

Effects of high-intensity focused ultrasound treatment on peripancreatic arterial and venous blood vessels in pancreatic cancer

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Abstract. The present study aimed to evaluate the safety of high-intensity focused ultrasound (HIFU) treatment on peripancreatic arterial and venous blood vessels in patients with pancreatic cancer. This trial included 15 patients with pancreatic cancer (9 females and 6 males; age, 39-81 years; median age, 62 years). All patients underwent preoperative computed tomography (CT) or magnetic resonance imaging (MRI) and color Doppler flow imaging (CDFI) to assess the vascular hemodynamics of peripancreatic arterial and venous blood vessels pre-treatment. These patients were re-examined within 1 week post-HIFU treatment. Then, vascular adverse events were observed and followed up clinically. Prior to HIFU treatment, vessel involvement was recorded in 13 patients, including tumor lesions invading 19 veins and 14 arteries, which refers to the growth of pancreatic tumor lesions surrounding blood vessels, or tumor growth into blood vessels. In addition, 9 veins and 13 arteries were <1 cm from the lesions. The hemodynamic parameters of peripancreatic vessels were measured using CDFI, including mean blood flow velocity, peak systolic blood flow velocity, vascular resistance index, vascular pulsatility index, vascular diameter, vascular blood flow and other indicators, to assess vascular perfusion in CT/MRI. There were no significant differences in preoperative and postoperative hemodynamic data ($P>0.05$). Overall, HIFU demonstrated no negative effects on peripancreatic arterial and venous blood vessels

in patients with pancreatic cancer, even with tumor lesions wrapped in blood vessels. In addition, no complications of vascular stenosis and vascular adverse events were observed in the present study.

Introduction

Pancreatic carcinoma is a highly malignant gastrointestinal cancer with a poor prognosis and a low 5-year survival rate (1). Recently, the incidence and mortality rates of pancreatic cancer have steadily increased in the United States, within Europe and in China (1-4). According to the American Cancer Society, there were ~55,440 novel pancreatic cancer diagnoses and ~44,330 pancreatic cancer-associated mortalities in 2018 in the USA (4,5). By 2030, pancreatic cancer is expected to become the second leading cause of cancer-associated mortality in the USA (1). Meanwhile, in 2015, the China Cancer Center demonstrated that pancreatic cancer ranks 8th in terms of incidence among male patients with a malignancy (2). The mortality rate of all types of cancer in Beijing and Shanghai ranks fifth (2,3). Pancreatic cancer often presents with lesions that invade adjacent blood vessels, such as mesenteric and splenic vessels, with the patient losing the opportunity of surgical resection (6). Therefore, patients with pancreatic cancer have limited treatment options and a poor quality of life. To improve the quality of life and prolong survival in such patients, local ablative procedures are used to treat pancreatic carcinoma (7). These treatments include irreversible electroporation (IRE) (8), radiofrequency ablation (RFA) (9) and high-intensity focused ultrasound (HIFU) (10), which have been widely used in the past few years, achieving good therapeutic effects in pancreatic carcinoma.

HIFU is a non-invasive procedure for the ablative treatment of localized tumors. The basic principle is that ultrasound is focused at the focal region and produces biological effects, including thermal, cavitation and mechanical effects, to achieve thermal ablation of the target tissue, with pathological changes, including coagulative necrosis (11). HIFU has been

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widely used in the treatment of uterine fibroids and hepatocellular carcinoma, with good therapeutic results (12). Previous studies have confirmed that HIFU therapy effectively alleviates cancer-associated abdominal pain, reduces tumor volume and may confer an additional survival benefit (11,13-23). However, vascular complications caused by this treatment have been reported, including secondary occlusion of the superior mesenteric artery (24) and portal vein thrombosis (25). The present study aimed to evaluate the safety of HIFU therapy by assessing blood vessel events in patients with pancreatic cancer.

Materials and methods

Patients and lesions. The present observational single-center study was approved by The Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (Chongqing, China; approval no. 12/2018). Every patient provided written informed consent before treatment initiation. Between April 2018 and April 2019, 15 patients with pancreatic carcinoma (Union for International Cancer Control (UICC) stage II-IV) (6) were enrolled, including 6 males and 9 females (mean age, 39-81 years; median age, 65±11 years). According to the TNM staging system (6), a total of two patients were diagnosed as stage II, six patients as stage III and seven patients were diagnosed as stage IV. Of the 15 patients, 7 had tumors of the pancreatic head and 8 had tumors in the body and/or tail of the pancreas. The inclusion criteria were: i) Confirmed diagnosis of pancreatic carcinoma (6); ii) tumor invading a blood vessel; and iii) distance between the pancreatic tumor and peripancreatic blood vessel <1 cm. The exclusion criteria were: i) Non-eligibility for general anesthesia; ii) calcification of blood vessels invaded by tumor lesions; iii) Child-Pugh class C (26); iv) hemorrhage and other severe diseases, such as severe heart failure, cerebrovascular disease and renal insufficiency and v) poorly managed diabetes.

All patients underwent CT or MRI and were assessed using color Doppler flow imaging (CDFI) to evaluate the vascular hemodynamic changes of peripancreatic arterial and venous vessels pre-treatment and at 1 week and 1-month post-HIFU treatment. The primary blood vessels around the pancreas included the splenic artery, splenic vein, superior mesenteric artery, superior mesenteric vein (SMV), hepatic artery, celiac artery and portal vein (PV). The hemodynamic parameters of each blood vessel were measured using CDFI, including mean blood flow velocity, peak systolic blood flow velocity (PSV), vascular resistance index (RI), vascular pulsatility index (PI), vascular diameter and vascular blood flow. Combined with pre- and post-HIFU treatment imaging modalities, such as MRI and CT, changes in blood vessel shape and inner diameter were assessed and vessel occlusion, thrombosis and hemorrhage were recorded.

Color Doppler ultrasound examination. An APLI0 500TUS-A500 color Doppler ultrasound system (TOSHIBA) was used with a wide-band convex array probe with a center frequency of 3.5 MHz and a mechanical index of 0.06-0.15.

Ultrasound examination was performed by an experienced sonographer. All patients with pancreatic cancer underwent ultrasound examination in the fasting state, using a 3.0-5.0 MHz

variable convex transducer. The operating steps were similar to the routine abdominal scan method (27), followed by abdominal parenchymal organs, the biliary system and retroperitoneal large blood vessels and their primary branches. There was final focus on the location, size, echo, boundary and blood flow of the lesion. Image quality was improved by excluded artifact interference, adopting an appropriate graded compression scan and focusing on observation and recording the relationship between pancreatic tumor lesions and blood vessels around the pancreas. The clearest slice was selected and the probe was fixed. The mean blood flow rate, systolic blood flow velocity peak, vascular resistance index, vascular pulsation index and vessel diameter at the closest point from the deep surface of the tumor lesion were measured.

HIFU therapy. HIFU was performed using a Model-JC Focused Ultrasound Tumor Therapeutic system (Chongqing Haifu Medical Technology Co., Ltd.) equipped with a diagnostic ultrasound probe (3.50-5.00 MHz) for real-time guidance and a therapeutic transducer (focal length, 10-25; diameter, 10-30 cm) operating at 0.5-2 MHz. The focal region was an ellipsoid with short and long axes of 3 and 8 mm, respectively.

Prior to HIFU treatment, all patients underwent colonic lavage with liquid food, laxatives and cleansing enema to protect the gastrointestinal tract in front of the target area. The gastric tube was then placed and gastric juice changes were observed with a vacuum suction device to prevent gastrointestinal damage and reduce the occurrence of postoperative pancreatitis, until 1-2 days after surgery. Skin preparation in the treated area was performed by degreasing with 75% ethanol and degassing with a vacuum aspirator to avoid skin burns. During HIFU treatment, the patient was placed in the prone position after general anesthesia. According to the proposed HIFU treatment plan, real-time ultrasound monitoring was used to determine tumor location and size, carefully identifying lesions invading blood vessels, as shown in Fig. 1.

The lesions were divided into slices 5-mm-thick and focus was placed on the deepest layer of a slice containing the maximum tumor area. A safety gap of ~15 mm was maintained in case the target area was close to important organs, including large blood vessels or the gastrointestinal tract and near the tumor edge. The target area of the tumor lesion was locally ablated from the deepest region to the surface and the treatment was repeated for each slice until the tumor was completely ablated. In the course of treatment, point scan was the main method at a power of 100-400 W. Notable signs of effective HIFU sonication included the presence of massive gray-scale changes (MGSCs) or an increase in gray-scale throughout the target area. Treatment was complete when the tumor volume was fully covered by MGSCs. The treatment parameters and patient characteristics are shown in Table I.

Data collection. A total of 15 patients with pancreatic cancer were treated with HIFU. According to the imaging manifestations of pancreatic cancer invading peripancreatic blood vessels, the relationship between blood vessels and the tumor were divided into two groups: i) Normal pancreatic tissue between the tumor and blood vessels, with the tumor <1 cm from major blood vessels; and ii) tumor adjacent to or

Table I. Baseline characteristics of patients with pancreatic cancer and who underwent high-intensity focused ultrasound treatment.

Characteristic	n
Total number of patients	15
Sex	
Male	6
Female	9
Age, years (median ± SD)	65±11
Site of pancreatic disease	
Head	7
Body or tail	8
CA19-9	
+	15
-	0
TNM stage	
II	2
III	6
IV	7
Intervention duration, min (mean ± SD)	81±37
Therapeutic sonication duration, sec (mean ± SD) duration (seconds)	725±370
Total energy, J (mean ± SD)	185,075±95,176
Average power, W (mean ± SD)	295±54
Lesion ablation rate, %	68.4%

CA19-9, carbohydrate antigen 19-9; SD, standard deviation; TNM, Tumor-Node-Metastasis.

surrounding the blood vessel. The association between tumor and blood vessel was recorded. All patients underwent CT or MRI and underwent abdominal blood vessel CDFI to analyze hemodynamic parameters. The follow-up period of the present study was between June 2018 and September 2019. Follow-up examinations included abdominal blood vessel CDFI, and CT or MRI every 1 or 2 months.

Evaluation of therapeutic efficacy and pain relief. The treatment efficacy was evaluated using contrast enhanced CT or MRI 1 week post-HIFU treatment and pain relief pre-treatment and at 1 week after treatment was assessed using the NRS pain score table (numerical rating scale of 0-10, with 0 indicating ‘no pain’ and 10 reflecting ‘maximum imaginable pain’) (7). Based on images obtained using contrast enhanced CT or MRI, no enhancement area was observed in the tumor lesion, which was considered to be completely ablated and necrotic. Blood vessel adverse events were defined as non-perfusion or partial perfusion. The rate of lesion ablation was calculated based on preoperative and postoperative contrast enhanced CT or MRI. 3D Image Processing software (version 1.0; Chongqing Haifu Medical Technology Co., Ltd.) was used to delineate the tumor and determine the tumor volume, non-perfused volume (NPV) and lesion ablation rate (%) as NPV/tumor volume x100.

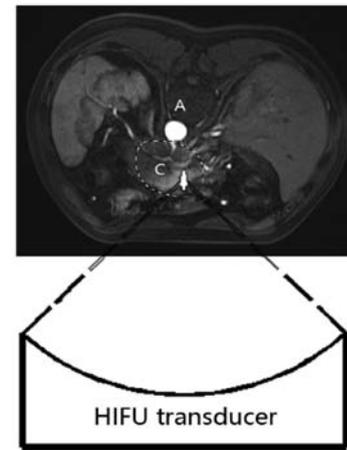


Figure 1. Schematic representation of patient positioning for high-intensity focused ultrasound ablation of pancreatic neoplasms. C, targeted pancreatic cancer; A, abdominal aorta; HIFU, high-intensity focused ultrasound.

Statistical analysis. Data were analyzed using SPSS version 22.0 software (IBM Corp.). Data are presented as the mean ± standard deviation. Preoperative and postoperative samples were compared using a paired t-test. P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics. All patients successfully completed the HIFU treatment procedure for pancreatic cancer and no clinical complications, such as persistent severe abdominal pain, gastrointestinal bleeding, obstructive jaundice and peritoneal irritation, were observed. The specific invaded and adjacent blood vessels are presented in Table II. A total of 33 blood vessels were invaded by tumor lesion and 22 were within 1 cm of the lesion, which were well identified using imaging. Compared with preoperative NRS pain score (4.0±2.0), postoperative NRS pain score (1.6±1.3) was significantly reduced (P<0.01), indicating pain relief after the operation. The lesion ablation rate was 68.4%, which was calculated using 3D image processing software, and the tumor marker CA19-9 was positive in all patients (Table I), which is useful for the diagnosis and treatment of the disease (6).

Hemodynamic data analysis. Specific arterial and venous hemodynamic parameters (PSV, MV, VF, PI, RI and VD) are presented in Tables III and IV. As presented in Table III, comparing the PI and RI of arterial vessels before and after HIFU treatment, there were no significant differences (P>0.05). Furthermore, there was no significant change in the PSV, MV, VF and VD of arterial blood vessels after HIFU compared with pre-treatment values (P>0.05). There was no significant change in the PSV, MV, VF and VD of venous blood vessels after HIFU compared with pre-treatment values (Table IV; P>0.05). These data indicated that the functions of these vessels had no obvious changes after HIFU treatment.

Adverse effects of HIFU treatment. The postoperative complications in patients included fever (n=1) and skin numbness in the treatment area (n=1). Both patients improved following

Table II. Information on the association between tumor lesions and blood vessels in patients with pancreatic cancer, treated with high-intensity focused ultrasound (n=15).

Blood vessel	Number of vessels invaded	Number of vessels within 1 cm
Splenic vein	9	1
Splenic artery	7	3
Superior mesenteric vein	6	4
Superior mesenteric artery	3	6
Portal vein	4	4
Celiac artery	2	2
Hepatic artery	2	2
Total	33	22

symptomatic treatment. No imaging changes of adjacent vessels, such as stenosis and occlusion, were observed in imaging data. No blood vessel adverse events were observed within 1 week after HIFU treatment and during follow-up. The results demonstrated that splenic vessels were the most frequently invaded blood vessels in pancreatic tumors (Table II). Following comparison of data from all patients, a 63-year-old female patient with pancreatic cancer, whose MRI showed that the tumor invaded the splenic vein and was adjacent to the splenic artery in the tail of the pancreas (Fig. 2Aa), which was similar to most pancreatic cancer patients in our study and had more representative data and had certain research value. Finally, the incidences of avascular adverse events and associated complications in pancreatic cancer treated with HIFU were lower compared with other local ablation methods, such as RFA and IRE (Table V).

Discussion

Pancreatic cancer is highly malignant and lacks a typical set of early stage symptoms. Most patients are diagnosed with advanced disease and are usually not eligible for surgical treatment due to tumor invasion of mesenteric roots and arterial vessels, or because of liver and peritoneal metastasis. As a result, the 5-year survival rate is very low and decreases year by year (6). As a non-invasive treatment modality, HIFU has achieved good therapeutic results in the treatment of various benign and malignant tumors. Asian and European patients benefit from survival and pancreatic cancer related pain relief after HIFU treatment (28). It was first reported in 2000 that HIFU successfully ablates and treats pancreatic cancer (29). Several studies have confirmed the safety and efficacy of HIFU in the treatment of pancreatic cancer (10,14-16,19-25,29-34). The most common complications observed following HIFU treatment of pancreatic cancer include skin burns (10,15,17,21-23,30-32), pancreatitis (10,18,23,31,32), duodenal fistula (23,31) and obstructive jaundice (19,34). Vascular adverse events occur infrequently, including vascular complications of secondary occlusion of superior mesenteric artery (24) and PV thromboses (25). To the

best of our knowledge, no cases of vessel rupture and bleeding have been described. Previous studies have shown that adjacent blood vessels are safe from HIFU ablation of the tumors near large hepatic and PVs in the liver (35,36). Zhang *et al* (35) reported that HIFU could safely and effectively ablate lesions close to large blood vessels without damage to such vessels, with no blood vessel adverse events observed. In addition, HIFU ablation of pancreatic cancer is safe for peripancreatic blood vessels. Strunk *et al* (16) reported that 94% of patients showed no patency change in associated vessels after HIFU treatment of locally pancreatic cancer with tumor invasion and encasement of blood vessels. Meanwhile, no vascular adverse events were recorded.

The aforementioned studies focused on the imaging changes of blood vessels assessed using CT/MRI and did not assess vascular function using hemodynamics analysis using CDFI. The purpose of the present study was to evaluate the effect of HIFU treatment on vascular function by measuring preoperative and postoperative hemodynamic parameters of peripheral blood vessels in pancreatic cancer cases using CDFI, observing the shape changes of blood vessels using imaging, to determine potential adverse events of adjacent blood vessels after HIFU treatment of pancreatic cancer.

In the present study, vascular shape assessment in all patients revealed that splenic vessels, superior mesenteric vessels and PVs were mainly involved. Based on images assessing potential filling defects in the analyzed blood vessels, occlusion or thrombosis was ruled out. The blood vessels associated with the tumors were observed and their inner diameters were measured. Finally, the imaging data obtained before and after HIFU treatment were compared. There were no shape changes of blood vessels, as well as no vascular adverse events, such as vascular occlusion, thrombosis and rupture of blood vessels. These results corroborated previous studies (16,35).

Based on the data obtained in the present study, hemodynamic parameters reflected the functions of peripancreatic blood vessels. Among hemodynamic indexes, PI and RI reflect the resistance of arterial vessels. Specifically, PI denotes blood vessel wall elasticity, while RI directly reflects resistance to blood flow (37). The elasticity of the associated vessels did not change significantly following HIFU treatment. PSV reflects the degree of vascular filling, indicating whether there is a change in blood supply to distal tissues and organs (38). In the present study, all patients received preoperative and postoperative CDFI examinations and the hemodynamic parameters of pancreatic tumor lesions and adjacent blood vessels were analyzed. In addition, a comparative analysis of venous and arterial blood vessels was performed. These data also indicated that HIFU treatment had no significant influence on the function of peripancreatic blood vessels and did not affect peripancreatic tissues or organs.

There were fewer complications and side effects after tumor lesion ablation in the present study compared with previous reports (14,28,33,34,39,40). Meanwhile, no notable clinical symptoms and manifestations of mesenteric vascular occlusion, such as persistent abdominal pain and peritoneal irritation, were observed. Pain was significantly reduced in most patients after HIFU treatment, but acute pain occurred immediately post-HIFU in one patient. It was observed that the transient stimulation reaction of HIFU ablation to the

Table III. Hemodynamics of tumor invasion or adjacent main arterial blood before and after HIFU treatment.

BV	n	PSV, cm/s			MV, m/s			VF, l/min			PI			RI			VD, cm		
		Before	After	P-value	Before	After	P-value	Before	After	P-value	Before	After	P-value	Before	After	P-value	Before	After	P-value
SPA	10	108±50	89±50	0.24	32±16	27±16	0.27	0.7±0.2	0.5±0.2	0.91	0.3±0.2	0.3±0.2	0.16	1.5±0.7	1.1±0.5	0.12	0.3±0.2	0.3±0.2	0.52
SMA	9	101±60	124±32	0.19	21±15	26±7	0.21	0.6±0.4	0.8±0.1	0.06	0.3±0.2	0.3±0.2	0.50	2.2±1.4	2.6±0.8	0.11	0.4±0.2	0.4±0.2	0.66
CA	4	128±27	118±38	0.24	32±5	34±11	0.56	0.9±0.3	0.7±0.5	0.80	0.5±0.2	0.5±0.2	0.88	1.4±0.6	1.4±0.6	0.29	0.5±0.1	0.5±0.1	0.85
HA	4	78±72	76±77	0.83	44±46	37±36	0.35	0.4±0.3	0.4±0.3	0.53	0.2±0.1	0.1±0.1	0.30	0.6±0.5	1.3±1.2	0.20	0.2±0.2	0.3±0.2	0.53

Data are presented as the mean ± standard deviation. BV; blood vessel; HIFU, high-intensity focused ultrasound; n, number of blood vessels; Before, 1 day before HIFU therapy; After, 1 week after HIFU therapy; SPA, splenic artery; SMA, superior mesenteric artery; CA, celiac artery; HA, hepatic artery; PSV, peak systolic blood flow velocity; MV, mean blood flow velocity; VF, vascular blood flow; PI, vascular pulsatility index; RI, vascular resistance index; VD, vascular diameter.

Table IV. Hemodynamics of tumor invasion or adjacent main venous blood before and after HIFU treatment.

BV	n	PSV, cm/s			MV, cm/s			VF, l/min			VD, cm		
		Before	After	P-value	Before	After	P-value	Before	After	P-value	Before	After	P-value
SPV	10	33±39	19±17	0.12	15±18	7±6	0.12	0.1±0.1	0.1±0.1	0.05 ^a	0.3±0.3	0.3±0.2	0.20
SMV	10	30±66	20±35	0.36	13±29	9±4	0.40	0.1±0.1	0.1±0.1	0.42	0.3±0.4	0.3±0.4	0.86
PV	10	17±10	19±15	0.63	6±4	6±5	0.80	0.3±0.2	0.3±0.3	0.60	0.9±0.4	0.7±0.4	0.12

Data are presented as the mean ± standard deviation. ^aP>0.05. BV; blood vessel; HIFU, high-intensity focused ultrasound; n, number of blood vessels; Before, 1 day before HIFU therapy; After, 1 week after HIFU therapy; SPV, splenic vein; SMV, superior mesenteric vein; PV, portal vein; PSV, peak systolic blood flow velocity; MV, mean blood flow velocity; VF, vascular blood flow; VD, vascular diameter.

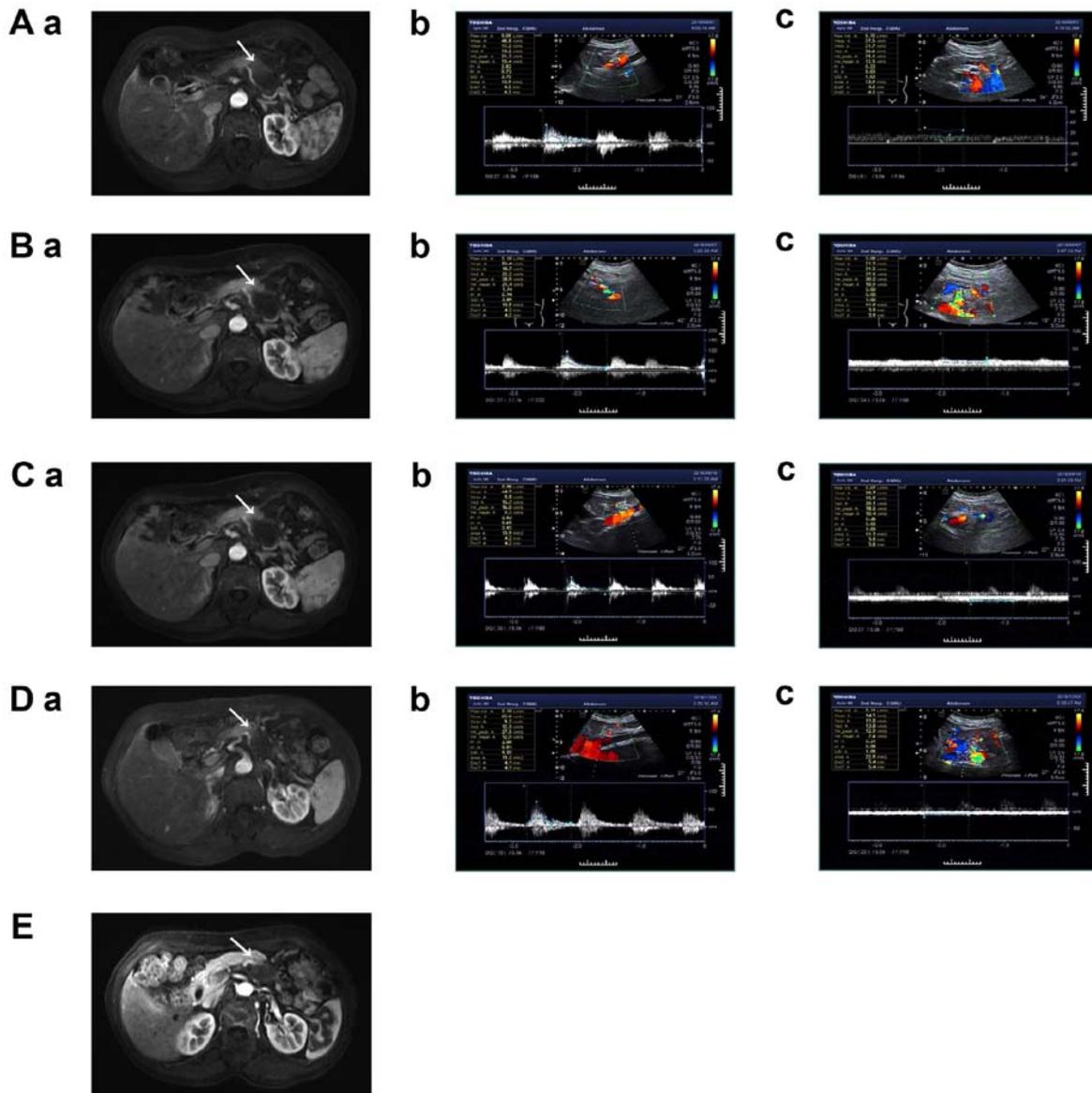


Figure 2. A 63-year-old female patient with pancreatic cancer in the tail of pancreas was evaluated radiologically (A) before HIFU, (B) at 1 week, (C) at 1 month, (D) at 4 months and (E) 10 months after HIFU, respectively. Arrows indicate a tumor lesion in the tail of the pancreas. Before HIFU, (Aa) enhanced MRI showed that the tumor invaded the splenic vein and was adjacent to the splenic artery. CDFI images showed normal blood flow in (Ab) splenic artery and (Ac) splenic vein. At 1 week after HIFU, (Ba) enhanced MRI showed no significant change in the morphology of splenic blood vessels, and no overt abnormal changes of hemodynamics of the (Bb) splenic artery and (Bc) vein in CDFI images. Follow-up 1 month after HIFU, (Ca) enhanced MRI showed that splenic vessel filling was normal in the enhancement phase, with no vascular stenosis or occlusion. There was no significant change in hemodynamics of the (Cb) splenic artery and (Cc) vein. At 4 months after HIFU, (Da) the vascular morphology of the splenic vein and the splenic artery were normal, and the hemodynamics of the (Db) splenic artery and (Dc) vein vessels were similar to those of the previous follow-up. At 10 months after HIFU, (E) enhanced MRI showed smaller lesion volumes compared with preoperative values, with no vascular stenosis or occlusion. There were no CDFI images due to insufficient intestinal preparation and intestinal gas interference. MRI, magnetic resonance imaging; HIFU, high-intensity focused ultrasound; CDFI, color doppler flow imaging.

pancreas improves after symptomatic analgesia and significantly reduced pain on postoperative day 2. The NRS pain score was significantly reduced compared with the preoperative results. The present study hypothesized that HIFU ablation of pancreatic tumor lesions could control tumor growth and reduce tumor compression to relieve pain, whereas HIFU thermal ablation has been reported to cause damage to peripheral nerves of the pancreas, thereby blocking pain nerve impulses (22,25,28).

In previous studies, it was observed that HIFU ablation of malignant tumors has some effects on adjacent tissues. In a study of preoperative HIFU ablation for borderline resectable

pancreatic cancer, the patient underwent surgical resection 1 week after HIFU treatment (41). Wang *et al* (41) observed faintly yellow burn marks on the vessel wall adjacent to the tumor lesion (the anterior-lateral part of the junction of the portal vein and the SMV) and normal vasoactive activity. These results are similar to those previous experiments reporting that HIFU effectively causes coagulative necrosis of the tissue near large blood vessels and that ablation at 0-5 mm close to the blood vessel may cause damage to the vessel wall, but such damage is reversible and could self-resolve within about 1 week (36). The present study separately evaluated the hemodynamic parameters of adjacent arterial and venous blood vessels, as well as vascular function.

Table V. Selected studies assessing high-intensity focused ultrasound, radiofrequency ablation and irreversible electroporation in pancreatic cancer.

Author, year	Patients, n	Access	Median survival	Pain reduction, %	Complication rate	Vascular complications	Other complications	(Refs.)
Zhou <i>et al</i> , 2014	3,022 (996 stage III/962 stage IV)	MR/US guidance	10.0 months	71.3	9.7	Portal vein Thrombosis (n=1); GI bleeding (n=1);	Skin burn (n=62) Fever (n=27) Acute pancreatitis (n=15) Pancreatic pseudocyst (n=1) Acute amylose (n=48) Jaundice (n=6) GI dysfunction (n=36) Other	(10)
Marinova <i>et al</i> , 2016	20	US guidance	No record	75	No record	No record	Transient subcutaneous edema (n=1), minor skin burns (n=1)	(13)
Marinova <i>et al</i> , 2018	50 (19 stage III)	US guidance	8.3 months after HIFU	80	26	No record	Pancreatic lipase increase (n=4), Induration of subcutaneous fat tissue (≤ 2 cm) (n=9)	(14)
Wang <i>et al</i> , 2013	224 (86 stage III)	US guidance	No record	No record	5.4	No record	Superficial second-degree skin burns (n=2), deep second to third degree skin burns (n=1), minor skin burns (n=9)	(15)
Strunk <i>et al</i> , 2018	50	US guidance	16.2 months	No record	6	Tumor-associated vascular (superior mesenteric vein, portal vein, or splenic vein) occlusion (n=3)	No record	(16)
Xiong <i>et al</i> , 2009	89 (39 stage III)	US guidance	11.2 months	78.6	11.2	No record	Superficial second degree skin burns (n=3); Subcutaneous sclerosis (n=6); Pancreatic pseudocyst (n=1)	(17)
Sofuni <i>et al</i> , 2014	30 (16 stage III)	US guidance	No record	66.7	10	No record	Pancreatic pseudocyst (n=2); Mild pancreatitis (n=1)	(18)
Anzidei <i>et al</i> , 2014	6	MR guidance	No record	100	No record	No record	No record	(19)
Strunk <i>et al</i> , 2016	15 (6 stage III/9 stage IV)	US guidance	6 months after HIFU	40	No record	No record	Skin burns (n=1) Subcutaneous sclerosis	(21)
Shi <i>et al</i> , 2017	71 (stage III)	US guidance	No record	92.9	No record	No record	Skin burning pain; Rib pain; Visceral pain	(22)

Table V. Continued.

Author, year	Patients, n	Access	Median survival	Pain reduction, %	Complication rate	Vascular complications	Other complications	(Refs.)
Dababou <i>et al</i> , 2017	729	MR/US guidance	No record	81	No record	Portal vein thrombosis	Skin burn; mild pancreatitis; pancreaticoduodenal fistula.	(23)
Vidaljove <i>et al</i> , 2015	43	US guidance	12.5 months	No record	11.3	No record	Minor skin burns (n=12); grade III skin burns (n=2) pancreatitis with gastro-intestinal bleeding (n=1)	(32)
Zhao <i>et al</i> , 2017	38 (stage III)	US guidance	10.3 months	No record	25	No record	Abdominal pain (n=12); Fever (n=9); Elevated CRP (n=8); Leucopenia (n=4); Elevated amylase (n=1); Other (n=4);	(33)
Ji <i>et al</i> , 2018	87	US guidance	No record	No record	28	No record	Fatigue (n=14); Abdominal pain (n=7); Fever (n=7); Nausea (n=5); Rash (n=4)	(34)
B, RFA								
Author, year	Patients, n	Access	Median survival	Pain reduction, %	Complication rate	Vascular complications	Other complications	(Refs.)
Cantore <i>et al</i> , 2012	107	Surgical (via laparotomy)	25.6 months	No record	17.8	Portal vein thrombosis (n=5)	Pancreatic fistulas (n=6), acute pancreatitis (n=3), duodenal injury (n=3), other	(9)
Girelli <i>et al</i> , 2010	50	Surgical (via laparotomy) with US guidance	No record	69	18	Portal vein thrombosis (n=4)	Pancreatic fistulas (n=2), duodenal bleeding (n=2), severe pancreatitis (n=1)	(42)
Girelli <i>et al</i> , 2013	100	Surgical (via laparotomy) with US guidance	20 months	100	15	Portal vein thrombosis (n=4)	Acute pancreatitis (n=3), pancreatic fistulas (n=3), duodenal ulcer (n=2), lymphatic fistula (n=1), n abdominal fluid (n=2)	(43)

Table V. Continued.

Author, year	Patients, n	Access	Median survival months	Pain reduction, %	Complication rate	Vascular complications	Other complications	(Refs.)
Frigerio <i>et al</i> , 2013	57	US guidance	19 months	No record	14	No record	Pancreatic fistulas, duodenal injury, gastric ulcer, jaundice, other	(49)
D'Onofrio <i>et al</i> , 2017	18	Percutaneous with US guidance	No record	No record	No record	No record	No record	(50)
C, IRE								
Author, year	Patients, n	Access	Median survival months	Pain reduction, %	Complication rate	Vascular complications	Other complications	(Refs.)
Martin <i>et al</i> , 2015	200	Urgical With intraoperative US Guidance	24.9 months	No record	37	Hepatic arterial thrombosis and nonocclusive superior mesenteric vein/portal vein thrombosis	Infection, pancreatitis, pancreatic fistulas, other	(8)
Mansson <i>et al</i> , 2016	24	Percutaneous With US guidance	7 months after IRE	No record	64	Portal vein thrombosis (n=2); Superior mesenteric vein thrombosis (n=1).	Infection (n=5), pancreatitis (n=2), duodenum ulcer bleeding (n=1), gastric retention (n=1); small bleeding (n=1); Upper gastrointestinal hemorrhage (n=1), pancreatic fistula (n=3), acute pancreatitis (n=1), delayed gastric emptying (n=1), gastrointestinal obstructions (n=2)	(44)
Yan <i>et al</i> , 2016	25	Surgical With intraoperative US Guidance	No record	No record	36	Portal vein thrombosis (n=1);	pancreatic fistula (n=3), acute pancreatitis (n=1), delayed gastric emptying (n=1), gastrointestinal obstructions (n=2)	(45)
Scheffer <i>et al</i> , 2017	25	Percutaneous With US guidance	11 months after IRE	No increase	40	High-grade superior mesenteric artery stenosis (n=1);	Pancreatitis (n=1), bleeding from duodenal ulcer (n=1), abscess (n=1), biliary obstruction and fistula (n=2), nausea, vomiting, diarrhea, delayed gastric emptying, abdominal pain, (n=6), pneumonia (n=1)	(46)
Kluger <i>et al</i> , 2016	50	Surgical	12.3 months	No record	30	Portal vein thrombosis (n=2)	Upper gastrointestinal bleeding (n=3), visceral ulcerations/perforations (n=1), intraperitoneal hemorrhage (n=3), other	(47)
Narayanan <i>et al</i> , 2017	50	CT Guidance	14.2 months after IRE	No record	20	No record	Abdominal pain (n=7), pancreatitis (n=1), sepsis (n=1), gastric leak (n=1)	(48)
Zhang <i>et al</i> , 2017	21	US/CT Guidance	No record	No record	No record	No record	Hypoglycemia (n=1), hypokalemia (n=1), chest tightness and high blood pressure (n=1), premature ventricular contractions (n=1)	(51)

HIFU, high-intensity focused ultrasound; RFA, radiofrequency ablation; IRE, irreversible electroporation; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; CRP, C-reactive protein.

It was hypothesized that weak venous vessel wall and tumor compression or invasion of the vein slows the blood flow rate, increasing the likelihood of thrombosis (25). However, the blood flow rate of arterial vessels is high, combined with good vascular elasticity. Compared with venous vessels, arterial vessels have lower probability of thrombosis and partial narrowing of blood vessels is more likely to occur. This is consistent with findings from Strunk *et al.* (16). In addition, physicians should be aware of the tumor squeezing blood vessels or tumor invasion of blood vessels during the HIFU therapy. It is understood that tumor compression or invasion of blood vessels reduces blood flow rate and favors coagulation (25). Meanwhile, the compression effect of contraction on blood vessels after tumor ablation, as well as the cavitation effect caused by ultrasound radiation, could damage the intima of blood vessels, inducing vasospasm and thrombosis and eventually causing partial occlusion of blood vessels (18).

Compared with other local ablation methods (RFA and IRE), HIFU has lower incidence rates of vascular adverse events and associated complications in pancreatic cancer. Portal vein thrombosis is the most common vascular-associated complication of pancreatic cancer following RFA and IRE treatment (8,9,42-51). In related studies, patients with pancreatic cancer received RFA and IRE and the primary complications included acute pancreatitis (8,9,42-46,48), abdominal pain (46,48), pancreatic fistula (8,9,42,43,45,49), duodenal ulcer or perforation (9,42-44,49), gastrointestinal bleeding (42,44-47) and biliary fistula (46). In HIFU, the main complications included acute pancreatitis, skin burn, abdominal pain (22,33,34) and elevated amylase expression levels (14,21,33,34), whereas vascular adverse events are rarely recorded and patients can recover and be discharged within a short time (24,25). In addition, HIFU treatment utilizes ultrasound without involving the use of needles, electrodes, probes or similar items, therefore HIFU is safer and less invasive compared with other local ablation methods and can be performed in patients with tumors near vessels, the intestine or the bile duct stent (7). In addition, HIFU treatment could avoid potential complications caused by puncture, especially bleeding and metastasis in the puncture channel (16). Therefore, HIFU ablation of pancreatic cancer treatment is beneficial.

The present study was limited by the small number of patients. The morbidity of pancreatic cancer is relatively lower compared with other gastrointestinal malignancies, therefore there were not large numbers of patients with pancreatic cancer suitable to be involved in the present single-center study. Future studies should include a larger number of selected patients. For example, tumor size and location were not considered as exclusion criteria and vascular hemodynamic data immediately after surgery were not available due to general anesthesia. Due to the short follow-up time of the present study, the long-term survival rate of patients was not assessed.

In conclusion, the present single-center study assessed the shape and hemodynamics of related vessels before and after HIFU treatment and no significant changes were found, with blood vessels maintaining their normal function. No adverse vascular events were associated with HIFU therapy in pancreatic cancer. Therefore, it was concluded that HIFU therapy for pancreatic cancer has no deleterious effects on peripancreatic arterial and venous blood vessels.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XG, HZ, KZ and DDD designed the present study. XG, YY, JZ, WY and LR performed the literature review. XG and CJ analyzed the data. XG and KZ drafted the initial manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The Second Affiliated Hospital of Chongqing Medical University (Chongqing, China) and performed in accordance with The Declaration of Helsinki. Written informed consent was provided by all patients prior to the study start (approval no. 12/2018).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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