

RESEARCH ARTICLE

Analgesic effect of high intensity focused ultrasound therapy for unresectable pancreatic cancer

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Abstract

Objective: To evaluate the pain-alleviating action, feasibility and efficacy of high intensity focused ultrasound (HIFU) for palliation of inoperable pancreatic cancer in humans.

Methods: Forty patients with advanced pancreatic cancer were treated with HIFU. There were 13 patients with stage III, and 27 patients with stage IV disease. The locations of the tumours were as follows: head of pancreas in 9 patients, body and/or tail of pancreas in 31 patients. Pain relief, local tumour control rate, median survival and complications were monitored after HIFU treatment. The primary endpoint was to assess pain relief rate and pain relief time (PRT). Secondary endpoints included local progression-free survival time, overall survival (OS), and side effects.

Results: There were no severe complications or adverse events related to HIFU therapy in any of the patients treated. Pain relief was achieved in 87.5% of patients, median PRT was 10 weeks. The median local progression-free survival time for all patients was 5 months. The median overall survival time was 10 months for patients with stage III disease, and 6 months for patients with stage IV disease. The median OS time, 6-month and 1-year survival rate for patients as a whole were 8 months, 58.8% and 30.1%, respectively.

Conclusions: Although this study may have limitations, preliminary results demonstrate the safety of clinical application of HIFU for pancreatic cancer and reveal it to be a promising mode of treatment for palliation of pain associated with pancreatic cancers.

Keywords: palliative care, pancreatic neoplasm, thermal ablation, ultrasonic therapy

Introduction

Pancreatic cancer is a highly lethal disease of worldwide importance. In 2005 there were approximately 1746 new cases of pancreatic cancer in Shanghai, China. The mortality of pancreatic cancer is almost 100% and it has become the fifth leading cause of cancer deaths [1]. On a worldwide basis, there are approximately 120,000 yearly male deaths compared to 107,000 female deaths [2]. The only way to cure patients with pancreatic cancer is to completely remove the tumour by surgery. As typical symptoms are imperceptible during early stages of pancreatic cancer, about 80% of patients are ineligible for

surgical resection because of metastatic or locally advanced disease [3]. Nearly three quarters of patients suffer from cancer pain which influences quality of life and prognosis. Chemotherapy with gemcitabine as first-line systemic treatment for patients with advanced pancreatic cancer has been suggested to improve pain, but pain returns with disease progression [4]. Up to now, besides erlotinib with gemcitabine, most chemotherapy doublets with gemcitabine have not produced better survival outcomes. Nevertheless, as reported in a phase III trial by Moore et al. [5], erlotinib with gemcitabine, which seems to be more effective than

standard gemcitabine, could only prolong median overall survival by a further 10 days. Once the disease progresses, there is no accepted standard care protocol; most patients receive palliative treatment in order to maximise quality of life.

High intensity focused ultrasound (HIFU) has been successfully used as a novel treatment of tumours in clinical application [6]. The primary mechanism for HIFU treatment is the thermal effect. HIFU treatment is able to generate a potential coagulative necrosis in targeted tissue without damaging peripheral vital anatomy structures. Wu et al. [7] published an early clinical trial describing the extracorporeal HIFU (Model JC) treatment of eight cases with pancreatic cancer in 2005, where all patients obtained relief of pain symptoms related to pancreatic cancer within 48 h following HIFU therapy. As control of pancreatic cancer pain in advanced disease is difficult to achieve and often associated with significant unwanted side effects, HIFU might be a new option. This article reports clinical experience of inoperable pancreatic cancer with the same HIFU tumour therapy device at a single institution. The principal objective of this study was to prospectively evaluate the analgesic effectiveness of HIFU. The secondary objective was to assess side effects, time to local tumour progression and OS in this patient population.

Patients and methods

The study was approved by the local ethics committee. Patients with histologically and/or cytologically proven locally advanced pancreatic carcinoma and/or metastatic disease were enrolled for study. It was required that the patient should have a Karnofsky performance scale (KPS) score of at least 70%, and adequate functions of bone marrow (WBC count $>2500/\text{mL}$, platelet count $>80,000/\text{mL}$, haemoglobin $>8 \text{ g/mL}$), renal (serum creatinine concentration $<1.5 \text{ mg/dL}$, blood urea nitrogen $<20 \text{ mg\%}$) and hepatic functions (serum transaminase level $<2\times$ the upper normal range) except hyperbilirubinaemia due to obstructive jaundice. In addition, all patients had constant pain of visceral origin localised to the region of the middle and upper back. Pain intensity was assessed for each patient using a numerical rating scale (NRS) from 0 to 10 (0 is no pain and 10 is worst pain imaginable) [8]. To enrol, the pain intensity (average in the last 24 h) rating had to be an NRS of 3/10 or higher or opioid required for pancreatic cancer-related pain control. The primary tumour of the patients, which could be assessed by abdominal computed tomography (CT) or magnetic resonance imaging (MRI) was required. To qualify for the study all patients were expected to

Table I. Patient characteristics and therapeutic parameters.

Characteristics	Value <i>n</i> (%)
Sex	
Male	24 (60)
Female	16 (40)
Karnofsky performance status	
90	1 (2.5)
80	7 (17.5)
70	32 (80)
Site of disease	
Pancreatic head	9 (22.5)
Body and/or tail	31 (77.5)
Stage of disease	
III	13 (32.5)
IV	27 (67.5)
CA19-9	
Positive	33 (82.5)
Negative	7 (17.5)
Prior chemotherapy-treated	35 (87.5)
Simultaneous radiotherapy-treated	7 (17.5)
	Value
Age (years)	
range (median)	31–80 (57)
Maximum tumour size (mm)	
Range (median)	20–100 (43)
Planning target volume (cm ³)	
Range (median)	9.2–102.1 (22.7)
Total therapeutic time (h)	
Range (mean)	0.75–3.2 (2.1)
Ultrasonic mean-power (W)	
Range (median)	117–388 (247)
Acoustic energy (kJ)	
Range (median)	83.7–1194.6 (294.8)

live more than 3 months. Patients were excluded if they had serious or uncontrolled concurrent medical illness, or a history of other malignancies. Nevertheless, patients who had undergone prior treatment were enrolled into the trial provided that there was 1 month's gap between the radiotherapy/chemotherapy. The characteristics of the patients are summarised in Table I. The majority of patients had a KPS 70% at study entry (80%), 13 patients had stage III disease, 27 had stage IV (23 patients had liver metastasis, one had both liver and lung metastasis, one had both liver and bone metastasis, two had both liver and pelvic metastasis) according to the tumor node metastasis (TNM) classification (6th edition) [9], 35 patients had a previous history of failure treatment with gemcitabine-containing chemotherapy, among which seven patients also received simultaneous radiotherapy. Five other patients either refused chemotherapy and/or radiotherapy, or were not felt to be suitable candidates for chemotherapy and/or radiotherapy. Two patients had undergone a biliary bypass procedure before

treatment; two, endoscopic stenting and one, cholecystojejunostomy.

Compared with the previous study by Wu [10], the same therapeutic HIFU system (Chongqing Haifu (HIFU) Tech, Chongqing, China) was used in this study to treat all patients, while a therapeutic ultrasound transducer is different; it is a 200 mm diameter transducer with a focal length of 135 mm operating at a frequency of 0.85 MHz. As the focal region of this transducer is 8 mm along the beam axis and 1.5 mm in the transverse direction, it has larger focal arc area and better performance on focusing. In addition, the power of the original transducer does not exceed 300 W, while the power of this transducer can be increased to 400 W. Therefore, using this transducer, it is easier to have coagulation necrosis of tumour tissue and reduce the impact on the tissue behind the focal region. The US imaging probe situated in the centre of the therapeutic transducer can provide real-time sonography to target the lesions and to assess acute coagulation necrosis in the targeted tissue during the therapeutic procedure. Every patient in the study received HIFU treatment only once.

During the treatment, HIFU was performed under sedation analgesia. The patient was placed prone and carefully positioned, so that the skin overlaying the lesion to be treated was in contact with degassed water. Real-time US was used to target the tumour by moving the integrated probe, and the tumour was divided into slices with 5 mm separation using US images. By scanning the HIFU beam in successive sweeps from the deep to the shallow regions of the tumour, the targeted regions on each slice were completely ablated. The total therapeutic time excluding making plans for the patients ranged from 45 min to 3.2 h (mean, 2.1 h). The median planning target volume was 22.7 cm³ (range: 9.2–102.1), and other main parameters are summarised in Table I. During HIFU ablation, the real-time US scans obtained immediately before and after individual exposures were compared to determine whether the echogenic changes of the HIFU-treated region had covered the desired treatment area. Blood pressure, pulse, respiration rate, temperature, and peripheral oxygenation were monitored during HIFU procedure.

Pretreatment evaluation included a complete medical history, physical examination, complete blood count, differential blood cell count, biochemistry analysis, serum level of tumour markers including carbohydrate antigen (CA) 19-9, chest X-ray, electrocardiogram (ECG) and CT of the abdomen.

Preoperative fasting and catharsis were used to evacuate the gas in the stomach and colon if possible. In order to reduce the likelihood of pancreatitis induced by HIFU, 14-peptide somatostatin, a strong

inhibitor of pancreas exocrine secretion, was used at the beginning of HIFU treatment. All patients received intravenous infusion of somatostatin (250 µg/h) for 12 h.

Toxicity and response evaluation

Treatment-related toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 2.0. One week after HIFU treatment, complete blood count with differentials, serum chemistry and urinalysis were carried out. Serum CA19-9 levels were measured by a radioimmunoassay 1 month after HIFU treatment and every 2 months thereafter until increase. Pain intensity using NRS was assessed 1 week after HIFU treatment and every 2 weeks thereafter until pain progression. Pain progression was defined as the pain intensity or analgesic requirements increased according to initial staging.

Because HIFU was targeted only at primary pancreatic tumours and not at distant metastatic lesions, we just evaluated the local response rate. Tumour response was evaluated by CT scan 1 month after HIFU treatment and every 2 months thereafter until tumour progression. A complete response (CR) was defined as a total resolution of all evidence of primary tumour. A partial response (PR) required a 50% reduction in the maximum perpendicular tumour measurements for at least 1 month. Stable disease (SD) was defined as less than 50% reduction and less than 25% increase of measurable tumour lesions. Patients were considered to have progressive disease (PD) if the measurable tumour lesions increased by greater than 25% according to initial staging.

Local progression-free survival (local-PFS) time was defined as the time from the date of initial treatment to the first documentation of primary tumour progression or death. Pain relief time was defined as the time from the date of initial treatment to the first documentation of pain progression or death. Overall survival time was measured from the date of initial treatment to date of death or the date of the last follow up.

Statistical methods

The primary endpoint was to assess pain relief rate and PRT. Secondary endpoints included local progression-free survival time, OS, and side effects. Response rate was estimated using the binomial probability, and exact 95% confidence intervals (CIs) were provided. Local progression-free and OS times were calculated by the Kaplan–Meier method. Survival was calculated from the date of admission to the date of death or last follow up. Survival curves

Table II. Pain control with HIFU therapy.

Pain	n (%)		
	Entire relief*	Partial relief	Not relief
Mild	6 (54.5)	4 (36.4)	1 (9.1)
Moderate	3 (11.5)	19 (73.1)	4 (15.4)
Severe	—	3 (100)	—
Unbearable	—	—	—
Total	9 (22.5)	26 (65)	5 (12.5)

*Pain numerical rating scores (NRS ≤ 1) after HIFU.

were calculated by the Kaplan–Meier method. Statistical calculations were performed using SPSS software (version 11.0).

Results

From October 2007 to June 2009, 40 patients were enrolled into this study.

Toxicities

Haematological toxicity was not observed in the study. No evidence of skin burn, bleeding or infection overlaying to treated lesion was observed after HIFU ablation. During the hospital stay, no signs of tumour haemorrhage, large blood vessel rupture, obstructive jaundice or gastrointestinal perforation were detected in any patient. There were no patients who developed clinical pancreatitis as a result of HIFU treatment and there were no treatment-related deaths. There were no severe complications or adverse events related to HIFU therapy in any of the patients in the study during the follow-up period. The results suggest that HIFU treatment of pancreatic cancer is safe and feasible. 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. Gastrointestinal pre-operative preparation of HIFU treatment not only helps to position the target lesion but also ensures the gastrointestinal tract escapes injury. In this clinical trial, preoperative fasting, catharsis and intraoperative bladders pressure are all applied to reduce the impact of gas.

Pain relief

Pain relief was objectively evaluated with a NRS (0 = 'no pain at all', 1–3 = 'mild pain', 4–6 = 'moderate pain', 7–9 = 'severe pain', 10 = 'unbearable pain') before and 1 week after HIFU. Thirty-five cases (87.5%) received partial or entire pain relief (65% and 22.5%, respectively) after HIFU

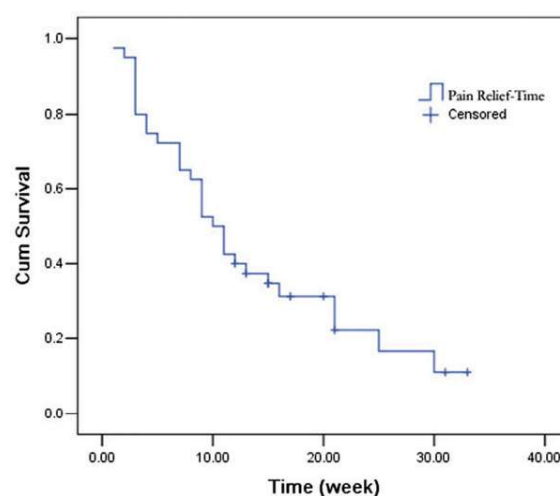


Figure 1. Curve of pain relief time. This is a PRT curve of all 40 patients, median PRT was 10 weeks (95% confidence interval, 7.7–12.3)

(Table II). Pain was relieved in 70% of the patients usually 1 or 2 days after HIFU, and the pain relief persisted. Median PRT was 10 weeks (95%CI, 7.7–12.3) (Figure 1).

Efficacy

All the patients were included in the response evaluation. Seven patients achieved a partial response based on the finding of necrosis on contrast enhanced CT (Figure 2), giving an overall response rate of 17.5%; 28 patients (70%) and five patients (12.5%) had no change and progressive disease, respectively.

The results of one patient who had PET/CT scans pre- and 3 months post-HIFU treatment demonstrated that the standardised uptake values (SUV) of the pancreatic cancer decreased after HIFU therapy, although no obvious tumour regression for ablation was identified on contrast enhanced CT (Figure 3).

After one month of HIFU, the serum CA19-9 level was reduced compared to the pretreatment level in 19 (57.6%) of 33 patients. The median local-PFS time for all patients was 5 months (Figure 4). The median OS time of patients with stage III and IV were 10 and 6 months, respectively. The median OS time, 6-month and 1-year survival rate for patients as a whole were 8 months, 58.8% and 30.1%, respectively (Figure 4).

Discussion

Pancreatic cancer pain is the most common and serious clinical symptom. In a prospective study of 1107 patients admitted to a palliative setting,

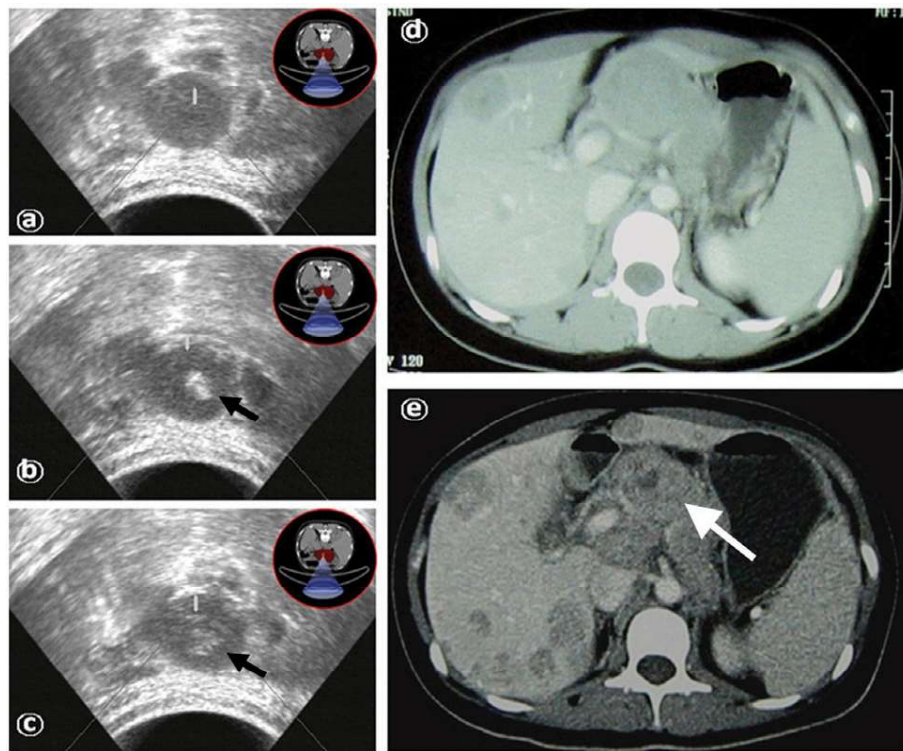


Figure 2. Gray-scale changes of HIFU obtained on real-time ultrasound (US) images during HIFU procedure. (a) US image obtained before HIFU shows a large pancreatic carcinoma lesion present in the body of the pancreas. (b) US images obtained during the HIFU procedure show hyperechogenicity in the treated tumour (arrows). (c) US images obtained immediately after the one-slice HIFU procedure show the hyperechogenicity of treated tumour in the one slice lesion (arrows). (d, e) Transverse contrast-enhanced conventional CT scans obtained before (d) and 1 month after (e) HIFU ablation. There was an obvious regression (arrows) in lesion size of primary tumour after HIFU despite the progress of the liver metastases. All five images are taken from the same patient.

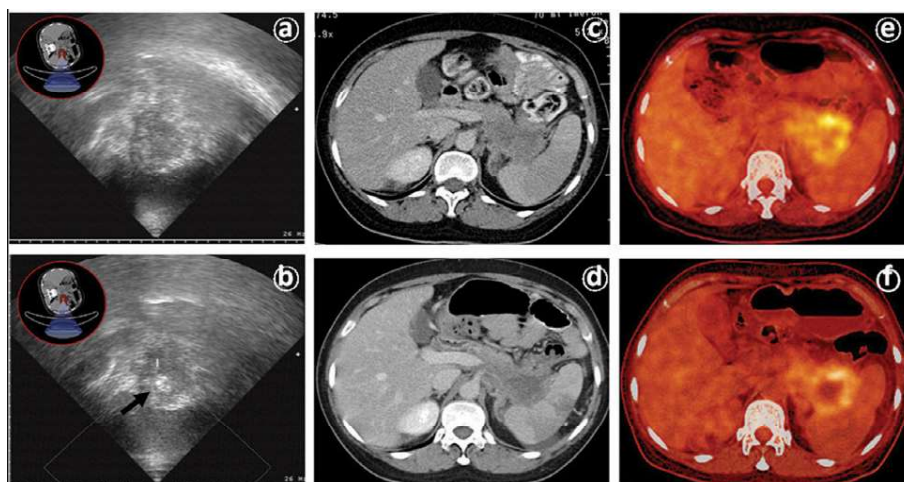


Figure 3. (a, b) Gray-scale changes of HIFU obtained on real-time ultrasound (US) images during HIFU procedure. (a) US image obtained before HIFU shows a large pancreatic carcinoma lesion present in tail of pancreas. (b) US images obtained immediately after HIFU procedure show the hyperechogenicity (arrows) of treated tumour in the one slice lesion. (c) A CT scan made before HIFU demonstrates a tumour in the tail of the pancreas. (d) A CT scan demonstrates no significant size change one month after HIFU treatment. (e) A PET-CT scan made before HIFU demonstrates a SUV_{max} of 7.5 g/mL. (f) The PET-CT scan made 3 months after HIFU demonstrates coagulative necrosis inside the tumour and the decreasing of the SUV_{max} value to 5.3 g/mL. All images are taken from the same patient.

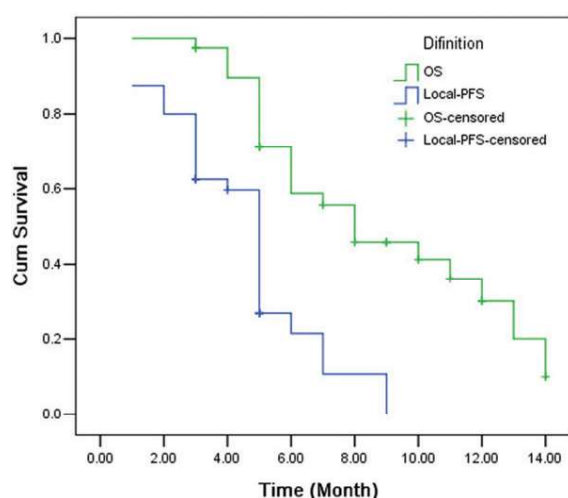


Figure 4. Time to local-PFS and OS. This is a Kaplan Meir survival curve of all 40 patients. The median local-PFS time for all patients was 5 months (95%CI, 4.6–5.4). The median OS time was 8 months (95%CI, 4.5–11.5).

approximately 44% of those with pancreatic cancer had severe pain [11]. The pain is progressive, and its character, quality, and temporal nature worsen as the illness progresses. Therefore, pain control is also an important factor of pancreatic cancer treatment. Early clinical trial results show that the HIFU treatment of pancreatic cancer has analgesic effect, although the mechanism of action still has not been precisely identified, and may be related to ultrasound energy destroying adjacent nerves, even coeliac plexus, while inducing tumour coagulation necrosis [12]. In rabbits, the results of experiments performed by Zeng et al. [13] about the ablative effect of HIFU on the coeliac ganglion showed that high intensity HIFU could damage coeliac ganglion in a short time without the injury of the adjacent aorta and spinal cord. This may suggest that non-invasive HIFU treatment could take the place of invasive chemical neurolytic coeliac plexus block (NCPB) to relieve the pancreatic cancer pain. The study reveals that 87.5% of patients received partial or entire pain relief, and this analgesic effect is long lasting. Median PRT was 10 weeks. It is also indicated in Wu's report that all the patients obtained pain relief after HIFU treatment. The effectiveness was 100% and the analgesic effect was lasting. Although, the median duration of pain relief after HIFU is 10 weeks, it is shorter than after NCPB which is usually within 3 or 4 months [14]. Potential dangerous complications of NCPB reported are pneumothorax, chylothorax, pleural effusion, convulsion and paraplegia. As compared to NCPB, HIFU does not require the insertion of an applicator into a target tissue, so it is much safer.

We deem that HIFU therapy with long-lasting analgesic effect was related to the local control

of lesions. The results showed that 17.5% of cases of primary tumour obtained PR, while 70% of cases of SD, and the median of local-PFS time was up to 5 months. The imaging obtained in the treatment also illustrates that coagulation necrosis was produced in the target tumour by HIFU-radiated ablation. Complex structure around the pancreas determines the palliative purpose of HIFU therapy in pancreatic cancer as a curative approach with HIFU ablation was not realistic. Nonetheless, HIFU is an effective means of controlling the disease especially at an advanced/metastatic stage for which no useful conventional therapy exists, and thus it may have widely clinical applications as a palliative treatment both to impede tumour growth and to relieve pain in patients.

Gemcitabine has shown superior clinical benefit and improved median survival in a randomised comparison with fluorouracil in advanced pancreatic cancer [4] and is now widely accepted as the first-line therapy. The only agent combined with gemcitabine has shown a small, but statistically significant improvement in survival among patients with advanced disease is erlotinib, a tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR) [5]. Multiple other agents with diverse mechanisms of action in combination with gemcitabine have been tested in randomised clinical trials, with no improvement in outcome [15]. If the disease progresses, in a highly selected group of patients who were not too sick, with minimally symptomatic disease, second-line chemotherapy can be offered to patients. Although few patients showed an objective response, the rate of disease control ranged from 17% to 39% and the reported median OS from the beginning of salvage chemotherapy after gemcitabine failure ranged from 3.1 to 7.6 months [16]. The treatment of patients with advanced or metastatic disease is palliative; with gemcitabine-based therapy the median overall survival is only approximately 6 months [17]. Despite this, HIFU was performed as a palliative treatment in all cases. The median OS time was 10 months for patients with stage III disease, and 6 months for patients with stage IV disease. The median OS time, 6-month and 1-year survival rate for patients as a whole were 8 months, 58.8% and 30.1%, respectively. In Wu's report [7] the overall median survival time of eight patients was 11.25 months (range, 2–17 months) and all of the eight patients received partial or complete pain relief. Compared with Wu's report, only 87.5% of the patients in this study obtained partial or complete pain relief and the median OS time for them as a whole was only 8 months. These differences may be related to the cases chosen in the studies. The cases in our study are in their relatively late stage. Of the

patients in Wu's study 62.5% were in stage IV while 67.5% of the patients in this study were.

We deem that control of primary tumour by HIFU treatment may help to prolong the survival time of patients with advanced/metastatic pancreatic cancer. To confirm whether HIFU treatment of pancreatic cancer has any survival benefit, a randomised controlled study is still necessary.

In conclusion, our results demonstrate that HIFU may effectively ablate pancreatic cancer and relieve pain. Moreover, it is safe and feasible. There are no controlled randomised trials to evaluate the impact on pain with other pain therapies, such as coeliac plexus block or the use of opioids alone. We are currently undertaking further clinical trials to solve the problems we had in this study in clinical therapy strategies.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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