive with median follow-up time of 11.5 mo (range 9-16 mo). The authors concluded that HIFU could be safe, effective and feasible in the treatment of patients with advanced pancreatic cancer.

Subsequently, several clinical studies were performed to investigate the safety and feasibility of HIFU for the treatment of patients with advanced-stage pancreatic cancer\cite{22,25}. They were one-arm phase I - II trials, and clinical results were very encouraging, as shown in Table 1. Orsi et al\cite{22} reported a preliminary experience of using HIFU for 6 patients with un-resectable pancreatic cancer. After treatment, either PET/CT or contrast-enhanced MR images showed complete ablation in 5 of 6 patients, and pain relief was observed in all patients. Median survival was 7 mo, and 1- and 2-year survival rates were 42.9% and 21.4% respectively. Local skin burn was not observed, but portal vein thrombosis was detected as a major complication in one patient after treatment. The same group also treated 2 inoperable patients with pancreatic cancer. It was a phase I prospective clinical trial, and clinical results were very encouraging, as shown in Table 1. The study concluded that HIFU could be safe, effective and feasible in the treatment of patients with advanced pancreatic cancer.

Continuous-wave HIFU treatment for patients with advanced pancreatic cancer

Table 1: Studies of continuous-wave high intensity focused ultrasound treatment for patients with advanced pancreatic cancer

| Study       | n  | Patients | Treatment method | HIFU Device | Outcome and survival | Complications |
|-------------|----|----------|------------------|-------------|----------------------|---------------|
| Wu et al\cite{21} | 8  | Advanced pancreatic cancer | One-session HIFU | Continuous HIFU irradiation, Model-JC HIFU System | Pain relief: 8/8 (100%); Median survival: 11.25 mo (2-17 mo) | None |
| Orsi et al\cite{22} | 6  | Late-stage pancreatic cancer, unresectable | One-session HIFU | Continuous HIFU irradiation, Model-JC HIFU System | Pain relief: 6/6 (100%); Median survival: 7 mo; Overall survival: 42.9% at 12 mo and 21.4% at 24 mo | Portal vein thrombosis: 1/6 (16%) |
| Wang et al\cite{24} | 40 | Advanced pancreatic cancer, unresectable | One-session HIFU | Continuous HIFU irradiation, Model-JC HIFU System | Pain relief: 35/40 (87.5%); Median survival: 8 mo (stage II: 10 mo; stage IV: 6 mo); Overall survival: 58.8% at 6 mo and 30.1% at 12 mo | None |
| Sung et al\cite{25} | 46 | Advanced cancer, unresectable | One-session HIFU | Continuous HIFU irradiation, Model-JC HIFU System | A significant reduction of pain score (P < 0.001); Median survival: 12.4 mo; Overall survival: 52.2% at 6 mo, 30.4% at 12 mo, and 21.7% at 18 mo | Mild abdominal pain: 16/46 (34%); severe abdominal pain with vomiting: 2/46 (4%); transient fever: 3/46 (6%); pancreaticoduodenal fistula: 1/46 (2%); gastric bleeding due to ulcer: 1/46 (2%); Abdominal distension, anorexia and nausea: 10/224 (4%); asymptomatic vertebral injury: 2/224 (1%); obstructive jaundice: 1/224 (1%) |
| Wang et al\cite{24} | 224 | Advanced Pancreatic cancer | One-session HIFU | Continuous HIFU irradiation, Model-JC HIFU System | Pain relief and survival data not reported | None |
| Gao et al\cite{26} | 39 | Locally advanced pancreatic cancer, unresectable | One-session HIFU alone: 14 pts; HIFU + gemcitabine: 25 pts | Continuous HIFU irradiation, Model-JC HIFU System | Pain relief: 31/39 (79.5%); Median survival: 11 mo; Overall survival: 82.1% at 6 mo, and 39.5% at 12 mo | None |
| Zhao et al\cite{27} | 37 | A phase II study of HIFU + gemcitabine for locally advanced pancreatic cancer, average tumor size 3.4 cm (1.7-8.5 cm). | GEMTINABINE on days 1, 8 and 15, and multiple HIFU sessions on days 1, 3 and 5. The combined treatment repeated every 28 d | Continuous HIFU irradiation, HIFUNIT-9000 HIFU System | Pain relief: 29/37 (78%); Fever: 26/37 (70%); neutropenia: 6/37 (16%); thrombocytopenia 2/37 (5%); nausea and vomiting 3/37 (8%); diarrhea 2/37 (5%) | None |

HIFU: High intensity focused ultrasound; pts: Patients.
Table 2  Studies of pulsed-wave high intensity focused ultrasound treatment for patients with advanced pancreatic cancer

| Study       | n   | Patients                          | Treatment Method                        | HIFU Device                  | Outcome and Survival | Complications          |
|-------------|-----|-----------------------------------|-----------------------------------------|------------------------------|----------------------|-------------------------|
| Wang et al[26] | 15  | Late-stage pancreatic cancer, unresectable, average tumor size 5.6 cm (2.2-8 cm) | Multiple-session HIFU monotherapy, average sessions 8.1 (2-12) | Pulsed HIFU irradiation, FEB-BY HIFU System | Pain relief: 13/13 (100%) | No survival data available | Mild abdominal pain: 2/15 (13%) |
| Li et al[27]  | 25  | Advanced pancreatic cancer, unresectable, average tumor size unclear | One-session HIFU: 19 pts; 2-session HIFU: 6 pts; average sessions 1.2 | Pulsed HIFU irradiation, FEB-BY HIFU System | Performance status and pain improvement: 25/25 (92%); median overall survival: 10 mo; 1-year survival: 42% | First-degree skin burn: 3/25 (12%) |
| Ge et al[28]  | 20  | A retrospective study for unresectable pancreatic cancer, average tumor size (4.5 ± 1.2) × (3.5 ± 1.0) cm | Multiple-session HIFU monotherapy; average HIFU session 9.3 ± 4.1 | Pulsed HIFU irradiation, FEB-BY HIFU System | Pain relief and survival data not reported | Mild abdominal pain: 5/25 (25%); subcutaneous fat callus: 4/25 (20%); 2nd-degree skin burn: 1/25 (5%); pancreatic effusion: 1/25 (5%) | Superficial skin burns: 3/89 (3.5%); subcutaneous fat sclerosis: 8/89 (6%); asymptomatic pseudocyst: 1/89 (1%) |
| Xiong et al[29]  | 89  | A retrospective study for unresectable pancreatic cancer, tumor size not reported | Multiple-session HIFU monotherapy: 84 pts; HIFU + gemcitabine: 5 pts; HIFU sessions ranging 4-10 | Pulsed HIFU irradiation, FEB-BY HIFU System | Pain relief: 54/67 (80%); median survival: 20.0 mo (stage II); 11.2 mo (stage III) and 5.4 mo (stage IV) | No survival data available | Pancreatitis: 1/12 (8%); skin burn: 5/12 (41%); subcutaneous fat sclerosis: 2/12 (16%) |
| Lee et al[30]  | 12  | Advanced pancreatic cancer, unresectable, average tumor size 3.5 cm (2.3-5.3 cm) | Multiple-session HIFU monotherapy: 9 pts; HIFU + gemcitabine: 3 pts; average HIFU sessions: 4.2 (1-18) | Pulsed HIFU irradiation, FEB-BY HIFU System | Median survival for those receiving HIFU alone: 10.3 mo; Overall survival for 3 patients receiving the combined treatment: 26.0, 21.6 and 10.8 mo, respectively | No survival data available | 

HIFU: High intensity focused ultrasound; pts: Patients.

Both patients suffered from episodes of severe nightly hypoglycemia, which was not efficiently controlled by medication. During 9-mo follow-up, local disease control and symptom relief were achieved in them without any complications. Wang et al[26] followed up HIFU-treated 40 patients with advanced pancreatic cancer (stage III, 13 patients; stage IV, 27 patients). Average tumor size was 4.3 cm (range 2-10 cm). After HIFU, pain relief was achieved in 87.5% of the patients. The median overall survival was 8 mo for all patients, including 10 mo in stage II and 6 mo in stage III patients. Six-month and 1-year survival rates were 58.8% and 30.1% respectively. No severe complications were observed during follow-up period.

Sung et al[31] treated 46 patients with advanced pancreatic cancer, including 18 in stage III and 28 in stage IV disease. Average tumor size was 4.2 ± 1.4 cm (range: 1.6-9.3 cm). After HIFU treatment, contrast-enhanced MR images showed 90%-100% ablation in 38 lesions, 50%-90% in 8 and within 50% in 3 lesions. Pain score (visual analog scale) was significantly reduced from 4.9 ± 1.1 to 2.1 ± 1.1 (P < 0.001). Overall median survival from initial diagnosis was 12.4 mo. Overall survival rates at 6, 12, and 18 mo from HIFU were 52.2%, 30.4%, and 21.79%, respectively, with a median survival of 7.0 mo. Minor complications (abdominal pain, fever and nausea) was observed in 28 (57.1%) of 49 HIFU treatment. Major complications were detected in 5 (10.2%) of 49 treatment, including 2-3 degree skin burn in 2, pancreaticoduodenal fistula in 2 and gastrointestinal tract bleeding due to gastric ulcer in one patient. The authors concluded that HIFU was safe and effective, and it could induce excellent local tumor control in most patients with advanced pancreatic cancer.

The largest clinical experience of using HIFU treatment for advanced pancreatic cancer was reported by Wang et al[26]. A total of 224 patients were enrolled in this study for safety analysis of HIFU treatment. Gastrointestinal dysfunction such as abdominal distension and anorexia with slight nausea was observed in 10 cases (4.5%) after HIFU treatment. One case with pancreatic head cancer developed obstructive jaundice 2 wk after HIFU treatment. Vertebral injury, identified by MRI, occurred in 2 cases, although no symptoms were seen. No severe complications were observed in all enrolled patients. These results indicated that HIFU was a safe, non-invasive treatment. However, no long-term follow-up and survival data were reported in this study.

HIFU combined with chemotherapy was also used to treat advanced pancreatic cancer. Gao et al[32] reported an initial use of HIFU alone or HIFU plus gemcitabine for the treatment of 39 patients with locally advanced pancreatic cancer. Among them, 14 patients received one-session HIFU monotherapy, and the remaining 25 patients underwent HIFU combined gemcitabine therapy. After treatment, no severe complications were observed, and pain relief was achieved in 31 (79.5%) of 39 patients who had previous pain. Median overall survival was 11.0 mo, and 6- and 12-mo survival rates for all patients were 82.1% and 39.5% respectively. However, medial survival...

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**Table 2**  Studies of pulsed-wave high intensity focused ultrasound treatment for patients with advanced pancreatic cancer

- **Study**
- **n**
- **Patients**
- **Treatment Method**
- **HIFU Device**
- **Outcome and Survival**
- **Complications**
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Figure 3. Contrast-enhanced T-weighted MR images obtained in a patient treated with high intensity focused ultrasound for advanced pancreatic cancer. The tumor was 4.5 cm in diameter and located in the body of the pancreas. A: Image obtained before high intensity focused ultrasound (HIFU) shows blood supply in the pancreatic lesion (arrows). B: Image obtained 2 wk after HIFU shows no evidence of contrast enhancement in the treated lesion (arrows), which is indicative of complete coagulation necrosis in the treated pancreatic cancer.

and 1-year survival were significantly higher in patients treated with HIFU plus chemotherapy while compared with those in patients treated with HIFU alone. There were statistical differences between two groups ($P < 0.01$). Zhao et al.\textsuperscript{[28]} also reported a phase II trial investigating the safety and efficacy of concurrent gemcitabine and HIFU for the treatment of 37 patients with locally advanced pancreatic cancer. The average tumor size was 3.4 cm (range 1.7–8.5 cm). All patients received gemcitabine 1000 mg/m\textsuperscript{2} on days 1, 8, and 15, and concurrent HIFU treatment (HIFUNIT-9000, AS Sci-Tech, Shanghai, China) on days 1, 3, and 5. The combined treatment regime was repeated every 28 d and continued until disease progression, patient refusal, or an unacceptable toxicity. The results showed that overall survival was 12.6 mo (95%CI: 10.2–15.0), and the estimates of overall survival at 12 and 24 mo were 50.6% (95%CI: 36.7–64.5%) and 17.1% (95%CI: 5.9–28.3%), respectively. Pain was relieved in 22 (78.6%) of 28 patients who had complained of abdominal pain consistent with tumor-related pain. After treatment, grade 1 or 2 fever was detected in 70.3% of patients. Six patients (16.2%) experienced grade 3 neutropenia, and 2 (5.4%) had grade 3 thrombocytopenia. Grade 3 nausea/vomiting and diarrhea were observed in 3 (8.1%), and 2 (5.4%) patients respectively. The authors concluded that concurrent gemcitabine and HIFU was a tolerated treatment modality with promising activity in patients with previously untreated locally advanced pancreatic cancer.

**Pulsed-wave HIFU treatment**

Compared to continuous-wave HIFU treatment, pulsed HIFU usually uses low energy with a multiple-session treatment regime. The first study of pulsed HIFU for advanced pancreatic cancer was reported by Wang et al.\textsuperscript{[29]} in 2002, and 15 patients received multiple-session pulsed HIFU treatment for the purpose of palliation. HIFU session ranged from 2 to 12 (average 8.1). The average tumor size was 5.6 cm (range 2.2–8 cm). Seven patients had a lesion located in the head of the pancreas, including 4 who had previously received gallbladder-intestine bypass operation. The remaining 8 patients had carcinoma of the body and tail of the pancreas. After HIFU, pain relief was observed in 13 (100%) of 13 patients who had previously cancer-related pain. Tumor size shrank in 3 patients while the other 12 patients had no change. Unfortunately, there were no survival benefit data available in this study. Mild abdominal pain was recorded as a complication in 2 of 15 patients.

Li et al.\textsuperscript{[30]} reported a clinical result of pulsed HIFU for the treatment of 25 patients with unresectable pancreatic cancer. Of them, 19 patient received one-session HIFU, and the remaining 6 had two session treatments. The treatment time was less than 60 min in each session. After HIFU treatment, 3 patients had first degree skin burn, but they recovered without any medication. Performance statue and pain improvement were observed in 23 (92%) of 25 patients during follow-up period. Overall average survival time was 10 mo, and 1-year survival rate was 42% for all patients. Ge et al.\textsuperscript{[31]} analyzed clinical results of HIFU treatment for advanced pancreatic cancer in a retrospective study. Twenty patients received multiple-session HIFU treatment, and the average number of HIFU sessions was 9.3 ± 4.1 for each patient. After treatment, mild abdominal pain was observed in 5 (25%) patients, and subcutaneous fat callus was found in 4 (20%) of 25 patients. One patient experienced 2nd-degree skin burn, and pancreatic effusion was also detected in 1 patient. However, no pain relief and survival data were reported in this study.

Xiong et al.\textsuperscript{[32]} reported the largest retrospective study of using pulsed HIFU treatment for advanced pancreatic cancer. Eighty-nine patients with pancreatic cancer were analyzed after HIFU, including 4 in stage II, 39 in stage III, and 46 in stage IV disease. Tumors were located in the pancreatic head in 34 patients (38.2%), and in the body and/or tail of the pancreas in 55 patients (61.8%), although tumor size was unclear. In order to treat an entire volume of the tumor, 4-10 HIFU sessions were needed for each patient. After treatment, pain relief was achieved in 54 (80.6%) of 67 patients who had pain prior to HIFU. The median survival was 26.0 mo in stage II patients.
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11.2 mo in stage III, and 5.4 mo in stage IV patients. Complications included superficial skin burns (3.4%), subcutaneous fat sclerosis (6.7%), and an asymptomatic pancreatic pseudocyst (1.1%). The authors concluded that although this retrospective study had significant limitations, preliminary results suggested that the clinical application of HIFU for pancreatic cancer appeared to be safe and was a promising modality of treatment for palliation of pain related to pancreatic cancer.

Similar to continuous HIFU treatment, pulsed HIFU combined with chemotherapy were also used to treat advanced pancreatic cancer. Lee et al. reported initial experience of using pulsed HIFU for the treatment of 12 patients with unresectable pancreatic cancer, including 9 treated with HIFU alone, and 3 treated with pulsed HIFU combined with gemcitabine. Median tumor size was 3.5 cm (range: 2.3-5.3 cm), and HIFU sessions ranged from 1 to 18 (average 4.8 sessions). After HIFU treatment, skin burn was observed in 5 patients including 1 in 1st-degree and 4 in 2nd-degree skin burn. Subcutaneous fat sclerosis caused by thermal injury was detected in 2 patients, and one patient developed acute pancreatitis with a large pseudocyst after treatment. The median survival for those receiving HIFU treatment alone was 10.3 mo. However, the overall survival of three patients treated by HIFU combined with gemcitabine was 26.0, 21.6 and 10.8 mo, respectively, suggesting that concurrent pulsed HIFU and chemotherapy could be potentially more effective in the treatment of unresectable pancreatic cancer.

**DISCUSSION AND CONCLUSION**

HIFU is an attractive emerging therapy for unresectable pancreatic cancer. It has been offered as a palliation option for improving the quality of life in patients with advanced-stage pancreatic cancer. Almost all studies have been conducted for the assessment of technical safety and feasibility, and clinical outcome have showed that HIFU therapy is safe and reproducible.

Many of early concerns that surrounded the safety of HIFU treatment for pancreatic cancer have been addressed in the pilot studies. As shown in the Tables 1 and 2, the incidence of complications directly caused by HIFU is relatively lower while compared with radiation therapy and minimally-invasive thermal ablation approaches. Mild complications include abdominal pain, nausea and vomiting, skin burn, and subcutaneous fat sclerosis. They usually occur in 3%-20% patients, and recover in a short time after HIFU treatment, without any medication. Severe complications are observed in 3 patients, including 1 case with portal vein thrombosis, 1 with pancreaticoduodenal fistula, and 1 with obstructive jaundice. Two patients experience pancreatitis with a large pseudocyst around the inflammation site, and 1 patient has gastrointestinal bleeding due to gastric ulcer after treatment. These demonstrate that HIFU is a promising approach with a few adverse effects for the treatment of unresectable pancreatic cancer. However, contraindications should be considered if a targeted lesion is too close to the duodenum and bile duct. It can extremely increase the risk of bowel perforation and bile leakage because of HIFU damage on these normal structures. Unfortunately, there is no exact safe distance between the tumor and adjacent vital structures available to HIFU treatment currently, and further studies are needed in animal models to define it.

Most clinical results to date are obtained in retrospective studies, and there are a few phase II prospective clinical trials performed in research settings for assessment of HIFU efficacy. These studies have shown that HIFU can significantly improve the quality of life in patients with advanced-stage pancreatic cancer. Pain relief is obviously observed in 78%-100% patients after treatment. Median survival time ranges from 7 to 12 mo, which is dependent on the TNM stage of disease. Case reports reveal that while HIFU is combined with chemotherapy (gemcitabine), median survival and overall survival rate seem better than HIFU alone, but this claim needs to be confirmed in randomized, two-arm clinical trials. In addition, almost all studies uses symptom relief, survival and MRI/CT changes as evidences of assessing treatment effects on pancreatic cancer, instead of histomorphological examination following HIFU treatment. Further studies are needed to investigate the characteristics of histological changes in pancreatic cancer after HIFU treatment.

Two various regimes of therapeutic strategy have been noticed in HIFU treatment. One is continuous HIFU, and the other is pulsed HIFU treatment. They are totally different in both technical parameter and therapeutic strategy, as shown in Table 3. Using high intensities ranging from 5 to 20 kW/cm², each continuous HIFU shot can induce coagulation necrosis of a targeted tumor. It is a one-session treatment, and can be used alone for the treatment of unresectable pancreatic cancer. There is no need to be repeated if the tumor is significantly ablated. In addition, the appearance of a hyperechoic region of in the focus is clearly observed on ultrasound imaging immediately after each shot, as shown in Figure 2. Either sedation or general anesthesia is required for patients during treatment procedure due to discomfort and pain. After treatment, the patients require hospitalization for several days.

In contrast, pulsed HIFU uses lower ultrasound intensities, which is usually less than 3 kW/cm². It is a multiple-session treatment, and needs to be repeated for many times ranging from 5 to 10 sessions if the patients are suitable. Some patients require sedation during treatment procedure, but most of them don't need it if there is no pain or discomfort. It is a one-day procedure, and there is no need for patients to stay in hospital after treatment. Recent studies have indicated that pulsed HIFU can significantly enhance chemotherapeutic agents against tumor cells, suggesting that pulsed HIFU may be a treatment approach using focused ultrasound for hyperthermia, instead of HIFU for inducing coagulation necrosis. Actually, focused ultrasound hyperthermia has
HIFU: High intensity focused ultrasound; US: Ultrasound.

been used as adjuvant to radiotherapy and chemotherapy for cancer treatment in the 1990s\textsuperscript{[37,38]}. It can raise the temperature of the tumor from 37°C to 42-45°C for 60 min. This may make some cancer cells more sensitive to radiation and chemotherapy, or harm other cancer cells that both therapies cannot damage\textsuperscript{[39,40]}. It is obvious that focused ulceration hyperthermia uses lower acoustic energy to heat tumor, and there is no coagulation necrosis that occurs in the treated tumor while compared with HIFU treatment. However, HIFU is a therapeutic approach to locally heat and destroy diseased tissues through thermal ablation. In order avoid any confusion related to the definition of HIFU and hyperthermia, it is highly recommended to use pulsed focused ultrasound hyperthermia rather than pulsed HIFU treatment in the future.

In conclusion, HIFU ablation has been shown a promising approach for the palliative treatment of advanced pancreatic cancer. The nature of non-invasiveness and highly treatment precision has made HIFU become more attractive emerging therapy. It has much potential for further clinical investigation and technical improvements. Currently, preliminary studies suggest that this approach is technical safe and feasible, and can be used alone or in combination with systemic chemotherapy. It can effectively alleviate cancer-related abdominal pain, and may confer an additional survival benefit with few significant complications. However, large, prospective, multi-center randomized clinical trials will be needed to assess the long-term efficacy, and determine the future role of this technique for the treatment of locally advanced pancreatic cancer. Once oncologic efficacy data from those trials are available, HIFU ablation will become an attractive treatment option for patients with pancreatic cancer.

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