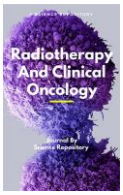

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Research Article

High-intensity focused ultrasound as an effective and safe treatment for palliation of pain related to pancreatic cancer

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ABSTRACT

This study was to evaluate the efficacy and safety of high intensity focused ultrasound (HIFU) in pain palliation of advanced unresectable pancreatic cancer. Twelve patients suffering cancer-related pain were treated with HIFU, and one case was treated a second time. The type and dose of analgesic drugs were obtained at baseline and during 12-week follow-up and converted to daily oral morphine dose. Post-HIFU pain relief, tumor ablation ratio, tumor reduction ratio in maximal tumor diameter, and adverse events were assessed. Pain was relieved in 11 cases (84.6%), with equal morphine dose reduction ratio from 23% to 100%. Complete pain relief was observed in 4 patients (30.8%), a partial pain relief was observed in 7 patients (53.8%), and no improvement of pain was observed in 2 patients (15.4%). Both tumor ablation ratio (P = 0.175) and tumor reduction in maximal diameter (P = 0.532) were not significantly associated with the reduction ratio of equal morphine dose. There were no severe adverse events related to HIFU therapy seen in any of the patients treated. Our data suggested that HIFU is an effective and safe treatment modality for palliation of the pain related to pancreatic cancer.

Introduction

The health burden of pancreatic cancer in China is increasing, accounting for 19.45% of all newly diagnosed cases worldwide [1]. Up to 60–90% of patients with advanced disease suffer cancer-related pain, which would exacerbate anxiety, reduce quality of life, hinder the implementation of palliative treatment, and shorten the patient's survival [2]. Therefore, pain relief is of particular importance for patients with pancreatic cancer suffering from cancer-related pain.

The current treatment options for relieving pancreatic cancer-related pain include analgesic drug therapy, chemoradiotherapy, and minimally invasive ablative therapies such as radiofrequency ablation, microwave ablation, and cryotherapy. However, the adverse events of analgesic drug therapy and chemoradiotherapy are pronounced [3, 4]. The main limitations and challenges of the minimally invasive ablative techniques are the organ location and the risk to develop pancreatitis or to damage the contiguous neurovascular structures [5]. In general, the clinical efficacy of these analgesic options is still far from ideal, offering transient pain relief and causing undesired side-effects.

High-intensity focused ultrasound (HIFU) is a relatively new totally noninvasive technique approved by the US Food and Drug Administration for the treatment of uterine fibroids. It is a technology that focuses beams of ultrasound waves at one point, where the highest magnitude of energy is deposited. In addition to heat generation with coagulation necrosis [6], the action mechanisms also include cavitation

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and systemic immunological effects [7]. Many studies have shown that HIFU is safe and effective in treating patients with benign uterine fibroids or adenomyosis. Recently, new applications in oncology, including the management of unresectable pancreatic cancer with cancer-related pain, have received increasing interest [8-10].

In the present study, we evaluated the safety and efficacy of HIFU for pain relief of inoperable pancreatic cancer. Furthermore, we also examined the associations of tumor ablation and tumor reduction in maximal tumor diameter with pain relief.

Materials and Methods

I Patients

A total of 12 pancreatic cancer patients with cancer-related pain were included in the present study. The inclusion criteria were (1) histological/cytological diagnosis of pancreatic adenocarcinoma, with cancer-related pain in the mid-back or epigastric regions; (2) tumor unresectable; (3) tumor sufficiently visible on ultrasound; and (4) adequate coagulation, renal and hepatic function eligible for HIFU treatment. The exclusion criteria were (1) eligibility for surgical resection; (2) estimated life expectancy of less than 3 months; (3) tumor not sufficiently visible on ultrasound; (4) extensive scarring along the acoustic path; or (5) obstructive jaundice caused by tumor compression. Eligibility for HIFU therapy was confirmed in a multidisciplinary tumor conference including surgeons, oncologists, radiotherapists and interventional radiologists. The procedures followed were in accord with the Declaration of Helsinki and its revisions. All patients provided written informed consent and the study protocol was approved by the Institutional Review Board of the participate hospital.

II HIFU treatment

The Model-JC200 Focused Ultrasound Tumor Therapeutic System (Chongqing HIFU Tech, Chongqing, China) was used to treat all patients under the guidance of real-time ultrasound. The main characteristic parameters of the instrument are as follows: power rating of 8.4 kVA, frequency of 0.5–2 MHz, and therapy power of 72–400 W. The therapeutic ultrasound beam was transmitted by a 20-cm-diameter ceramic transducer with a focal length of 15 cm, operating at 0.8 MHz. HIFU was performed under procedural sedation and analgesia. Pretreatment planning and therapy were performed in sagittal scanning mode. Ultrasound energy was delivered using a dot mode. Sonication power was adjusted for each patient depending on adjacent risk structures and treatment tolerance. After HIFU treatment, the patients remained hospitalized for 2–7 days.

III Baseline tumor imaging and pain control

Baseline tumor imaging was performed within 2 weeks before HIFU using contrast-enhanced CT and MRI. Contrast-enhanced US was also performed prior to HIFU treatment. Baseline tumor volumes and the maximal tumor diameter were calculated based on the CT/MRI imaging information. The Numerical Rating Scale (NRS) score of cancer-related pain, and the type and dose of analgesic drugs were collected at baseline. Dose of opioid analgesics was converted to daily oral morphine hydrochloride according to the National Comprehensive Cancer Network Guidelines [11]. Dose of nonsteroidal anti-inflammatory drugs (NSAIDs) was converted to daily oral morphine hydrochloride according to the literature [12].

IV Treatment evaluation

To evaluate treatment efficacy and exclude major complications, contrast-enhanced CT, MRI and/or US were performed within 3 days after HIFU. Long-term follow-up included contrast-enhanced CT or MRI was executed at 6-12 weeks after HIFU. Tumor ablation ratio (%) was estimated as a ratio of non-contrast-enhancing area to the complete target area. Tumor reduction ratio (%) was calculated as the ratio of the difference between baseline and post-HIFU 6-12 weeks to the baseline in maximal tumor diameter. Adverse events were observed according to the Society of Interventional Radiology clinical practice guidelines [13].

V Follow-up of pain relief

Pain response, including changes in pain medication over time were assessed during up to 12-week follow-up. The reduction ratio of equal morphine dose (%) was calculated as the ratio of the difference between baseline and post-HIFU to the baseline in equal morphine dose. Complete pain relief was defined as no pain (NRS score of one or less) and no need for analgesics after HIFU. Partial pain relief was defined as no pain and less analgesic drugs compared with those at baseline.

VI Statistical analysis

Descriptive data including age, maximal tumor diameter and HIFU treatment were presented as mean ± standard deviation (SD). The *t*-test was used to compare the maximal tumor diameter at baseline and after HIFU. Correlations of tumor ablation ratio and tumor reduction ratio with the reduction ratio of equal morphine dose were assessed using Spearman's test. All statistical analyses were performed with Stata 13.0 (Stata, College Station, TX, USA), and P values < 0.05 were considered statistically significant.

Results

I Patient characteristics

A total of 12 patients with pancreatic cancer (six men, six women, aged 63.8 ±11.9 years) were treated with US-guided HIFU (Table 1). Six patients presented with tumor-node-metastasis (TNM) stage III, and six with stage IV disease. Five patients presented with hepatic metastasis, and one with bone metastasis. Before HIFU treatment, two patients underwent chemotherapy, and one chemoradiotherapy. After HIFU, eight patients received chemotherapy, and one chemoradiotherapy.

II HIFU treatment data

HIFU was successfully performed in all patients. Eleven patients were treated in a single session, and one female in two sessions with a time interval of 5.6 months. Treatment time, defined as the time from the beginning of localization to the last sonication, ranged from 63 to 210 min (mean ± SD, 123.0 ± 36.1 min). The ablation time, also called the

exposure time, ranged from 266 to 1306 s (657.0 ± 302.5 s). The acoustic focal peak intensities ranged from 170 to 400 W (262.0 ± 82.2 W) and the total energy ranged from 45.5 to 520.6 KJ (182.8 ± 130.1 KJ).

Table 1: Demographic and clinical characteristics of patients with pancreatic cancer

Parameter	Value
Age, mean ± SD (range), years	63.8 ± 11.9 (50-83)
Male/Female	6/6
Maximal tumor diameter, mean ± SD (range), cm	4.2 ± 1.1 (1.9-5.7)
CA19-9 (U/ml)	
>37	11
<37	1
Pancreatic tumor location	
Head and neck	9
Body	2
Tail	1
TNM stage	
III	6
IV	6
Metastasis (*n*=6)	
Hepatic	5
Bone	1
Pre-HIFU treatment	
None	9
Chemoradiotherapy	1
Chemotherapy	2
Post-HIFU treatment	
None	3
Chemoradiotherapy	1
Chemotherapy	8

HIFU: high-intensity focused ultrasound; SD: standard deviation; TNM: tumor-node-metastasis; CA19-9: carbohydrate antigen 19-9

III Tumor ablation and tumor reduction

The tumor ablation ratio of HIFU treatment ranged from 60% to 89%, with an average ablation ratio of 74.5 ± 9.1%. The maximal tumor diameters at baseline and after HIFU were 1.9-6.5 cm (4.46 ± 1.23 cm) and 1.9-6.4 cm (4.35 ± 1.37 cm), respectively, and no significant difference was observed (P = 0.657). Moreover, tumor ablation ratio was not significantly associated with tumor reduction ratio (P = 0.389).

IV Pain relief

The pain medication at baseline and at 4 weeks after HIFU are summarized in Table 2. At baseline, all 13 cases suffered cancer-related pain and had achieved pain relief with analgesic drugs, with NSAIDs, weak opioid and strong opioid for four, five and four cases, respectively. After HIFU treatment, complete or partial pain relief was achieved in 11 cases (84.6 %) with equal morphine dose reduction ratio from 23% to 100%, and five and two cases required less analgesics and ladder-step down analgesics (from tramadol to celecoxib for one case, and from oxycodone to tramadol for another), respectively, for pain control. Pain relief persisted during 12-week follow-up (n =11 at 4-week and n = 8 at 12-week follow-up).

In further analysis, both tumor ablation ratio (P = 0.175) and tumor reduction ratio (P = 0.532) were not significantly associated with the reduction ratio of equal morphine dose.

V Adverse events

Seven of 12 patients experienced slight transient abdominal pain for up to 24 h immediately after HIFU. In one patient an induration of subcutaneous fat tissue within the upper anterior abdominal wall was observed, resolving spontaneously within 3 weeks. Increase of serum amylase was observed in 5 patients 3 days after HIFU; however, this was without clinical pancreatitis-related symptoms and restored to the normal level within 1 week without specific treatment.

Table 2: Equal morphine dose reduction after HIFU treatment among pancreatic cancer patients

Case	Pre-HIFU		Post-HIFU		Dose Reduction (%)*
	Analgesic Drug	Equal Morphine Dose (mg/d)	Analgesic Drug	Equal Morphine Dose (mg/d)	
1	Celecoxib	10	/	0	100
2	Celecoxib	10	/	0	100
3	Tramadol	60	/	0	100
4	Tramadol	60	/	0	100
5	Tramadol	60	/	0	100
6	Tramadol	60	Celecoxib	10	83
7	Oxycodone	160	Tramadol	60	63
8	Celecoxib	10	Celecoxib	5	50
9	Oxycodone	70	Oxycodone	40	43
10	Fentanyl/morphine	310	Fentanyl	240	23
11	Fentanyl/morphine	340	Fentanyl/morphine	255	25
12	Celecoxib	10	Celecoxib	10	0
13	Fentanyl	180	Fentanyl	180	0

HIFU: high-intensity focused ultrasound

* Equal morphine dose after HIFU *vs.* before HIFU

Discussion

HIFU offers the potential for a multimodal therapeutic approach for patients with pancreatic cancer, providing pain palliation and the possibility of local tumor control. In the present study, we showed that complete or partial relief of cancer-related pain was achieved in 84.6 % cases with equal morphine dose reduction from 23% to 100%. Although all patients had a technically successful HIFU treatment, with a mean tumor ablation ratio of 74.5% (SD of 9.1%), no significant tumor reduction in maximal diameter was observed during up to 12-week follow-up.

Good control of pain relief by HIFU therapy has been widely reported in advanced pancreatic cancer patients [14-16]. In a recent meta-analysis, Dababou *et al*. reported that as many as 81% of patients experience pain relief after HIFU, with sustained response reported even 17 months after therapy [17]. In line with previous data, our study presented an 84.6 % (11/13) pain improvement, with no pain progression in 8 patients during 12-week follow-up. Taken together, HIFU appears to be an effective tool for pain palliation in advanced pancreatic cancer. As for the benefit assessment of HIFU on the pain palliation, the most commonly used method is the NRS quantitative pain estimate [18]. However, in clinical practice, most pancreatic cancer patients have been administrated analgesic medications to relieve pain prior to HIFU therapy. Therefore, the pre- and post-HIFU quantitative pain score comparison may not be applicable to all pancreatic cancer patients. In the present study, conversion of all analgesic drugs to daily oral morphine hydrochloride made it possible for us to evaluate quantitatively the reduction of pain following HIFU. Our data suggest for the first time that accurate calculation of the reduction ratio of the analgesic drug dose is an alternative method for the benefit assessment of HIFU, especially for those patients who have achieved good pain control prior to HIFU therapy.

In the present study, no significant post-HIFU tumor reduction was observed when compared to that at baseline, which was a common finding after HIFU [5]. Indeed, in the short term, the volume of the tumor may appear unchanged or increased due to local edema [19, 20]. Further, we observed no significant association of tumor reduction with pain relief, reflected by the reduction of equal morphine dose. In previous studies, pain improvement after HIFU therapy was observed in 63.6-76.2% of patients with stable or progressive disease [21, 22]. These findings suggested that tumor size reduction does not appear to be a sensitive way to evaluate the HIFU effect on pain relief.

Tumor ablation ratio has been regarded as an indicator for successful HIFU procedure. However, in our small cohort study, tumor ablation ratio was not significantly associated with tumor reduction or the analgesic drug reduction ratio, indicating that tumor ablation ratio may not be suitable as a predictor for HIFU efficacy, neither in terms of the effect on pain relief nor for the evaluation of objective tumor response. Future studies, based on larger sample size, are needed to verify our findings.

In our small cohort of patients, there was one case of local induration of subcutaneous fat tissue within the upper anterior abdominal wall after HIFU. Eight patients developed local slight short-lasting abdominal pain, and in five patients there were a mild increase of serum amylase on blood analysis without any clinical signs of pancreatitis. All these adverse events required no specific treatment, without prolonged hospitalization. Major complications reported previously such as intestinal perforation, skin burn, jaundice aggravation, occlusion of superior mesenteric artery, and vertebral damage [23, 24], were not observed in our study. Our data provided further evidence to the current viewpoint that, with the improvement of the technique and increase in physicians' experience, the HIFU procedure has become rather safe [25].

Several limitations should be noted in the present study. Firstly, the number of samples was small and thus strong conclusions, especially for the correlation of tumor ablation with tumor reduction and pain relief, cannot be drown. Secondly, most of the patients included in our analysis have underwent chemotherapy or chemoradiotherapy pre- and/or post-HIFU, which may confound the evaluation of HIFU efficacy [15, 26]. Specified studies are needed to better discriminate the potential of HIFU as single therapy and the effects of combination therapies on pain relief. Finally, whether pain relief following HIFU can be converted to survival benefit was not investigated in the present study.

Although limited by small sample size, the results suggest that HIFU is an effective and safe treatment for relieving pain in patients with pancreatic cancer. Further studies are necessary to determine if tumor ablation ratio of HIFU therapy has impact on pain relief.

Conflict of Interest

The authors declare that they have no competing interests.

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