

ORIGINAL ARTICLE

Early Clinical Experience Using High Intensity Focused Ultrasound for Palliation of Inoperable Pancreatic Cancer

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ABSTRACT

Objective To evaluate the safety and efficacy of high intensity focused ultrasound for palliation of inoperable pancreatic cancer in humans. **Patients** Eighty-nine patients with advanced pancreatic cancer were treated with high intensity focused ultrasound. There were 4 patients with stage II, 39 patients with stage III, and 46 patients with stage IV disease. The location of the tumors was as follows: head of pancreas 34 patients, body and/or tail of pancreas 55 patients. **Methods** Pain relief, local tumor control rate, median survival and complications were observed after high intensity focused ultrasound treatment. **Results** In the clinical treatments in humans the following local tumor control was seen: complete response, 0%; partial response, 14.6%; no change, 57.3%; progressive disease, 28.1%. Pain relief was achieved in 80.6% of patients who had pain prior to high intensity focused ultrasound therapy. The median survival was 26.0 months for patients with stage II disease, 11.2 months for patients with stage III disease, and 5.4 months for patients with stage IV disease. One-year survival rate was as follows: stage II, 100%; stage III, 41.0%; and stage IV, 6.5%. Two-year survival rate was as follows: stage II, 75.0%; stage III, 10.3%; and stage IV, 0%. Complications included superficial skin burns (3.4%), subcutaneous fat sclerosis (6.7%), and an asymptomatic pancreatic pseudocyst (1.1%). There were no severe complications or adverse events related to high intensity focused ultrasound therapy seen in any of the patients treated. **Conclusions** Although this retrospective study has significant limitations, preliminary results suggest that the clinical application of high intensity focused ultrasound for pancreatic cancer appears to be safe and is a promising modality of treatment for palliation of pain related to pancreatic cancer.

INTRODUCTION

A majority of patients diagnosed with pancreatic cancer have advanced disease at the time of diagnosis and are not amenable for surgery with intent to cure. The prognosis of patients with pancreatic cancer is one of the worst among all cancers. From the EURO CARE study, based on 31,312 European cases, overall survival at 1, 3 and 5 years was 16%, 5% and 4%, respectively [1]. While surgery currently provides the only possibility for cure, 85-90% of newly diagnosed pancreatic tumors are considered unresectable due to locally advanced disease or presence of metastasis [2]. Pain is a common symptom in patients with pancreatic

cancer with 60-90% of patients with advanced disease reporting pain [3]. Pain control is an important component of palliation and is commonly performed using opioid therapy and celiac plexus neurolysis. Opioid narcotics have undesired side-effects ranging from mild constipation to respiratory depression and altered mental status. In addition, some opioids have a dysphoric effect that can significantly impact the patients' quality of life [4]. Celiac plexus neurolysis can be performed in patients who have severe intractable pain that is poorly controlled on opioids; however, the procedure is invasive, requiring endoscopic ultrasound or CT-guidance. Initial uncontrolled and retrospective case series suggested that partial or complete pain relief was achieved in 70-90% of patients undergoing celiac plexus blockade; however, a meta-analysis of five randomized controlled trials demonstrated that the overall benefit was small with only a 6% reduction in the mean visual analog score compared to baseline [5]. High intensity focused ultrasound (HIFU) ablation is a non-invasive method of ablation therapy using focused ultrasound energy from an extracorporeal source that is targeted within the body resulting in thermally induced necrosis and apoptosis [6, 7, 8]. HIFU, also termed

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Abbreviations HIFU: high intensity focused ultrasound

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focused ultrasound surgery, is delivered from an ultrasound transducer that is focused either mechanically (spherically curved or using a focusing lens) or electronically by phasing an array of transducers. The focal characteristics of most clinically available transducers are similar to a grain of rice. The acoustic intensities used in HIFU differ from diagnostic ultrasound in that the time averaged acoustic intensity at the focus is several orders of magnitude greater for HIFU. Diagnostic ultrasound typically produces time averaged acoustic intensities around 100 mW/cm² whereas HIFU can deliver intensities at the focus that is over 10 kW/cm².

Acoustic energy is absorbed and heat is generated by delivering high acoustic intensities to tissue. Because of focusing, the acoustic intensities are high only within the focal region; however, outside the focal region the acoustic intensities are substantially lower, minimizing the risk of unintended injury to tissue outside the focal region. The focal temperature can be rapidly increased to over 60°C causing cell death in the focal region within a few seconds, while minimal tissue heating occurs outside the focus. If the temperature is elevated to over 100°C then boiling occurs at the focus and coagulative necrosis occurs immediately. However, if the temperature is not elevated to over 100°C then a phenomenon termed thermal fixation can occur where the cells do not undergo lysis and the tissue architecture remains relatively intact but the cells are no longer viable. This has been seen in patients treated with HIFU followed by surgical resection [8]. As the lesion evolves the cells degenerate resulting in coagulative necrosis; however, this effect is significant for the treatment of the pancreas where cell lysis has potential to release autodigestive enzymes and lead to pancreatitis. With HIFU treatments that result in thermal fixation, pancreatic cells do not undergo lysis until the intracellular enzymes have been completely denatured and inactivated, theoretically reducing the risk of pancreatitis with HIFU therapy.

Although the majority of the initial cell death within a high intensity ultrasound field is due to cell necrosis

from thermal injury, high intensity ultrasound can also induce apoptosis. The primary mechanism of cell death from hyperthermia is due to apoptosis [7].

The procedure requires no incisions or needle punctures and is often performed without sedation [9]. An illustration of how HIFU therapy is administered for ablation of pancreatic tumors is provided in Figure 1. HIFU therapy has been undergoing rapid development over the last decade such that several clinical HIFU devices are now commercially available. There are several reports in the literature describing the use of HIFU for treatment of pancreatic cancer, cholangiocarcinoma, hepatocellular carcinoma, metastatic liver disease, prostate cancer, breast cancer, renal cell carcinoma, osteosarcoma, uterine fibroids and other various solid tumors [10, 11, 12, 13, 14].

The use of HIFU for the palliative treatment of pancreatic cancer may be useful in patients that develop symptoms that would benefit from local tumor control. A report of HIFU treatment in 251 patients with advanced pancreatic cancer, TNM stage II-IV, suggest that HIFU treatment can reduce the size of pancreatic tumors without causing pancreatitis, and prolong survival [15]. Since this was only an observational study, no meaningful conclusion can be made regarding the utility of HIFU therapy on survival; however, an interesting finding was that 84% of patients with pain due to pancreatic cancer obtained significant relief of their pain after treatment with HIFU. Subsequently, there have been several additional case-series and non-randomized studies, primarily published in the Chinese literature, reporting similar findings of safety and pain relief with some studies even suggesting a survival benefit [9, 16, 17, 18, 19, 20, 21]. To date there is a single small case series of 8 patients in the English literature reporting the use of extracorporeal HIFU to treat pancreatic cancer [14]. All 8 patients had pain related to pancreatic cancer prior to initiating HIFU therapy with all patients obtaining relief of pain symptoms within 48 hours following HIFU therapy. The authors reported no skin burns, tumor hemorrhage, large blood vessel rupture, bowel perforation, or pancreatitis following HIFU therapy.

HIFU has been used clinically in China since 1999 to treat over 20,000 patients for a wide range of indications with an excellent safety profile. Clinical results from China suggests that HIFU may be an alternative treatment for patients with locally advanced disease [9, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23]. This article reports the early human clinical experience on inoperable pancreatic cancer with the FEP-BYTM (Yuande Biomedical Engineering Limited Corporation, Beijing, China) HIFU tumor therapy device at a single institution.

PATIENTS AND METHODS

Patients

This retrospective case series includes all 89 patients with inoperable pancreatic cancer treated with HIFU at

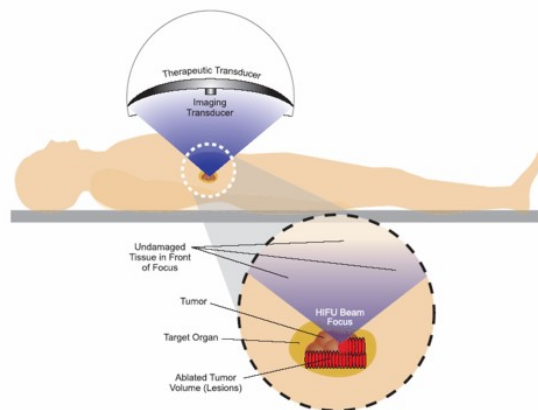


Figure 1. Illustration of extracorporeal high intensity focused ultrasound treatment of pancreatic tumors using the FEP-BY02TM system. High intensity focused ultrasound treatment is non-invasive using a transducer that is located above the patient that is in the supine position. Reproduced with permission [5].

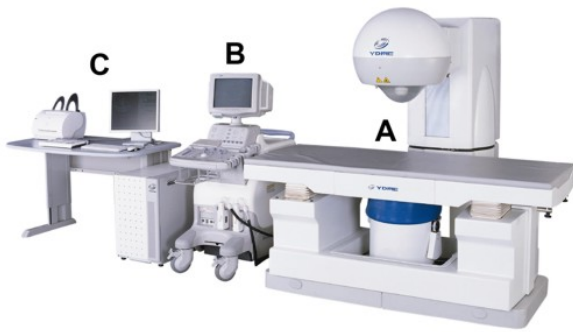


Figure 2. FEP-BY™ high intensity focused ultrasound device for tumor therapy. Components include a treatment table with upper and lower high intensity focused ultrasound transducers (A), B-mode ultrasound imaging system (B), and computer control system (C). In addition, there is an electrical power system and water treatment system (not pictured). Reproduced with permission (Yuande Biomedical Engineering Corp. Ltd., Beijing, China).

Peking University Peoples' Hospital from July 1998 to October 2007. Patients were all considered to have inoperable pancreatic cancer confirmed by an experienced pancreatic surgeon. The criteria for unresectability included evidence of distant metastatic disease, imaging evidence (CT, MRI or endoscopic ultrasound) of involvement of the celiac trunk or superior mesenteric artery, significant medical comorbidities that precluded these patients from an attempt at surgical resection, or refusal to undergo surgery. Patients were permitted to have received previous chemotherapy and/or radiotherapy. Patients were also allowed to continue chemotherapy or radiation therapy while undergoing HIFU therapy. Out of the 89 patients 56 (62.9%) were men and 33 (37.1%) were women with an overall average age of 65



Figure 3. FEP-BY™ high intensity focused ultrasound transducer. The transducer is made of 251 individual piezoceramic elements and is concave with a geometric focus of 26 cm. The center hole in the transducer is for the ultrasound imaging probe. Reproduced with permission (Yuande Biomedical Engineering Corp. Ltd., Beijing, China).

years (range: 47-84 years). Tumors were located in the pancreatic head in 34 patients (38.2%) and pancreatic body and/or tail in 55 patients (61.8%). Twenty-six (76.5%) out of the 34 patients with tumors in the pancreatic head presented with jaundice requiring either a metal biliary stent or surgery to relieve the biliary obstruction prior to HIFU treatment. Four patients (4.5%) had International Union Against Cancer (UICC) stage II disease (3 patients had medical comorbidities that precluded them from undergoing surgery and one patient refused surgery), 39 patients had stage III disease (43.8%), and 46 patients had stage IV disease (51.7%).

Among the 89 patients treated with HIFU, 39 patients received HIFU therapy after failure of treatment with chemotherapy and/or radiotherapy (43.8%). Five patients (5.6%) received HIFU therapy concurrently with chemotherapy (gemcitabine 1,000 mg/m² in a 30-minute infusion on days 1, 8, 15, then every 4 weeks). The other 45 patients (50.6%) received only HIFU therapy, either because the patient refused chemotherapy and/or radiotherapy, or because the patient was not felt to be a suitable candidate for chemotherapy and/or radiotherapy.

Instrumentation

The FEP-BY™ HIFU tumor therapy device (Yuande Biomedical Engineering Limited Corporation, Beijing, China) was used to deliver extracorporeal HIFU therapy (Figure 2). It is composed of four subsystems: 1) treatment table; 2) water degassing system; 3) diagnostic B-mode ultrasound imaging system (GE Logiq 5, Seongnam, Korea) with an imaging transducer mounted coaxially to the HIFU transducer; and 4) the HIFU transducer (Figure 3), which is a fixed focus concave transducer composed of multiple piezoelectric ceramics having an overall aperture of 37 cm with a focal length of 26 cm. The elements of the HIFU transducer are driven in phase at a frequency of 1.04 MHz. The -6 dB focal dimensions are 8 mm in length and 3 mm in diameter.

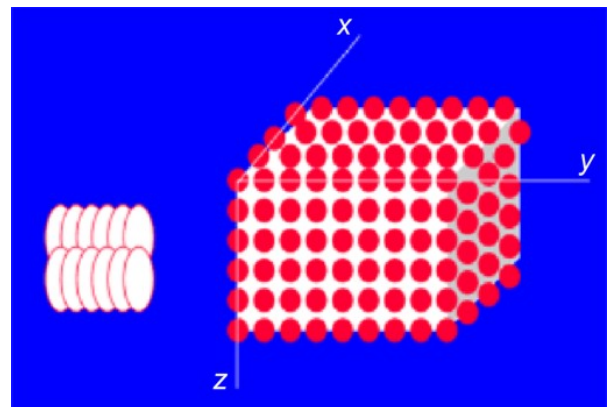


Figure 4. The spot accumulation method of high intensity focused ultrasound treatment. Treatment spots are placed in an overlapping fashion. The interval spacing in the x-y plane is 4-5 mm. The interval spacing in the z direction is 6-8 mm.

HIFU Treatment

For HIFU treatments, patients were treated using the upper HIFU transducer while in the supine position on the treatment table. The water bladder was filled with degassed water and coupled to the skin with ultrasound coupling gel. The tumor target was identified with the B-mode ultrasound imaging transducer, and the treatment plan was determined. HIFU treatment was delivered using the spot accumulation method where individual spots are treated in an overlapping fashion to treat a volume of tissue (Figure 4). Anesthesia was not administered to any of the patients. The patients fasted beginning the night before a HIFU procedure and the placement of a nasogastric tube was required prior to two HIFU treatment sessions in order to remove gas from the stomach that was obscuring the tumor. The HIFU treatment parameters were as follows: Acoustic power of 250-430 W (acoustic power varied depending on the depth of tumor); pulse length of 310-460 ms with a duty factor of 33-50%, and 50-80 pulses per treatment spot. The therapy was divided into several



Figure 5. Contrast enhanced-CT scan of a 63-year-old female demonstrating a tumor in the body of the pancreas prior to high intensity focused ultrasound therapy (a.) with evidence of ablation and necrosis following high intensity focused ultrasound therapy (b.).

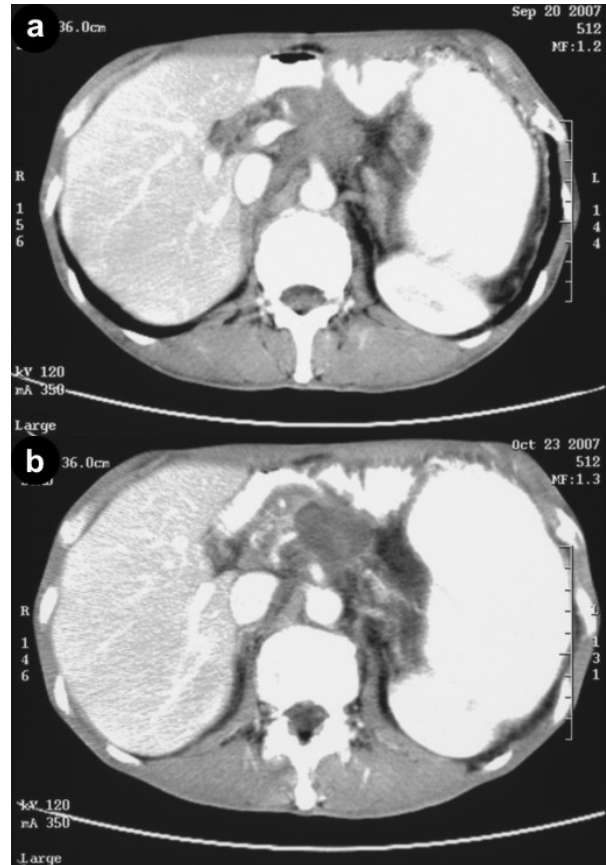


Figure 6. Contrast enhanced-CT scan of a 52-year-old male demonstrating a tumor in the body of the pancreas prior to high intensity focused ultrasound therapy (a.) with evidence of ablation and necrosis following high intensity focused ultrasound therapy (b.).

sessions such that each treatment session was approximately 60 minutes. The treatment of an entire tumor volume required 4-10 sessions to complete therapy.

Treatment Evaluation

Pain response and complications were observed after completion of HIFU treatments and at one month post-treatment. Pain response was routinely assessed during follow-up visits using a numeric pain scale (0-10). Contrast enhanced CT or MRI was used to determine the objective tumor response and to assess for any evidence of ablation (absence of perfusion on imaging). In addition PET/CT (GE Discovery ST16 PET-CT system, GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA) was performed before and after HIFU therapy in 5 patients.

STATISTICS

Mean, median, standard deviation (SD), range, and frequencies were used as descriptive statistics. Survivals were evaluated by means of the Kaplan-Meier method. Modification of SUV following HIFU therapy was tested by means of the Wilcoxon signed rank test for paired data. The statistical analyses were made by using the Stata 10 (College Station, TX, USA) statistical package.

ETHICS

This is a retrospective study of treatment results using an approved medical device. Informed written consent for treatment was obtained from each patient and the study protocol conforms to the ethical guidelines of the "World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004, as reflected in a priori approval by the ethics review committee.

RESULTS

Objective Tumor Response

There were no patients who had a complete response, 14.6% of patients had a partial response (n=13), 57.3% of patients had no change (n=51), and 28.1% of patients had progressive disease (n=25). A partial ablation was achieved in 30 patients (33.7%; Figures 5 and 6) and no ablation was identified on imaging in the other 59 patients (66.3%) based on the finding of necrosis on contrast enhanced CT or MRI. The results of 5 patients who had PET/CT scans pre- and post-HIFU treatment demonstrated that the maximum and mean standardized uptake values (SUV_{max} and

Table 1. Mean (±SD) SUV values on PET-CT scans in five patients before and after high intensity focused ultrasound.

	Pre-HIFU	Post-HIFU	P value ^a
SUV _{max} (g/mL)	7.2±2.2	4.3±1.9	0.043
SUV _{mean} (g/mL)	5.4±1.8	3.1±1.5	0.043

^a Wilcoxon signed rank test for paired data

SUV_{mean}) of the pancreatic cancer decreased following HIFU therapy although no obvious evidence for ablation was identified on contrast enhanced CT or MRI (Figure 7 and Table 1).

Pain Response

Sixty-seven patients (75.3%) complained of abdominal or back pain consistent with tumor-related pain prior to HIFU therapy. Pain was relieved in 54 patients (80.6%) who had pain prior to HIFU therapy. The complete remission of pain (0 pain score and no need for opioid analgesics) was observed in 21 patients (31.3%), a partial remission of pain (decrease in pain score by 2 or more) was observed in 33 patients (49.3%), and no improvement of pain was seen in 13 patients (19.4%). Pain relief was observed in 88.0% (22/25) of patients who had an objective tumor response and in 76.2% (32/42) of patients who did not demonstrate an objective tumor response.

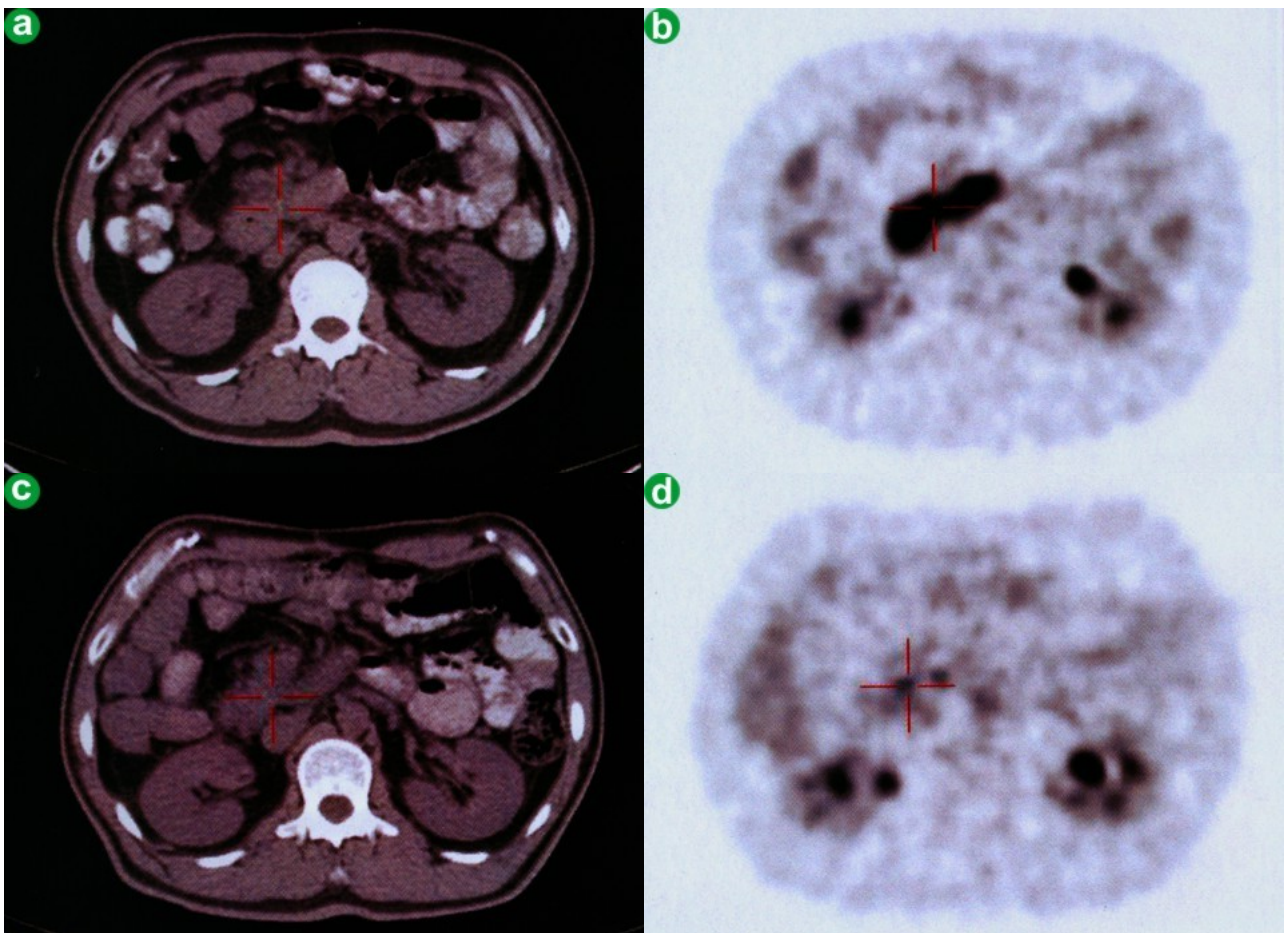


Figure 7. a. A CT scan made before high intensity focused ultrasound demonstrating a tumor in the head of the pancreas. b. A PET-CT scan made before high intensity focused ultrasound demonstrating a SUV_{max} of 9.1 g/mL. c. A CT scan demonstrating no significant change one month following high intensity focused ultrasound treatment. d. The PET-CT scan made one month after high intensity focused ultrasound demonstrated that the SUV_{max} value decreased to 3.1 g/mL. All four images are taken from the same patient.

Patient Survival

The median survival for stage II was 26.0 months and 2 patients are still alive with follow-up durations of 25 months and 36 months, respectively. The median survival for stage III was 11.2 months and the median survival for stage IV was 5.4 months. The overall median survival was 8.6 months. The survival rate at 1 year was as follows: stage II, 100%; stage III, 41.0% and stage IV, 6.5%. The survival rate at 2 years was as follows: stage II, 75.0%, stage III, 10.3% and stage IV, 0%.

Complications

There were 3 patients (3.4%) with superficial second degree skin burns that did not require any special treatment and recovered within one week. There were 6 patients (6.7%) with subcutaneous sclerosis due to thermal injury to the subcutaneous fat of the anterior abdominal wall, identified as firmness within the abdominal wall on palpation, which resolved one to three months following completion of HIFU treatment and did not require any treatment. There was one patient (1.1%) with a pancreatic pseudocyst (diameter of the cyst was 3.6 cm) that was identified on post-treatment ultrasound two days following the last HIFU session. The patient was asymptomatic and was treated with somatostatin for one week. No severe complications or adverse events related to HIFU therapy were seen in any of the patients treated. There were no patients who developed clinical pancreatitis as a result of HIFU treatment and there were no treatment related deaths.

DISCUSSION

In this study, it was observed that preexisting severe back and abdominal pain consistent with tumor-related pain resolved or was partial relieved for most patients (80.6%) after HIFU treatment. Furthermore, no severe complications were observed. The results suggest that HIFU treatment of pancreatic cancer is safe and appears to palliate pain related to pancreatic cancer. This study also demonstrated that HIFU therapy can cause partial necrosis of pancreatic tumors in 33.7% of patients. In addition, in some patients where necrosis was not observed on contrast enhanced-CT or MR imaging, imaging with PET/CT demonstrated a decrease in the SUV_{max} and SUV_{mean} value of the treated pancreatic cancer following HIFU treatment. Although ablation with evidence of necrosis was observed in 33.7% of tumors treated with HIFU, the rate of pain relief was 80.6%. The mechanism for pain relief in these patients may be related to damage of pain fibers innervating the tumor by HIFU without causing necrosis of the tumor. The precise mechanism that HIFU treatment palliates pain requires further investigation.

Palliation of pain is an essential aspect in the management of patients with pancreatic cancer. The first line therapy in the management of pain in patients

with pancreatic cancer is the use of analgesic medications including narcotics.

The main factors that impact the efficacy of HIFU for pancreatic tumors includes an adequate acoustic window, limited respiratory movement of the tumor and dose of HIFU energy delivered. The most important factor impacting the safety of HIFU therapy is having an adequate acoustic window for the transmission of the HIFU energy to the target without intervening bowel gas. Therefore, it is critical to evacuate the gas in the stomach and colon if possible. Clinically, gas in the stomach can be avoided by having the patient fast beginning the night prior to the treatment. Also, using of the upper transducer aids in displacing bowel gas by applying slight abdominal pressure to the target area. The safety of HIFU is of critical importance in the palliation of advanced pancreatic cancer. Complications observed in animal experiments included thermal injury to the gastric mucosa and colon necrosis [23]. These complications occurred because HIFU energy was delivered to air-filled bowel resulting in rapid deposition of ultrasound energy at the air-bowel interface. Respiratory movement is another important factor impacting the efficacy of HIFU. Respiratory tracking methods are currently in development. Furthermore, standardized protocols for delivering HIFU therapy to achieve safe and consistent ablation have been proposed (unpublished data).

HIFU for treatment of pancreatic cancer is widely available in China with limited availability in South Korea and England. Several studies in pancreatic cancer are planned in Europe and the United States. To perform safe and effective HIFU treatments, physicians need to understand the basics of HIFU physics, which differ substantially from diagnostic ultrasound. Furthermore, physicians should be comfortable with ultrasound imaging of abdominal structures.

Several reports in the literature suggest that contrast enhanced-CT or MRI scan can be used to evaluate the efficacy of thermal ablation [24, 25]; however, contrast enhanced-CT scan or MRI can only assess for necrosis by noting the absence of vascularity within the tumor and is unable to assess the metabolic activity of the tumor. PET or PET-CT can be useful for diagnosing and staging of pancreatic cancer and for evaluating response to treatment [26, 27, 28]. In this study PET-CT was used to assess the efficacy of HIFU therapy in five patients. The results demonstrate that the SUV_{max} and SUV_{mean} value of the treated pancreatic cancer decreased after HIFU treatment even if contrast enhanced-CT imaging did not demonstrate necrosis. PET-CT scan may potentially be a better imaging method to evaluate the effect of HIFU treatment in pancreatic cancer.

This study demonstrates that there were no severe complications or adverse events related to HIFU therapy seen in any of the patients treated. HIFU treatment of the pancreas appears to be safe when the device is operated properly. The results of follow-up

showed the median survival after HIFU treatment for patients with stage II disease was 26.0 months and for patients with stage III disease was 11.2 months; however, it should be emphasized that this is a retrospective study from a single center and is obviously subject to biases inherent to retrospective studies. To determine if HIFU treatment of pancreatic cancer has any survival benefit a randomized controlled multi-center study is necessary. A prospective, multicenter, randomized, sham-controlled study is in preparation in the United States.

CONCLUSIONS

Although this retrospective study has significant limitations, preliminary results suggest that the clinical application of HIFU for pancreatic cancer appears to be safe and is a promising modality of treatment for palliation of pain related to pancreatic cancer.

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