High Intensity Focused Ultrasound Treatment for Patients with Local Advanced Pancreatic Cancer

Hui-feng Gao, Kun Wang, Zhi-qiang Meng, Zhen Chen, Jun-hua Lin, Zhen-hua Zhou, Peng Wang, Wei-dong Shi and Ye-hua Sheng

Department of Integrated Oncology, Fudan University Shanghai Cancer Centre, Shanghai, China

Corresponding author: Kun Wang, Ph.D., Department of Integrated Oncology, Fudan University Shanghai Cancer Centre; Department of Oncology, Shanghai Medical College, Fudan University, 270 Dongan Road, Shanghai 200032, China; Tel.: +86-21- 6417-5590, Fax: +86-21- 6443 -7657; E-mail: kunwang_fudan@163.com

ABSTRACT

Background/Aims: To evaluate the safety and efficacy of high intensity focused ultrasound (HIFU) therapy in patients with local advanced pancreatic cancer. Methodology: 39 patients with local advanced pancreatic cancer were treated with HIFU, including 26 male and 13 female patients. The locations of the tumours were as follows: head of pancreas in 7 patients, body and/or tail of pancreas in 32 patients. Pain relief, time to progression (TTP), median survival and complications were analysed after HIFU treatment. Results: There were no severe complications or adverse events related to HIFU therapy in any of the patients treated. Pain relief was achieved in 79.5% of patients. Median TTP was 5.0 months. The median overall survival time was 11 months. 6-month and 1-year survival rate for patients were 82.1% and 36.8% 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 local advanced pancreatic cancers.

INTRODUCTION

Pancreatic cancer is a highly lethal disease worldwide. A total of 45,220 new pancreatic cancer cases and 38,460 pancreatic cancer deaths are estimated to occur in the United States in 2013 (1). In China, the incidence of pancreatic cancer is increasing by approximately 1,746 estimated new cases in Shanghai in 2005 for both sexes. It has become the fifth cause of the cancer death of cancer disease (2). Due to the poor prognosis, the mortality is almost 100% (3). Surgical resection gives the best chance for a possible cure. As typical symptoms are imperceptible in the early stage, 85%-90% of newly diagnosed pancreatic tumors are considered unresectable due to local advanced disease or presence of metastasis (4). High intensity focused ultrasound (HIFU) has been successfully used as a novel hyperthermia therapy of tumors in clinical application. HIFU is able to lead a potential coagulative necrosis in-depth tissue without damaging peripheral vital anatomy structures. HIFU application in the palliative treatment of pancreatic cancer could be useful in patients with symptoms that would benefit from local tumor restriction. The first report (5) of HIFU treatment case in pancreatic cancer used Model FEP-BY01 machine. HIFU is now applied for pancreatic cancer treatment in China. This article reports clinical experience of pancreatic cancer with the extracorporeal Model JC HIFU therapy device (Chongqing Haifu Tech, Chongqing, China) at a single institution. The principal objective of this study was to prospectively evaluate the safety and efficacy of HIFU in patients with local advanced pancreatic cancer.

METHODOLOGY

Eligibility criteria

Eligible patients with histologically and/or cytologically proven locally advanced pancreatic carcinoma were enrolled for study. In addition, the patient should have constant cancer-related pain of visceral origin localized to the region of the middle and upper back. A Karnofsky performance scale (KPS) score of ≥60% was required. In addition, adequate bone marrow (white blood cell count >2,500 /mL, platelet count >80,000 /mL, hemoglobin >8 g/mL), kidney (serum creatinine concentration <1.5 mg/dL, blood urea nitrogen <20 mg%) and liver (serum transaminase level <2 times the upper normal range) function was required; an exception was made for hyperbilirubinemia due to obstructive jaundice. Patients were also excluded if their lesion was undetectable by ultrasound or if the patients had a serious or uncontrollable concurrent medical illness.

Treatment methods

The patients who refused chemotherapy, or had a previous history of failure treatment of chemotherapy and/or radiotherapy, received only HIFU therapy. Others received combined therapy. These patients received gemcitabine 1,000 mg/m² intravenously over 30 min on days 1, 8, and 15, and concurrent HIFU therapy in the first week. The treatment was given every 28 days and continued until disease progression, patient refusal, or an unacceptable toxicity. HIFU treatment times were decided by two experienced HIFU doctor after assessment of follow-up CT or MRI.

Equipment

The machine (Model JC) is provided by Chongqing Haifu Tech, Chongqing, China. It has many functions including real-time ultrasound (US) localization and monitoring for tumor lesion, three-dimensional targeted scanning, calculating treatment volume in targeted areas, and feedback control of treatment dose.
The therapeutic parameters and methods of HIFU treatment

Pre-operation preparation
Before treatment, fasting, cathartic, skin cleaning in treatment area should be conducted for patients.

Anesthesia method and treatment parameters of patients
Sedation and analgesia anesthesia method is conducted for patients. The parameters of therapeutic ultrasound transducer are the followings: 1) frequency 0.85 MHz; 2) focal length 135.0 mm; 3) diameter 20 cm; 4) scanning methods: fixed-point method.

Treatment methods
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 tumor by moving the integrated probe, and the tumor was divided into slices with 5mm separation using US images. By scanning the HIFU beam in successive sweeps from the deep to the shallow regions of the tumor, the targeted regions on each slice were completely ablated.

Evaluation of efficacy and side effects
After HIFU treatment, complete blood count with differentials, serum chemistry and urinalysis and Serum CA19-9 levels were measured. Treatment-related toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 2.0. Pain intensity was assessed for each patient using a numerical rating scale (NRS) from 0 to 10 (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. Tumor response was evaluated by CT or MRI scan 1 month after HIFU treatment. A complete response (CR) was defined as a total resolution of all evidence of primary tumor. A partial response (PR) required a 50% reduction in the maximum perpendicular tumor measurements. Stable disease (SD) was defined as less than 50% reduction and less than 25% increase of measurable tumor lesions. Patients were considered to have progressive disease (PD) if the measurable tumor lesions increased by greater than 25% according to initial staging.

Statistical methods
Statistical calculations were performed using SPSS software (version 13.0). This study conducts Log-rank test for differences testing and Spearman rank correlation analysis for HIFU dosimetric analysis. Statistical results are reported as p values.

RESULTS
Patient characteristics
There are altogether 39 cases of local advanced pancreatic cancer patients in this study, 26 cases of which are male and 13 of which are female. The ages of these patients are between 42 years to 79 years (median age 58 years). All the patients accepted in this study are not suitable for surgery, 7 patients have pancreatic head cancers and 32 patients have pancreatic body or tail cancers. Besides, 35 cases have the indicator Ca19-9 level increased (>37 U/mL). 14 patients received only HIFU therapy (10 patients had a previous history of failure treatment with chemotherapy and/or radiotherapy. Four other patients were not felt to be suitable candidates for chemotherapy and/or radiotherapy with KPS = 60). 25 patients received combined therapy; 33 patients in the study received only once of HIFU therapy, 4 patients received twice HIFU therapy and others more than two times.
FIGURE 3. For patients who were treated by both HIFU and chemotherapy, the median survival was 12.0 months and 1-year survival rate was 49.9%.

Long-term prognosis after HIFU
The median overall survival time was 11.0 months and median TTP was 5.0 months; 6-month and 1-year survival rate for patients were 82.1% and 39.5% respectively. For patients who were treated by HIFU single, the median survival was 8 months and 1-year survival rate were 14.3%. For patients who were treated by both HIFU and chemotherapy, the median survival was 12.0 months and 1-year survival rate were 49.9% (Figure 3). The survival time was significantly different (p < 0.01) between the HIFU group and combined therapy group. But, the TTP was no significantly different (p > 0.01) between the HIFU group and combined therapy group.

DISCUSSION
Local advanced pancreatic cancer remains a challenging malignancy to treat. Approaches that use chemotherapeutics, radiotherapy, or both have significant efficacy limitations (6). As a non-invasive, non-surgical treatment, HIFU for treatment of pancreatic cancer is widely available in China (7,8). HIFU for the palliative treatment of local advanced pancreatic cancer may be useful in patients who develop symptoms that would benefit from local tumor control (9). The primary mechanisms of HIFU are associated with the delivery of energy to the target tissue that causes coagulative necrosis by thermal effects and possibly cavitation. Different with other ablation therapies, HIFU does not require the insertion of an applicator into a target tissue and an extracorporeal source can be used to treat large-volume tumors with realtime imaging guidance (7). In animal experiments and clinical studies, it has been proven that ultrasound can propagate through the abdominal wall and ablate target tumor, thereby treating tumors in pancreas (10). This study shows that there were no severe complications of adverse events related to HIFU therapy observed in any of the patients treated.

Pain is the most common and serious clinical symptom in patients with pancreatic cancer. Resulting from both tumor expansion and tumor invasion of the celiac and mesenteric plexus, the pain can be both neuropathic and inflammatory. The typical pain of local advanced pancreatic cancer is a dull, fairly constant pain of visceral origin localized to the region of the middle and upper back. In the management of patients with local pancreatic cancer, pain control is an essential aspect. Pain management consists of a combination of antitumor therapy, analgesic drug therapy, anesthetic blocks, and behavioral approaches. In clinical practice, chronic 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 (11). 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 tumor coagulation necrosis. The study reveals that 87.5%–100% of patients received partial or complete pain relief (7,12). The patients’ daily activities, quality of life, and psychological status will be markedly improved after pain relief.

For decades, gemcitabine has been the most widely used chemotherapeutic agent in local advanced pancreatic cancer. The unique mechanism of action and favorable toxicity profile of gemcitabine have allowed exploration of many novel gemcitabine-based combination regimens as treatment for pancreatic cancer. Besides erlotinib, multiple other agents with diverse mechanisms of action in combination with gemcitabine have been tested in randomized clinical trials.
treats, with no improvement in outcome (13). That means, unfortunately, until now no effective modality has been identified for the treatment of patients with local advanced pancreatic cancer. The median survival time is 6–10 months for patients with local advanced pancreatic cancer. In this study, comparing patients who were treated by HIFU single with who were treated by both HIFU and chemotherapy, median survival duration was 8.0 months versus 12.0 months (p <0.05). The survival rate at 12 months was 14.3% for HIFU single patients and 49.9% for both HIFU and chemotherapy patients. Notably, patients who were treated by both HIFU and chemotherapy had a longer median survival than patients who were treated by HIFU single. HIFU is an attractive technique that might achieve local tumor control as well as increasing permeability of drug molecules. The possibility of synergistic effect between HIFU and chemotherapy agent was suggested (14,15). In patients with an ECOG performance status of 0 or 1, concurrent chemotherapy and HIFU is a tolerated treatment modality with promising activity.

On the other side, almost 70% of patients with pancreatic cancer are at least 65 years old at diagnosis, so side effect related to external radiation and antitumor drugs may be very severe (7). In this study, the patients who had a previous history of failure treatment with chemotherapy and/or radiotherapy and who were not felt to be suitable candidates for chemotherapy and/or radiotherapy with KPS = 60, received HIFU treatment successful. To those patients who are unable or unwilling to receive treatment with chemotherapy and/or radiotherapy, HIFU therapy is an available choice. It is worth noting that 4 patients received HIFU therapy twice and 2 patients received it more than twice. Different with radiotherapy, HIFU therapy is not limited by dose-limiting toxicity. That means patients with local pancreatic cancer may benefit from HIFU treatment repeatedly. Although this study may have limitations, we deem that treatment of local advanced pancreatic tumors with HIFU may result in local tumor response or a clinically beneficial outcome by improving pain, functional status, quality of life, and survival. A randomized controlled study is necessary to determine our assumption. In conclusion, HIFU is a safe and effective therapeutic option for patients with local advanced pancreatic cancer. This treatment may be effective for local tumor control. This approach would be a feasible option, both for curative and palliative purposes.

REFERENCES