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Original Contribution

High-Intensity Focused Ultrasound Ablation Combined With Pharmacogenomic-Guided Chemotherapy for Advanced Pancreatic Cancer: Initial Experience

Lifeng Ran, Wei Yang, Xing Chen, Jun Zhang, Kun Zhou, Hui Zhu, Chengbing Jin *

Clinical Center for Tumor Therapy, The 2nd Affiliated Hospital of Chongqing Medical University, Chongqing, China

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ABSTRACT

Objective: To investigate the safety and efficacy of high-intensity focused ultrasound (HIFU) ablation combined with pharmacogenomic-guided chemotherapy in treating patients with advanced pancreatic cancer (PC).
Methods: Thirty-one patients with unresectable PC (stage III 17, stage IV 14) were enrolled in this study. The patients were divided into group A (pharmacogenomic-guided chemotherapy following HIFU treatment, $n = 13$) and group B (traditional chemotherapy following HIFU treatment, $n = 18$). Contrast-enhanced computed tomography and magnetic resonance imaging were used to evaluate tumor response. Pain intensity was assessed using the numerical rating scale. The Kaplan–Meier method and log-rank test were used to analyze survival.
Results: The mean pain intensity score in 18 patients decreased from 6.6 ± 2.2 before HIFU to 3.3 ± 1.0 after HIFU ($p = 0.000$). The mean duration of pain relief was 5.2 ± 3.2 mo in group A and 2.4 ± 1.3 mo in group B ($p = 0.026$). There was no significant difference of the non-perfused volume ratio (83.5% ± 22.3% in group A and 85.3% ± 16.8% in group B) between the two groups. The median survival time was 14 mo in group A and 5 mo in group B. The 6 and 12-mo survival rates were 74.1% and 59.3% in group A, and 32.4% and 19.4% in group B, respectively. The difference in survival between the two groups was significant ($p = 0.04$). No severe complications (≥grade 3) related to HIFU were observed. Bone marrow depression was the main adverse reaction related to chemotherapy, with grade 3 bone marrow depression observed 2 (15.4%) patients in group A and 7 (38.9%) patients in group B.
Conclusion: HIFU combined with pharmacogenomic-guided chemotherapy is safe and effective in treating patients with advanced PC. It provides better clinical outcomes in pain relief, quality of life and survival benefits for patients with advanced PC compared to HIFU combined with traditional chemotherapy. This combined approach may have the potential to become an important supplement to the treatment of advanced PC.

Introduction

Pancreatic cancer (PC) is one of the most malignant tumors in the digestive system, with only 8% of PC patients surviving more than 5 y [1]. The majority of patients (85%–90%) are already in the advanced stage at the time of diagnosis, with no opportunity for surgery, making the disease incurable. The primary goal of treatment for PC patients who are not eligible for surgery is palliative, with intention of potentially prolonging survival. High-intensity focused ultrasound (HIFU) ablation has been developed as a safe non-invasive treatment for PC in the past two decades. Previous studies have shown that HIFU can effectively and safely ablate pancreatic carcinoma, helping to control pain and improve quality of life in PC patients [2–4]. However, since the pancreas is located very close to the gastrointestinal tract or biliary tract, HIFU is not able to safely and effectively ablate the entire tumor masses that are near these organs. This can lead to tumor residue and recurrence, which may impact tumor control and the patient's survival. Therefore, it is crucial to combine HIFU with other treatment options such as chemotherapy to eliminate the residual tumors, enhance local tumor control and extend patient's survival time.

Chemotherapy is typically the preferred systemic therapy for advanced PC patients with good performance status. Chemotherapy regimens based on gemcitabine or 5-fluorouracil are currently recommended as first-line treatment for pancreatic carcinoma. However, the

* Corresponding author. Clinical Center for Tumor Therapy, The 2nd Affiliated Hospital of Chongqing Medical University, 74 Linjiang Road, Yuzhong District, Chongqing 40010, China.
E-mail address: jincb@hospital.cqmu.edu.cn (C. Jin).

Lifeng Ran and Wei Yang contributed equally to this work.

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efficacy of these regimens remains unsatisfactory, and the choice of initial chemotherapy regimen can be confusing [5,6].

By utilizing genetic testing to identify different genotypes and specific anti-tumor targets, more effective chemotherapeutic regimens may be designed to improve survival and quality of life while reducing side effects [7–9]. Ribonucleotide reductase M1 (RRM1) is the gene that encodes the regulatory subunit of ribonucleotide reductase and is the main target of gemcitabine. RRM1 and RRM2 together form the rate-limiting enzyme RR in the DNA synthesis pathway. Previous clinical studies have indicated that gemcitabine is effective for patients with low RRM1 mRNA expression [10]. Detection of the RRM1 gene can help guide the use of gemcitabine. Similarly, the thymidylate synthase gene can guide the use of fluorine chemotherapeutic drugs [11]. Therefore, this study aims to explore the safety and efficacy of HIFU treatment combined with pharmacogenomic-guided chemotherapy in the treatment of patients with advanced PC and to explore the significance of this combined approach.

Materials and methods

Patients

This study was approved by the ethics committee at the Second Affiliated Hospital, Chongqing Medical University (No. 2019-277). From March 2016 to February 2018, 31 consecutive patients diagnosed with advanced PC, who met the inclusion criteria, were enrolled in this study. The inclusion criteria were as follows: (i) Eastern Cooperative Oncology Group (ECOG) performance status 0–2; (ii) unresectable; (iii) radiographically measurable or evaluable lesion, or evaluable clinical observation of clinical indicators such as abdominal pain; (iv) patients and their families agreed to receive HIFU combined with chemotherapy and were willing to bear the risks; (v) no contraindications to HIFU treatment or chemotherapy. The exclusion criteria were: (i) ECOG performance status >2; (ii) unable to maintain prone position for more than 2 h; (iii) unable to tolerate anesthesia; (iv) tumors undetectable by ultrasound scanning; (v) patients with active infection; (vi) proximity to major vascular structures (superior mesenteric artery or celiac trunk) or bowel involvement.

The patients were divided into two groups. In group A, 13 patients received pharmacogenomic-guided chemotherapy following HIFU treatment and in group B 18 patients received traditional chemotherapy following HIFU. Genetic testing was performed by Fudan Clinical Pathology and Diagnostic Center in Shanghai, China. Gene sequencing was mainly conducted using reverse transcriptase-polymerase chain reaction (PCR). The gene sequences related to the efficacy and side effects of chemotherapy drugs recommended in the guidelines for pancreatic carcinoma, including gemcitabine, fluorouracil, platinum and paclitaxel, were tested. All patients received HIFU treatment before chemotherapy in both groups. The baseline characteristics of the two groups are shown in Table 1.

Table 1
Baseline Characteristics of the Two Groups ($\bar{x} \pm s$)

Items	Genetic Testing Guided Chemotherapy	Traditional Chemotherapy	*p*
Number of cases	13	18	
Gender (male/female)	5/8	14/4	0.060
Age	64.4 ± 11.3	65.5 ± 9.2	0.764
ECOG			
0	1	2	0.891
1	11	14	
2	1	2	
UICC stage of disease			
III	7	10	0.925
IV	6	8	
Tumor site of pancreatic disease			
Head	7	9	0.432
Body and/or tail	4	3	
Head and body	2	6	
Metastasis			
Yes	6	7	0.686
Non	7	11	
CA19-9			
Positive	11	14	0.988
Negative	2	4	
Greatest dimension of pancreatic tumor (cm)	3.8 ± 1.4	4.7 ± 1.3	0.123

CA19-9, carbohydrate antigen 19-9 (tumor marker); ECOG, Eastern Cooperative Oncology Group performance status (0-5); UICC, tumor classification of the Union for International Cancer Control.

HIFU treatment

Evaluation before HIFU procedure included blood chemistry, vital organ function test including the function of liver, kidney, heart and abdominal computed tomography/magnetic resonance imaging (CT/MRI) scanning. Due to pancreatic neoplasia proximity to the gastrointestinal tract, a bowel preparation similar to colonoscopy preparation was required to avoid potential complications of gastrointestinal tract injury. The bowel preparation began 1 d before HIFU procedure, including liquid food, no milk or other gas-producing products, taking laxatives and fasting for 12 h.

The HIFU procedure was performed using the Model-JC HIFU system (Chongqing Haifu Medical Tech Co., Ltd., Chongqing, China). The device was equipped with a diagnostic ultrasound probe (MyLab 70, Esaote, Genova, Italy) in the center of the HIFU transducer for real-time monitoring of the treatment procedure. Therapeutic ultrasound beams were produced by a 20-cm diameter transducer with a focal length of 160 mm, operated at a frequency of 0.8 MHz. Details of the device and treatment procedure have been described in previous publications [12,13]. HIFU treatment was performed under either general anesthesia or intravenous sedation to prevent the patient's discomfort and movement. During the procedure, patients were positioned prone on the treatment bed, so that the skin overlaying the targeted lesion could easily be in contact with degassed water. A balloon filled with degassed water was placed between the patient's upper abdominal wall and the transducer to push the stomach and bowel away to avoid any injury to gastrointestinal structures within the acoustic pathway. The targeted tumor was clearly identified by the integrated diagnostic ultrasound imaging. The targeted lesion was defined and divided into parallel slices of 5-mm intervals by real-time ultrasound imaging. HIFU treatment was conducted using multiple single exposures ranging from 1 to 3 s. To ablate a relevant volume of the target tumor, many of these small HIFU lesions were positioned side by side systematically to produce a line-shaped lesion. By moving the focus in successive sweeps from the distal to proximal regions of the target area, the tumor can be successfully destroyed in this slice. Complete ablation of the entire target lesion was achieved by repeated ablation of the regions of the slices. During the HIFU procedure, tumor responses to the treatment were identified by the grayscale changes at the focus on ultrasound images immediately following each HIFU exposure.

Chemotherapy

All patients began chemotherapy 1-2 wk after receiving HIFU treatment. Patients who underwent genetic testing had their chemotherapy regimens guided by the results of the testing. For patients without genetic testing, chemotherapy regimens were based on the guidelines provided by the China Cancer Society Pancreatic Cancer Professional Committee for comprehensive treatment of PC. Each chemotherapy drug was administered at the standard dosage and following the

specified usage methods. Throughout the chemotherapy process, any toxic and side effects of chemotherapy, such as gastrointestinal reactions and bone marrow suppression, were monitored and recorded. If any side effects occurred, appropriate treatments were provided accordingly.

Post-treatment assessments

Before HIFU treatment, patients underwent contrast-enhanced CT or MRI to assess the location, size and volume of pancreatic tumors. Within 1 mo after the HIFU treatment follow-up imaging was conducted to evaluate the responses of HIFU ablation in all patients. Compared to pre-treatment CT or MR images, contrast enhancement disappeared in the treated tumor after the HIFU procedure, indicating coagulation necrosis of the target tumor. The non-perfused volume (NPV) ratio was used to evaluate the responses of HIFU ablation. Complete disappearance of contrast enhancement indicated complete ablation with no residual viable tumor in the target region. The NPV ratio of each target tumor was calculated using the formula: $(1/6 \times \pi \times D1 \times D2 \times D3)/(1/6 \times \pi \times d1 \times d2 \times d3) \times 100\%$, where D1, D2, D3 were the maximum values measured for the longitudinal, anteroposterior and transverse diameters of the non-contrast perfused portion of the target tumor in contrast-enhanced CT or MR images after HIFU treatment, and d1, d2, d3 were the maximum values measured for the longitudinal, anteroposterior and transverse diameters of the target tumor before HIFU, respectively [14].

Patient were followed up every 3 mo for 2 y, and then every 6 mo thereafter. During the follow-up period, changes in patient's clinical symptoms such as pain were recorded. Peripheral blood cell counts, serum biochemistry including liver function and amylase, and tumor markers were also measured.

Statistical analysis

All data were entered into the SPSS database and analyzed using SPSS version 22.0. The changes in pain intensity scores and levels of serum biochemistry before and after HIFU treatment were compared using the paired *t*-test. Correlation analysis was conducted between PC ablation rate and survival time. Survival rate analysis was performed using the Kaplan–Meier method. Mean survival time and 12-mo survival rate were calculated. The log-rank test was used to compare the survival rates between group A and group B. The significance level for the test is $\alpha = 0.05$.

Results

Baseline characteristics

The clinical characteristics of the patients enrolled in this study are presented in Table 1. A total of 31 patients were included, with 17 at stage III and 14 at stage IV according to the UICC staging, 8th edition. The patients were divided into two groups. Group A received pharmacogenomic-guided chemotherapy ($n = 13$) and group B received traditional chemotherapy ($n = 18$). The mean age of patients was 64.4 ± 11.3 y in group A and 65.5 ± 9.2 y in group B. The average size of the pancreatic tumor was 3.8 ± 1.4cm in group A and 4.7 ± 1.3cm in group B. There were no significant differences in gender, age, Eastern Cooperative Oncology Group performance status, staging, tumor site of pancreatic disease, carbohydrate antigen 19-9 level (CA19-9), or size of pancreatic tumor between the two groups.

Table 2 shows the chemotherapy drugs used for the patients. In group A, based on genetic testing results combined with the recommendation of the China Cancer Society Pancreatic Cancer Professional Committee for comprehensive treatment guidelines for PC, 6 out of 13 patients received chemotherapy with gemcitabine plus platinum, 4 with gemcitabine, 2 with fluorouracil plus gemcitabine and 1 with gemcitabine plus paclitaxel. In group B, following the same guidelines, 7 out of 18 patients received chemotherapy with gemcitabine plus platinum, 7 with gemcitabine, 3 with fluorouracil and 1 with gemcitabine plus fluorouracil.

Table 2
Chemotherapy Drugs Used for Patients in Both Groups

Items	Fluorouracil	Gemcitabine	Platinum	Paclitaxel
Group A	2	13	6	1
Group B	4	15	7	0

Tumor response

All patients received HIFU ablation. The average acoustic power and exposure time were 265.9 ± 58.7 W (range: 121–397 W) and 18.6 ± 8.6 min (range: 4.0-41.9 min), respectively. The powers were adjusted based on the changes in ultrasound grayscale during the HIFU process. Contrast-enhanced MRI or CT showed that contrast enhancement disappeared in the treated tumor after HIFU ablation, indicating successful ablation with a positive tumor response (Fig. 1). Complete ablation of pancreatic lesions was achieved in 7 patients, 3 in group A and 4 in group B. In patients with partial ablation, most were due to the tumor being adjacent to the gastrointestinal tract to prevent injury. The mean NPV ratio of pancreatic tumors was 84.6% ± 19% (range, 30%–100%). There was no significant difference in the NPV ratio (independent samples *t*-test, $p = 0.797$) between group A (83.5% ± 22.3%) and group B (85.3% ± 16.8%), as shown in Table 3.

Serum CA19-9 was measured in 25 patients, with a mean level of 730.5 ± 430.7 U/mL before treatment. Within 2 wk after HIFU, the mean level of serum CA19-9 decreased to 479.0 ± 401.1U/mL. There was a significant difference between them (paired *t*-test, $p = 0.041$).

Changes in pain intensity

Table 4 displays changes in pain intensity before and after HIFU treatment. Pain intensity was assessed using the numerical rating scale method. Prior to HIFU treatment, 18 out of 31 patients experienced pain, including abdominal and back pain. The average pain intensity score decreased from 6.6 ± 2.2 before treatment to 3.3 ± 1.0 after HIFU, showing a statistically significant difference (paired *t*-test, $p = 0.000$). There was a significant difference in pain intensity change between groups A and B (paired *t*-test, $p = 0.020$ and 0.001). The mean duration of pain relief was 5.2 ± 3.2 mo in group A and 2.4 ± 1.3 mo in group B, with a statistically significant difference (independent samples *t*-test, $p = 0.026$).

Survival outcome

All patients in this study were followed up after receiving combined treatment. The follow-up period was calculated from the start of HIFU treatment. The mean follow-up duration was 8.4 ± 5.9 mo (range, 1–25 mo). At the end of the follow-up, 20 patients died (18 due to tumor progression and 2 from gastrointestinal bleeding), while remaining 11 patients were still alive, including 6 in group A and 5 in group B. Overall survival was evaluated using the Kaplan–Meier method. The median survival time was 9 mo (95% CI: 2.5–15.5 mo), and the survival rates at 6, 12, 18 mo were 54.4%, 41.7% and 22.8%, respectively, as shown in Figure 2.

By using the log-rank test, the survival of patients in this study was compared between groups A and B. The median survival time (based on the start of HIFU treatment) was 14 mo (95% CI: 9.2–18.8 mo) in group A and 5 mo (95% CI: 3.5–6.5 mo) in group B. The survival rates at 6, 12 mo were 74.1% and 59.3% in group A and 32.4% and 19.4% in group B, respectively. The difference in survival between the two groups was significant (log-rank test, $p = 0.04$), as shown in Figure 3.

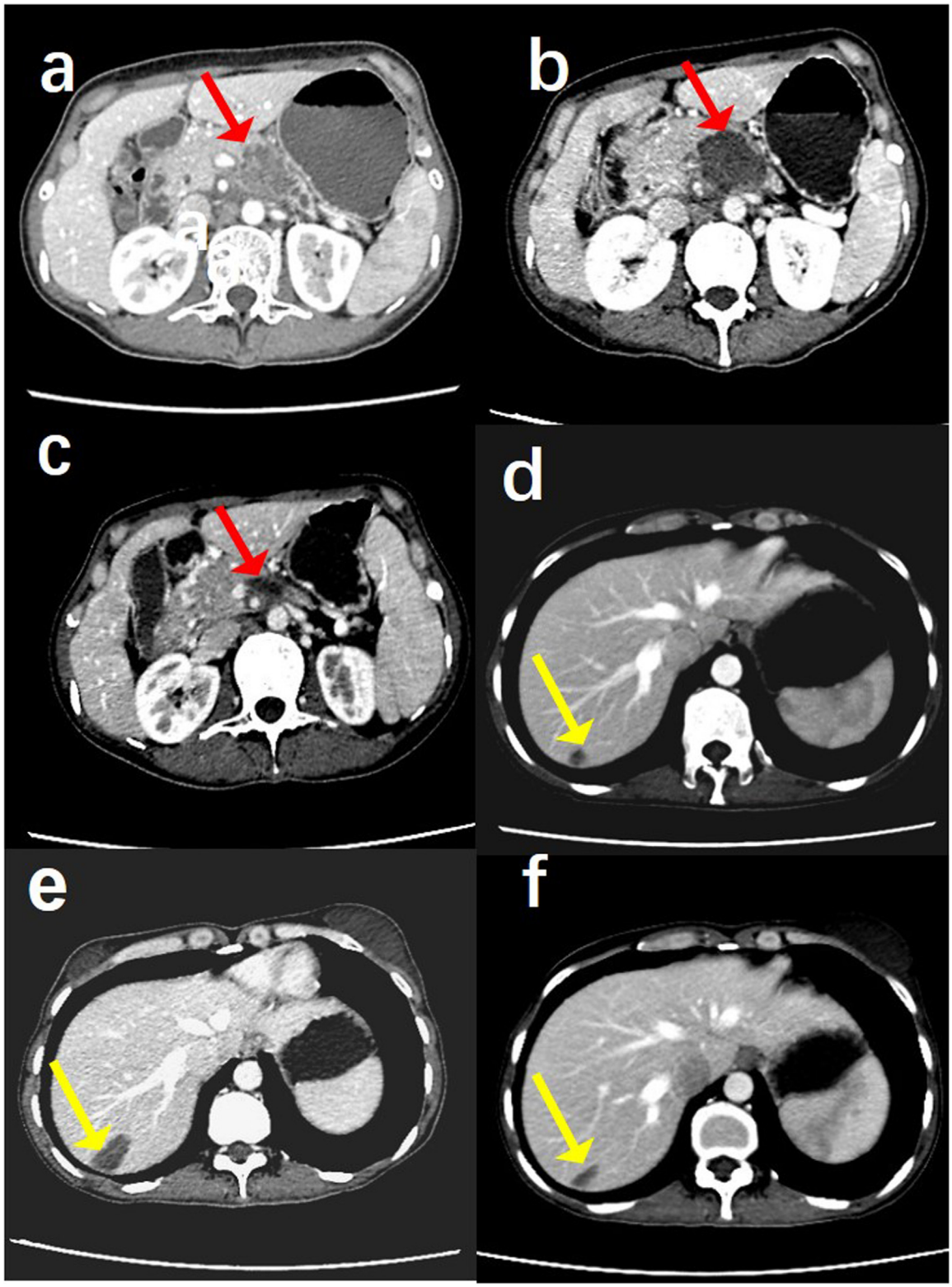

Figure 1. The changes in contrast-enhanced CT images before and after HIFU treatment in a 41-y-old female patient with advanced pancreatic carcinoma (UICC stage IV). (a) Before HIFU treatment, the enhanced CT image shows the tumor located in the body and tail of the pancreas (red arrow). (b) One week after HIFU, no contrast enhancement is seen in the treated tumor (red arrow). (c) Six months after HIFU, the enhanced CT image shows significant shrinkage of the treated tumor (red arrow). (d) Before HIFU treatment, the image shows one liver metastasis (yellow arrow). (e) One week after HIFU, the metastatic liver tumor is effectively ablated with no contrast enhancement in the enhanced CT image (yellow arrow). (f) Six months after HIFU, significant shrinkage of the treated liver metastasis is evident (yellow arrow).

Table 3
Non-perfused Volume (NPV) Ratio of HIFU-Treated Pancreatic Tumors in Two Group

Group A		Group B		*P* (Independent Samples *t*-Test)
Patient No	NPV Ratio (%)	Patient No	NPV Ratio (%)	
1	100.0	1	85.0	
2	95.7	2	95.0	
3	80.6	3	89.0	
4	90.6	4	95.0	
5	90.0	5	90.0	
6	91.4	6	89.0	
7	87.1	7	76.0	
8	100.0	8	79.5	
9	40.0	9	85.4	
10	100.0	10	93.6	
11	90.0	11	100.0	
12	30.0	12	100.0	
13	90.0	13	88.2	
		14	30.0	
		15	70.0	
		16	100.0	
		17	70.0	
		18	100.0	
Mean ($\bar{\chi} \pm s$)	83.5 ± 22.3		85.3 ± 16.8	0.797

Table 4
Changes in Pain Intensity Before and After HIFU Treatment (Numerical Rating Scale) ($\bar{\chi} \pm s$)

	Before HIFU	After HIFU	*p* Value
Group A	6.3 ± 2.4 (n = 7)	3.0 ± 0.6	0.020
Group B	6.8 ± 2.1 (n = 11)	3.5 ± 1.1	0.001
Total	6.6 ± 2.2 (n = 18)	3.3 ± 1.0	0.00

Adverse reactions and complications

According to the Common Toxicity Criteria (Version 5), Table 5 summarizes the main adverse reactions and complications of all patients. Mild edema at the treatment site was noted in 4 patients, which was typically temporary and resolved on its own before discharge without requiring further treatment. Blood amylase levels increased 24 h after HIFU treatment in 6 patients and returned to normal levels within 3 to 5 d after fasting and receiving somatostatin infusion. Skin burns were reported in 2 patients, with one patient recovering from a grade 2 burn (hardening) after surgical debridement, and the other patient with a grade 1 burn (orange-skinned changes) recovering after 3 d of observation without treatment.

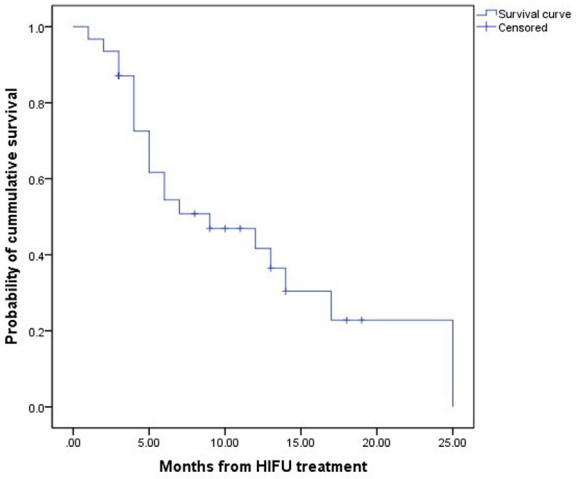

Figure 2. The survival curve of 31 pancreatic carcinoma patients who underwent treatment with HIFU. The survival time was calculated from the start of HIFU treatment. The graph displays the survival probability of patients after an average period of 8.4 ± 5.9 mo (range, 1–25 mo) of follow-up.

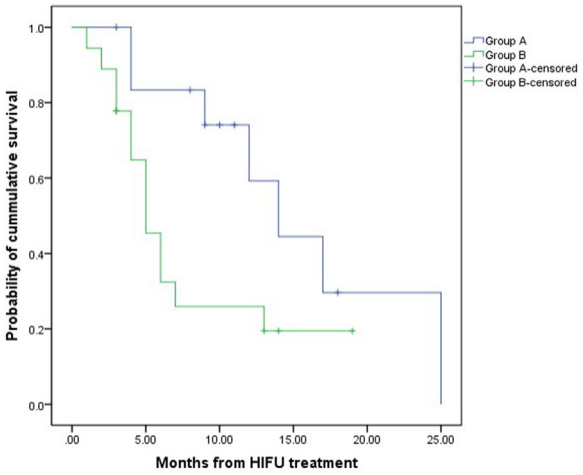

Figure 3. Cumulative survival curves for the genetic testing guided chemotherapy and traditional chemotherapy groups, using the Kaplan–Meier method. The survival time was calculated from the start of HIFU treatment. The log-rank test indicates a statistically significant difference between the two groups (p = 0.040).

Table 5
Adverse Reactions Related to HIFU and Chemotherapy.

Items	Common Toxicity Criteria Grade (Version 5)			
	1	2	3	4
Edema at treatment site	3	1	0	0
Skin burn	1	1		
Bone marrow depression				
Group A	6	4	2	
Group B	6	5	7	

HIFU, high-intensity focused ultrasound.

All patients underwent chemotherapy following HIFU, with bone marrow depression being the main adverse reaction. Grade 3 bone marrow depression was observed in 2 patients (15.4%) in group A and 7 patients (38.9%) in group B. There was no significant difference in bone marrow depression between the two groups (Chi-square test, p = 0.415). Human recombinant colony-stimulating factor was used to help recover blood cells including red blood cells, white cells and platelets. Generally, peripheral blood cell counts returned to normal after 3 to 5 d of continuous treatment with human recombinant colony-stimulating factor.

Discussion

PC is one of the most malignant tumors in the digestive system and only 8% of patients survive more than 5 y [1]. In recent years, the incidence of PC has been on a significant upward trend, possibly due to the increasing prevalence of obesity, an aging population and other unknown factors [15–17]. Currently, surgery is the only way to achieve long-term survival in the clinical management of PC. Unfortunately, most patients are already in the advanced stage at the time of diagnosis and have lost the opportunity for surgery. For patients with unresectable PC, systemic chemotherapy and locoregional therapies including radiotherapy and ablation are usually applied to improve long-term survival and quality of life [18–21].

As a non-invasive thermal ablation treatment, HIFU ablation has been used as a palliative option to treat advanced PC. Previous studies have shown that HIFU can effectively and safely ablate pancreatic carcinoma to relieve pain and improve quality of life in patients with advanced-stage PC [2–4]. In this study, contrast-enhanced CT or MRI showed an absence of contrast enhancement in the treated tumor after HIFU ablation, indicating successful ablation (Fig. 3). In patients with elevated CA19-9 levels, the serum CA19-9 decreased significantly after HIFU. The results revealed that HIFU can effectively ablate pancreatic tumors. Although several previous studies have shown that HIFU ablation is safe for pancreatic carcinoma, we observed that skin burns occurred in 2 patients and one patient with a grade 2 skin burn (hardening) recovered after debridement and sutures, indicating that the importance of observing skin changes during the HIFU procedure to prevent skin burns.

Due to the proximity of the pancreatic tumor mass close to important organs such as the gastrointestinal tract and biliary tract, HIFU cannot safely and effectively ablate the portion of tumor masses adjacent to these organs. This results in tumor residue and recurrence, which affects tumor control and the patient's survival. Some early studies have found that repeated HIFU ablation may effectively ablate pancreatic tumor and reduce tumor bulk, to improving tumor control and prolonging the survival time of patients [13,22]. Additionally, several studies have shown that HIFU treatment can render immunologically "cold" tumors like PC into "hot" tumors, and potentially enhancing the effects through the immunological impact of HIFU [23–25]. However, there has been no randomized controlled trial to test whether HIFU alone can significantly improve the survival of patients with PC. Combining HIFU with chemotherapy may enhance efficacy compared to using either chemotherapy alone [26–28]. Systemic chemotherapy is the standard of care for advanced pancreatic carcinoma. However, combining chemotherapy regimens is often not feasible due to substantial toxicity [5]. A meta-analysis study has shown that the survival rates in advanced patients have only minimally improved using different chemotherapy regimens [6].

Previous studies have indicated that designing of chemotherapeutic regimens based on different genotypes and specific anti-tumor targets guided by genetic testing may enhance survival and quality of life while reducing side effects [5–7]. In this study, the incidence of grade 3 adverse events was lower in patients with pharmacogenomic-guided chemotherapy than in those receiving traditional chemotherapy. The median survival time and survival rates at 6 and 12 mo were significantly improved in patients with pharmacogenomic-guided chemotherapy regimens compared to those with traditional regimens. These results suggest that pharmacogenomic-guided chemotherapy may decrease severe adverse events of chemotherapy and improve survival in patients undergoing this combined approach.

Pain is one of the most important factors that affects the quality of life in patients with advanced PC. In this study, the mean score of pain intensity decreased significantly after HIFU, indicating that HIFU can effectively control cancer pain and improve the quality of life in advanced PC patients. We observed that the mean duration of pain relief was significantly better in patients with HIFU combined with pharmacogenomic-guided chemotherapy than in patients with HIFU combined with traditional chemotherapy regimens, suggesting that HIFU combined with pharmacogenomic-guided chemotherapy may be more effective in improving the quality of life in advanced PC patients.

However, our study has some limitations. First, this is a retrospective study with a small sample size from a single center, which may introduce bias to the results. Additionally, results from both the HIFU-alone group and the chemotherapy-alone group were not included in this study, which is a limitation of the research. Finally, the limited range of genetic testing related to PC may impact the selection of chemotherapy drugs recommended by the guidelines, potentially hindering the use of new drugs such as immune checkpoint inhibitors and some molecular targets [29–31]. Therefore, a multicenter randomized controlled study should be conducted to validate our findings.

Conclusions

HIFU is safe and effective in treating advanced PC patients. Combining HIFU with pharmacogenomic-guided chemotherapy may be more effective in controlling pain, improving quality of life and extending survival time in patients with advanced PC. This combined approach could become a valuable addition to the treatment of advanced PC. However, a future multicenter randomized controlled study is necessary to confirm our findings.

Declaration of competing interest

The authors declare that there is no conflict of interest.

Ethics approval

The ethics approval was obtained by the 2nd Affiliated Hospital of Chongqing Medical University.

Availability of data and materials

The research data is confidential.

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