Repeated high-intensity focused ultrasound combined with iodine-125 seed interstitial brachytherapy offers improved quality of life and pain control for patients with advanced pancreatic cancer: A 52-patient retrospective study

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Abstract. Patients diagnosed with pancreatic cancer who have 5-year survival rates of ~5% are typically in the advanced stage. Pancreatic cancer has become the third leading cause of cancer-related death in the United States and there is still a lack of effective treatments to improve patient survival rate. Hence, the purpose of the present retrospective study was to assess the potential clinical impact of repeated high-intensity focused ultrasound (HIFU) combined with iodine-125 (^{125}I) interstitial brachytherapy for the treatment of patients with advanced pancreatic cancer who were ineligible for or declined surgery and chemotherapy. A total of 52 patients diagnosed with advanced pancreatic cancer were included in the study. At least one course of HIFU therapy combined with percutaneous ultrasound-guided ^{125}I seed implantation was administered to each patient. The clinical assessment included an evaluation of Karnofsky Performance Scale (KPS) score at baseline, and at 1 and 2 months after combined therapy. Pain intensity was additionally evaluated with the numerical rating score (NRS). Overall survival (OS) times and survival rates at 3, 6, 9 and 12 months after combined treatment were evaluated. Adverse events commonly associated with HIFU and ^{125}I seed implantation were recorded, and the severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events, version 4. All 52 patients received successful repeated HIFU treatment combined with ^{125}I seed implantation and were included in the analysis of efficacy and safety. The median OS time of patients was estimated to be 13.1 months (95% CI, 11.3-14.8). The survival rates at 3, 6, 9 and 12 months were 100.0, 86.5, 61.5 and 53.8%, respectively. The mean KPS score was 62.7±6.3 at baseline, 73.7±7.9 at 1 month and 68.8±6.5 at 2 months after combined treatment. KPS score increased significantly after combined therapy. The mean NRS score was 6.7±1.6 at baseline, and 4.7±1.7 and 5.4±1.5 at 1 and 2 months after combined treatment, respectively. The number of patients with severe pain and the NRS score were both significantly lower at 1 and 2 months after ^{125}I seed implantation compared with those at baseline. No serious complications were detected during the follow-up period. In conclusion, the present study demonstrated the survival benefit and improvement in quality of life of patients with advanced pancreatic cancer receiving repeated HIFU treatment combined with ^{125}I interstitial brachytherapy, which may provide new ideas and methods for the treatment of pancreatic cancer.

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Introduction

Globally, pancreatic cancer is ranked seventh in terms of causing cancer-related fatalities, resulting in 432,242 deaths in 2018 (1). The majority of patients with pancreatic cancer are diagnosed at an advanced stage or found to have an unresectable tumor (2,3), and this is the primary contributor to a decrease in survival rate of <10% (4,5). Although survival rates have improved only slightly since advances in medical treatment, the morbidity of pancreatic cancer continues to increase (2).

Tumor-associated pain is a highly prevalent symptom in individuals diagnosed with pancreatic cancer that manifests in >80% of cases (6). Despite the utilization of various palliative chemotherapy regimens and standard palliative therapies, nearly 75% of patients with locally advanced disease experience significant cancer-related abdominal or back pain, significantly diminishing their quality of life. Given the unfavorable prognosis of these patients and as a significant number of patients are unwilling or unable to tolerate chemotherapy, the primary objective of therapy for pancreatic cancer in advanced stages is to optimize the quality of life and enhance overall survival (OS) (7).

Several minimally invasive local treatments have been used to reduce pain and improve survival rate in patients diagnosed with unresectable pancreatic cancer. High-intensity focused ultrasound (HIFU) is a non-invasive, repeatable thermal ablation technique (8). HIFU aims to deliver the energy required to raise and maintain the focal region above 60˚C, in order to cause coagulative necrosis and immediate cell death without affecting surrounding organs through heat effect, cavitation or potential immunological effects (9-11). In addition to achieving local tumor control and alleviating tumor-associated pain, repeated HIFU has the potential to positively influence both progression-free survival and OS in patients (7,12,13). Radioactive iodine-125 (^{125}I) seed implantation is a commonly employed treatment option for malignant tumors due to its effectiveness, minimal invasiveness and low risk of complications (14,15). Compared with external radiotherapy, it has the advantages of a short treatment time; continuous radiotherapy, which can irradiate the tumor cells of different division cycles continuously, improving the radiosensitivity and producing a high radiobiological effect; and repeatability, as well as a low incidence of radiation-related adverse reactions (14). In a previous study where patients underwent systemic chemotherapy, thermal therapy, molecular target therapy, immune treatment, gene treatment, Chinese medicine treatment, radiation therapy including iodine-125 seed interstitial brachytherapy, nutrition support or symptomatic treatment, the clinical benefit rate of the seed implantation group was 92.3%, which was significantly greater than that of the control group (41.7%; P<0.01) in patients with unresectable pancreatic cancer. The clinical evaluation indicators included pain relief, consumption of analgesic drugs, physical condition [Karnofsky Performance Scale (KPS) score] (16) and body weight in this study (17).

Previous reports have confirmed the efficacy of HIFU combined with external radiotherapy in treating pancreatic cancer (18,19). A decrease in blood flow caused by HIFU ablation may impede heat dissipation, resulting in damage to tumor cells due to hypoxia and enhancing the efficacy of radiotherapy (19). Radiotherapy has been proven to be effective at targeting oxygen-rich cells, while hyperthermia has also been shown to be effective at treating hypoxic cells (20,21). Therefore, we hypothesized that the combination of repeated HIFU treatment and radioactive ^{125}I seed implantation may further improve the clinical outcome, as the curative effect of the existing treatments is generally poor for treating advanced pancreatic cancer. A retrospective case series analysis was conducted to assess the safety and feasibility of the combination of these two minimally invasive treatments for treating patients with advanced pancreatic cancer.

Patients and methods

Research type. This research was conducted as a single-center, non-controlled and non-blinded retrospective study.

Patients. A total of 52 patients diagnosed with advanced pancreatic cancer between March 31, 2015, and March 31, 2021, were included in the present study. The date of last follow-up was August 31, 2021. Patients were enrolled according to the following inclusion criteria: i) An age of ≥18 years; ii) histologically or cytologically diagnosed pancreatic carcinoma [Union for International Cancer Control (UICC stages III and IV] (22); iii) KPS score ≥50, and an expected survival time of >3 months; iv) sufficiently visible tumor on ultrasound (diameter ≥2 and ≤8 cm); v) platelet count ≥75x10^9/l (normal reference range, 125-350x10^9/l) and prothrombin time (PT) that is normal or prolonged by <3 seconds (normal reference range, 9.4-12.5 sec) (23) vi) ineligible for or refused to undergo surgery and unwilling or unable to tolerate chemotherapy; and vii) receipt of more than one HIFU treatment combined with radioactive ^{125}I seed implantation in the pancreatic lesions. The exclusion criteria were as follows: i) Underwent surgery, chemotherapy or external radiation; ii) there was no suitable path for percutaneous pancreatic puncture; iii) serious cardiac and cerebrovascular events; iv) unable to cooperate with efficacy evaluation and treatment; and v) there were severe safety problems, obvious effects or lack of effects that required termination of treatment. Study approval was obtained from The Ethics Committee of Huadong Hospital Affiliated to Fudan University (approval no. 2021K040; Shanghai, China), and oral consent for the publication of clinical data was obtained from all patients.

HIFU instrument and therapy. HIFU was conducted using a HIFUNIT-9000 system (Shanghai A&S Science Technology Development Co., Ltd.). This system is an ultrasound-guided device equipped with an overhead treatment probe (24). No anesthesia was required for HIFU treatment. The main parameters of the HIFU equipment used were as follows: Sound intensity, 5-10 kW/cm^2; power, 60-100%; therapy depth, 2-15 cm; and focal spot, 3x3x8 mm. The number of transducers was 3 to 6, which is consistent with number of acoustic irradiations of a single focal spot (8-16 times). The ratio of the unit launch time to the intermission time was 1:2. The position of the pancreatic lesions was initially determined using ultrasound, computed tomography (CT), magnetic resonance imaging and/or positron emission tomography/CT. Real-time ultrasound was utilized to precisely identify and target the pancreatic tumors via the use of an integrated probe. The focus of the ablation energy was carefully controlled to move sequentially along the X, Y and Z axes until the target lesion was fully encompassed from point to surface and ultimately throughout the entire body. Each session lasted for 40-50 min and occurred once per day for a total of five sessions in a course. If a tumor with a larger volume could not be completely scanned within the initial five sessions, additional treatment

were administered until the predetermined target area was fully covered. Patients were instructed to avoid milk or other aerogenic food and to fast for 6-8 h before HIFU therapy. The interval between the two treatment courses was at least 4 weeks.

Ultrasound-guided seed implantation. CT scans were obtained 1-2 weeks prior to seed implantation to assess the exact location and volume of the tumors. The dose distribution was subsequently calculated via tumor brachytherapy via the Seeds Implanted & 3D Planning System (TPS; Beijing Feitian Zhaoye Technology Co., Ltd.). The ^{125}I seeds, manufactured by Shanghai Xinke Pharmaceutical Co., Ltd., were made from silver rods that absorbed ^{125}I. These seeds were then enclosed in a titanium capsule, which was welded using laser technology. Each seed had a diameter of 0.8 mm and a length of 4.5 mm. The wall of the titanium capsule had a thickness of 0.05 mm. The ^{125}I seeds produce γ rays with two energy levels: 5% at 35 keV and 95% at 28 keV. These materials have a half-life of 59.6 days, a half-value thickness of 0.025 mm of lead, a penetration depth of 17 mm, an incipient rate of 7 cGy/h and activities ranging from 0.4 to 0.8 mCi. The procedure was performed percutaneously under the guidance of ultrasound and local infiltration anesthesia. Under real-time ultrasound guidance, 18-gauge needles were inserted into the tumor mass at intervals of 1.0 cm in a parallel array. The needles extended at least 0.5-1.0 cm beyond the margins of the pancreatic lesions. Using a specialized applicator (Syncor Pharmaceutical, Ltd.), ^{125}I seeds were carefully implanted after needle insertion, with a spacing of 1 cm between seeds within the same needle (25). Given the impact of fibrosis resulting from hyperthermia on radiation effects, HIFU should be performed either after or concurrently with radiotherapy (26). However, patients who suffer from pain often prioritize treatments involving less trauma in the real world. Therefore, HIFU treatment preceded seed implantation therapy in the patients in the present study. Patients were instructed to avoid milk or other aerogenic food, and to fast for 6-8 h. Oral laxatives were additionally taken for bowel preparation before radioactive particle implantation. The interval between HIFU treatment and ^{125}I seed implantation was 1-4 weeks.

Patient follow-up and evaluation. OS was defined as the period spanning from the date of the pathologically confirmed diagnosis until either the date of the last follow-up or the date of death. Survival was selected as the primary endpoint, and physical status and pain as the secondary endpoints. Patient follow-up occurred at 1 and 2 months after ^{125}I seed implantation, and then follow-up was subsequently conducted every 3 months to obtain survival and related adverse reaction data. Censoring took place if patients were still alive at the last follow-up or if they died due to other causes. The patients' medical history, physical examinations, laboratory examinations, pain responses, performance status scores and tumor imaging prior to treatment were collected, as well as the results at the 1- and 2-month intervals after ^{125}I seed implantation. KPS scores ranging from 0 to 100 were utilized. The pain response was assessed using a numeric rating scale (NRS) (27) ranging from 0 to 10, where 0 represented no pain and 10 represented unbearable pain, with scores of 1-3 indicating mild pain, scores of 4-6 indicating moderate pain and scores of 7-10 indicating severe pain. The laboratory tests included a complete urinalysis, blood analysis, amylase and CA19-9 levels, serum chemistry, electrocardiogram and chest X-ray. Tumor imaging involved the use of B-mode ultrasound and CT.

Safety assessment. Adverse events commonly associated with HIFU and ^{125}I seed implantation were recorded, and the severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events, version 4 (28). The occurrence of adverse events associated with HIFU, such as burns, fever, pancreatitis, abdominal pain, hemorrhage, jaundice, intestinal necrosis and gastrointestinal perforation, as documented in previous studies (12,18), was monitored throughout the entire follow-up period. Additionally, after the implantation of ^{125}I seeds, the occurrence of fever, upper gastrointestinal bleeding or perforation, pancreatitis, pancreatic fistula, radiation enteritis and cholangiolitis was monitored.

Statistical analysis. All the statistical analyses were conducted using SPSS (version 24; IBM Corp.). The median, mean, range, standard deviation (SD) and exact 95% confidence intervals (CIs) were calculated. Non-normally distributed data are expressed as medians (ranges). Normally distributed data are presented as the mean ± standard deviation. Categorical variables were compared using χ^2 analysis or Fisher's exact test, and exact 95% CIs were computed. A variance test confirmed that the overall variance of KPS and NRS scores at the three time points was homogeneous, with P-values of 0.578 and 0.637, respectively. ANOVA and Dunnett's test were used to make a multiple comparisons of KPS and NRS scores before and after HIFU combined with ^{125}I seed implantation therapy. Survival time was evaluated using the Kaplan-Meier method. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A retrospective evaluation was conducted on 52 patients, for whom the median age was 66 years. The tumors were mainly located in the head of the pancreas (44.2%). Among the 52 patients, the mean diameter was 4.3±1.0 cm. The pathological type was confirmed in all patients via percutaneous pancreatic puncture or endoscopic ultrasonography-guided fine-needle aspiration. Clinical stage IV pancreatic cancer accounted for 65.4% of the cases according to the UICC. The number of HIFU treatment courses patients received ranged from 2-6 times with a median course number of 3.2 times. All patients successfully underwent ^{125}I seed implantation. The detailed characteristics of the patients are outlined in Table I.

Clinical response evaluation. ANOVA test results of KPS and NRS scores both revealed significant differences among the three time points (Tables II and III). The mean KPS score of the patients was 62.7±6.3 (95% CI, 61.3-70.6) at baseline, 73.7±7.9 (95% CI, 68.8-80.2; $P<0.001$) at 1 month and 68.8±6.5 (95% CI, 64.7-72.5; $P<0.001$) at 2 months after combined treatment. KPS score significantly increased following combined therapy ($P<0.001$), as evidenced by improvements in sleep

Table I. Patient characteristics.

Characteristic	Value
Sex, n (%)	
Male	34 (65.4)
Female	18 (34.6)
Mean age (range), years	66.0±10.1 (46-87)
Tumor location, n (%)	
Head	23 (44.2)
Neck	4 (7.7)
Body	5 (9.6)
Body-tail	16 (30.8)
Tail	4 (7.7)
UICC stage, n (%)	
III	18 (34.6)
IV	34 (65.4)
Mean tumor size (range)	
Diameter, cm	4.3±1.0 (2.1-7.1)
Volume, cm^3	51.2±43.8 (6.8-266)
Pathological type, n (%)	
Ductal adenocarcinoma	38 (73.1)
Adenocarcinoma	10 (19.2)
Adenosquamous carcinoma	4 (7.7)
Mean no. of HIFU courses (range)	3.2±1.6 (2-6)
Iodine-125 seeds	
Intensity (range), mCi	0.55±0.06 (0.4-0.7)
Mean number (range)	36.2±11.1 (13-70)
Mean dose (range), mCi	21.1±7.6 (4.8-42)

HIFU, high-intensity focused ultrasound; UICC, Union for International Cancer Control.

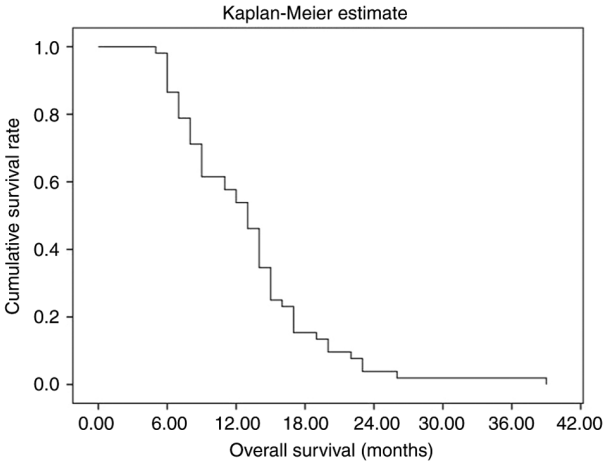

Figure 1. Actuarial survival curve for 52 patients.

time, nutritional status and functional level. Thus, the overall quality of life improved. A total of 3 patients had a KPS score of 90 at 1 month after combined therapy.

The mean NRS pain assessment score was 6.7±1.6 (95% CI, 5.2-6.8) at baseline, and 4.7±1.7 (95% CI, 3.4-5.5; P<0.001) and 5.4±1.5 (95% CI, 4.1-5.9; P<0.001) at 1 and 2 months after combined treatment, respectively. The number of patients with severe pain and the recorded NRS score were both significantly lower at 1 and 2 months after ^{125}I seed implantation than at baseline (P<0.001). The KPS and NRS scores are shown in Tables II and III.

Survival. The median OS (mOS) time of patients in the present study was estimated to be 13.1 months (95% CI, 11.3-14.8). The longest survival time was 39 months. The 3-, 6-, 9- and 12 month survival rates were 100.0, 86.5, 61.5 and 53.8%, respectively. In addition, the 2-year survival rate was 3.8% (Fig. 1).

Adverse events. Mild fever occurred in 2 (3.8%) cases and 1 (1.9%) case after HIFU treatment and ^{125}I seed implantation, respectively. The patients were subjected to physical cooling and recovered 1-25 days later. After HIFU treatment and ^{125}I seed implantation, mild symptoms of gastrointestinal dysfunction, such as abdominal distension and loss of appetite, were observed in 1 (1.9%) and 2 (3.8%) patients, respectively, and normality was reached in ~1 week. Abdomen and waist pain occurred in 3 (5.8%) patients after ^{125}I seed implantation, of which 2 cases were mild and 1 was moderate, and gradually subsided within 1 week when they received non-steroidal pain killers. The serum amylase level increased mildly in 2 (3.8%) patients 1 day after ^{125}I seed implantation, and these patients recovered within 1 week. No serious complications, such as superficial skin or subcutaneous tissue injury, upper gastrointestinal tract bleeding, infection, severe pancreatitis, radiation enteritis, pancreatic fistula or gastrointestinal tract perforation, were detected during the follow-up period.

Discussion

Patients with pancreatic cancer are mostly diagnosed with advanced or unresectable disease, and existing chemotherapy, radiation therapy, targeted therapy or even immunotherapy are unsatisfactory and do not significantly improve their quality of life (1,4). Treatment for patients with advanced pancreatic cancer should aim to improve quality of life, prolong survival, avoid toxic or traumatic treatment, and achieve the goal of tumor control as much as possible (29,30). HIFU and ^{125}I seed implantation are typical examples of these methods. The mOS time of patients in the present study was estimated to be 13.1 months. The 3-, 6-, 9- and 12-month survival rates were 100.0, 86.5, 61.5 and 53.8%, respectively. These findings are encouraging, as they demonstrate improved survival compared with findings of previous studies (31-38) on HIFU treatment and iodine-125 seed interstitial brachytherapy. In addition to achieving local tumor control and alleviating tumor-associated pain, HIFU can significantly impact both progression-free survival and OS in patients (31). Studies conducted in Asia have reported a mOS time ranging from 6 to 11 months and a median progression-free period lasting 5 to 8.4 months in patients with pancreatic cancer receiving HIFU treatment (32-34). ^{125}I seed implantation has garnered significant attention due to its potential to increase the radiation dosage applied to pancreatic tumors while minimizing harm to adjacent

Table II. Comparison of KPS score before and after HIFU combined with ^{125}I seed implantation therapy.

Groups	KPS score						95% CI	P-value (ANOVA)[a]	P-value (Dunnett's)
	90, n (%)	80, n (%)	70, n (%)	60, n (%)	50, n (%)	Mean ± SD			
Pre-therapy	0 (0.0)	2 (3.8)	13 (25.0)	34 (65.4)	3 (5.8)	62.7±6.3	61.3-70.6	P<0.001	-
1-month post-therapy	3 (5.8)	20 (38.5)	22 (42.3)	7 (13.5)	0 (0.0)	73.7±7.9	68.8-80.2	-	P<0.001[b]
2-months post-therapy	0 (0.0)	8 (15.4)	30 (57.7)	14 (26.9)	0 (0.0)	68.8±6.5	64.7-72.5	-	P<0.001[c]

[a]ANOVA test results of KPS data at three time points. [b]1-month post-therapy vs. pre-therapy; [c]2-months post-therapy vs. pre-therapy. KPS, Karnofsky performance scale; CI, confidence interval.

Table III. Comparison of NRS score before and after HIFU combined with ^{125}I seed implantation therapy.

Groups	NRS score					95% CI	P-value (ANOVA)[a]	P-value (Dunnett's)
	No pain scoring 0, n (%)	Mild pain scoring 1-3, n (%)	Moderate pain scoring 4-6, n (%)	Severe pain scoring 7-10, n (%)	Mean ± SD			
Pre-therapy	0	2 (3.8)	16 (30.8)	34 (65.4)	6.7±1.6	5.2-6.8	P<0.001	-
1-month post-therapy	0	12 (23.1)	30 (57.7)	10 (19.2)	4.7±1.7	3.4-5.5	-	P<0.001[b]
2-months post-therapy	0	6 (11.5)	30 (57.7)	16 (30.8)	5.4±1.5	4.1-5.9	-	P<0.001[c]

[a]ANOVA test results of KPS data at three time points. [b]1-month post-therapy vs. pre-therapy; 2-months post-therapy vs. pretherapy. NRS, numerical rating score; CI, confidence interval.

organs (35). For patients with pancreatic cancer at more than stage III undergoing ^{125}I seed implantation, the mOS time was 12.8 months, for a total effective rate of 91%, both of which are superior to traditional therapy (36). The patients in the present cohort were mostly diagnosed with stage IV disease, with an mOS of 13.1 months. A retrospective study indicated that patients who received a combination of HIFU and gemcitabine experienced the greatest improvement in survival, with an mOS time of 7.4 months (37). Li *et al* (38) conducted a study that demonstrated a significant increase in the 1-year survival rate for patients who underwent chemotherapy in combination with ^{125}I seed implantation than in those who did not undergo chemotherapy (60.7% vs. 35.9%; P=0.034). The present study observed that the 1-year survival rate was 53.8% after repeated HIFU treatment combined with ^{125}I seed implantation, which is similar to or even better than the previously reported data. The improvement in the survival rate may be related to the thermal effect of HIFU (18). Radiotherapy has been proven to be effective at targeting oxygen-rich cells, while hyperthermia has also been shown to be effective at treating hypoxic cells (20,21).

Tumor-related pain is a highly prevalent symptom in patients diagnosed with pancreatic cancer and occurs in >80% of cases (6). HIFU and ^{125}I seed implantation can significantly reduce cancer-related pain, and they may serve as complementary or even alternative approaches to opioid and plexus neurolysis (39-41). In one study, the NRS scores of 37 patients diagnosed with pancreatic cancer who successfully underwent ^{125}I seed implantation were significantly lower than the preoperative scores after 1 week, 1 month and 2 months of implantation (P<0.05) (15). In the present patient cohort, the number of patients with severe pain and the NRS score were both significantly lower at 1 and 2 months after ^{125}I seed implantation than at baseline (P<0.001). The mechanical effect of HIFU appears to induce neuromodulation and alleviate pain by temporarily blocking nerve activity (42). Tumor cavitation leads to coagulation necrosis, causing damage or apoptosis of pain fibers innervating the tumor (43,44). KPS scores improved significantly after combined therapy, as evidenced by fewer complications and improvements in nutritional status, sleep duration and functional level, leading to an overall enhancement in quality of life (45). The score mainly benefits from good pain control and tumor-growth control.

According to the aim of the study, the score of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 scale (EORTC QLQ-C30) may be better than the KPS score for evaluating the quality of life, which was one of the limitations of the present study. This is because the EORTC QLQ-C30 scale has higher reliability that assesses 30 factors including physical function, pain, fatigue, appetite and sleep disorders.

As HIFU treatment is non-invasive, has few adverse reactions and is well tolerated by patients, it can be repeated (8). When the therapeutic effect is stable disease or progressive disease, the interval between repeated HIFU treatments for the same site should be >4 weeks, and repeated HIFU treatment is performed every 1-3 months in general (13). There is no uniform standard for the specific time interval. Each patient in the present cohort

was treated with repeated HIFU treatment. The HIFU treatment was administered to patients 2-6 times for pancreatic lesions, for a median duration of 3.2 cycles. Ning *et al* (46) demonstrated the benefit to survival time of repeated HIFU operations without a significant increase in the incidence of side effects. In the study, incomplete HIFU ablation was common in most patients, and repeated HIFU operations were conducted for the patients who were able to pass through HIFU well and were in good economic condition. A recent study (47) indicated that each patient underwent a minimum of two cycles of HIFU ablation, with a 1-month interval between each treatment. The response rate to HIFU ablation was 79.4%. Prolonged survival was associated with an Eastern Cooperative Oncology Group performance status (48) and subsequent HIFU ablation. No studies have reported the limitations of the number of HIFU courses. The current study presented the experience of one center, but the specific treatment intervals and treatment courses need to be explored in future large sample and multicenter prospective studies. As particle implantation therapy is invasive, the damage from puncture requires time to heal (generally ~1 week), and there is an interval between the puncture and observation of the combined therapy; thus, the interval between HIFU and particle implantation therapy is generally 1-4 weeks. Since combination therapy comprising repeated HIFU and ^{125}I particle implantation has rarely been reported, this is only the clinical experience of the High-Intensity Focused Ultrasound Center of Oncology Department, Huadong Hospital Affiliated to Fudan University and it may need to be verified by further studies in the future.

In conclusion, repeated HIFU treatment combined with ^{125}I seed interstitial brachytherapy is effective and safe. Compared with existing treatment strategies, the benefits for patients are similar or even better. However, few similar studies have reported on this combination treatment. The outcomes of this study are highly encouraging for patients who are unwilling or unable to tolerate surgery or chemotherapy, despite the small sample size, lack of controls and potential statistical bias. The limitations of this study also include the absence of stratified analysis and prognostic factor analysis. Large, prospective and multicenter randomized clinical trials are needed to assess the long-term efficacy of these treatments and determine the appropriate treatment intervals.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YL proposed the study concept, designed the study, participated in the data collection, interpreted the data and drafted the manuscript. YZ participated in the data collection. YJ participated in the data analysis and interpreted the data. JZ participated in the data analysis. LZ revised the grammatical problems in the draft, refined the study concept and analyzed imaging data. ZB was involved in analyzing and interpreting the data and also revised the manuscript critically for important intellectual content. HZ refined the study concept and designed the study, and revised the manuscript critically for important intellectual content. YL and HZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of Huadong Hospital Affiliated to Fudan University (Shanghai, China) approved the present study (approval no. 2021K040).

Patient consent for publication

Oral consent for publication of clinical data was obtained from all patients.

Competing interests

The authors declare that they have no competing interests.

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