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
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) Non-eligibility for general anesthesia; ii) calcification and peripancreatic blood vessel <1 cm. The exclusion criteria were: i) Non-eligibility for general anesthesia; ii) severe heart failure, cerebrovascular disease and renal insufficiency; iii) Child-Pugh class C (26); iv) hemorrhage and other severe diseases, such as hemorrhage were recorded.

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
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.

**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 venous 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...
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 revealed 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), pancreateatitis (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

| 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                           |

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

| BV  | n   | 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    |
| 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    |
| 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    |
| 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| 0.42    | 0.6±0.5| 1.3±1.2| 0.20    |

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   | Before | After | P-value | 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*   | 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. *P<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; PI, vascular pulsatility index; RI, vascular resistance index; VD, vascular diameter.
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 et al, 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 amylase (n=48); Jaundice (n=6); GI dysfunction (n=36); Other | (10) |
| Marinova et al, 2016 | 20 | US guidance | No record | 75 | No record | No record | Transient subcutaneous edema (n=1), minor skin burns (n=1); Pancreatic lipase increase (n=4), Induration of subcutaneous fat tissue ≤2 cm (n=9); Superficial second-degree skin burns (n=2), deep second to third degree skin burns (n=1), minor skin burns (n=9) | (13) |
| Wang et al, 2013 | 224 (86 stage III) | US guidance | 8.3 months after HIFU | 80 | 26 | No record | No record | (14) |
| Strunk et al, 2018 | 50 | US guidance | No record | No record | 5.4 | No record | No record | (15) |
| Xiong et al, 2009 | 89 (39 stage III) | US guidance | 11.2 months | 78.6 | 11.2 | Tumor-associated vascular occlusion (superior mesenteric vein, portal vein, or splenic vein) (n=3) | Superficial second degree skin burns (n=3); Subcutaneous sclerosis (n=6); Pancreatic pseudocyst (n=1); Pancreatic pseudocyst (n=2); Mild pancreatitis (n=1) | (16) |
| Sofuni et al, 2014 | 30 (16 stage III) | US guidance | No record | 66.7 | 10 | No record | No record | (17) |
| Anzidei et al, 2014 | 6 | MR guidance | No record | 100 | No record | No record | No record | (18) |
| Strunk et al, 2016 | 15 (6 stage III/9 stage IV) | US guidance | 6 months after HIFU | 40 | No record | No record | No record | (19) |
| Shi et al, 2017 | 71 (stage III) | US guidance | No record | 92.9 | No record | No record | No record | (20) |

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| Author, year | Patients, n | Access | Median survival | Pain reduction, % | Complication rate | Vascular complications | Other complications | (Refs.) |
|--------------|-------------|--------|----------------|-------------------|------------------|-----------------------|---------------------|--------|
| Dababou et al, 2017 | 729 | MR/US guidance | No record | 81 | No record | Portal vein thrombosis | Skin burn; mild pancreatitis; pancreaticoduodenal fistula; | (23) |
| Vidaljove et al, 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 et al, 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); Fatigue (n=14); Abdominal pain (n=7); Fever (n=7); Nausea (n=5); Rash (n=4); | (33) |
| Ji et al, 2018 | 87 | US guidance | No record | No record | 28 | No record | | (34) |

**B. RFA**

| Author, year | Patients, n | Access | Median survival | Pain reduction, % | Complication rate | Vascular complications | Other complications | (Refs.) |
|--------------|-------------|--------|----------------|-------------------|------------------|-----------------------|---------------------|--------|
| Cantore et al, 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 et al, 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 et al, 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 | Pain reduction, % | Complication rate | Vascular complications | Other complications                                      | (Refs.) |
|--------------|-------------|----------------------|-----------------|------------------|-------------------|------------------------|---------------------------------------------------------|---------|
| Frigerio et al, 2013 | 57          | US guidance          | 19 months       | No record        | 14                | No record              | Pancreatic fistulas, duodenal injury, gastric ulcer, jaundice, other | (49)    |
| D’Onofrio et al, 2017 | 18          | Percutaneous US guidance | No record    | No record        | No record       | No record              | Pancreatic fistulas, duodenal injury, gastric ulcer, jaundice, other | (50)    |

C, IRE

| Author, year | Patients, n | Access               | Median survival | Pain reduction, % | Complication rate | Vascular complications | Other complications                                      | (Refs.) |
|--------------|-------------|----------------------|-----------------|------------------|-------------------|------------------------|---------------------------------------------------------|---------|
| Martin et al, 2015 | 200        | Surgical 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 et al, 2016 | 24         | Percutaneous 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), duodenal 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 et al, 2016 | 25          | Surgical US Guidance | No record        | No record        | 36                | Portal vein thrombosis (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) | (45) |
| Scheffer et al, 2017 | 25         | Percutaneous 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 et al, 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 et al, 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 et al, 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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