

A retrospective comparative study on the treatment of non-metastatic pancreatic cancer using high-intensity focused ultrasound versus radical surgery

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ABSTRACT

Objective: To compare the efficacy and safety of high-intensity focused ultrasound (HIFU) and radical surgery for non-metastatic pancreatic cancer (PC).

Materials and methods: We retrospectively analyzed 89 stage I/II/III PC patients who underwent HIFU ($n=43$) or surgery ($n=46$) at the Third Xiangya Hospital from January 2020 to December 2021. Pain relief, Karnofsky Performance Scale (KPS), overall survival (OS), treatment-related complications and risk factors for OS were assessed.

Results: There was no significant difference in the pain relief rate at 30 days post-treatment between the two groups. However, compared with the surgery group, the HIFU group showed significantly lower post-treatment VAS scores ($p=0.019$). In the surgery group, the KPS at 30 days post-treatment was lower than pretreatment KPS (70 vs 80; $p=0.015$). This relationship was reversed in the HIFU group (80 vs 70; $p=0.024$). Median OS favored surgery over HIFU (23 vs 10 months; $p<0.001$), with a higher 1-year OS rate (69.57% vs 32.6%; $p<0.001$). However, there was no significant difference in OS between the two groups for stage III patients ($p=0.177$). Complications rated \geq grade III were 2.33% in the HIFU group and 32.6% in the surgery group. Multivariate analyses showed that age, KPS, and treatment methods were independent prognostic factors for OS.

Conclusion: HIFU demonstrates advantages over surgery in terms of early KPS, VAS improvements, and safety for pancreatic cancer; however, long-term outcomes favor surgery. For III-stage disease, HIFU was noninferior to surgery in overall survival.

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Introduction

Pancreatic cancer (PC) is the most lethal malignant tumor of the digestive system and is expected to become the second leading cause of cancer death by 2030 [1,2]. In clinical practice, PC is difficult to detect at an early stage because it is located in the deepest part of the abdomen and lacks specific clinical symptoms. More than 80% of patients are diagnosed at an advanced stage, with an overall 5-year survival rate of less than 5%. Even for those who receive radical surgery therapy, the 5-year survival rate is less than 20% [3,4], posing a significant threat to human health worldwide.

To date, radical surgery remains the primary option for potentially curing pancreatic cancer and providing the longest survival for patients. The two main types of radical surgical

procedures for PC are pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), depending on the anatomic location of the tumor [5]. PD is typically performed for tumors in the head, uncinate process, and neck of the pancreas, while DP is usually preferred for tumors in the body or tail of the pancreas, often requiring splenectomy. Although significant advancements have been made in surgical techniques and medical equipment in recent decades, the rates of perioperative morbidity and mortality remain high. A meta-analysis by Probst et al. found mortality rates of 2% for PD and 1% for DP, with overall complication rates of 53% and 59%, respectively [6]. Similarly, a meta-analysis by Matthias et al. reported a 90-day mortality rate of 2.6% for minimally invasive pancreatic surgery and 2.5% for open pancreatic surgery, with instances of complications rated \geq III by Clavien-Dindo classification at 32.8% and

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26.8%, respectively [7]. Even for patients without serious complications, the hospital stay after radical surgery is often more than a week. Older patients with PC, particularly those with multiple cardiovascular or other comorbidities, are at a higher risk of treatment-related complications compared to younger patients, despite receiving adequate perioperative care and incurring high medical costs [8–10]. For patients who are hesitant about the risks and costs of surgery, non-surgical treatments such as ablation could be a valuable alternative option.

High-intensity focused ultrasound (HIFU) is an emerging noninvasive therapeutic technique for PC. It is performed by focusing ultrasound waves to produce thermal, mechanical, and cavitation effects at specific target areas, leading to the destruction of tumors [11]. Research has confirmed the ability of ultrasonic energy to safely penetrate large vessels and conduct ultrasound ablation in pancreatic tissues. There have been numerous studies on HIFU for PC, and the results have demonstrated its effectiveness in providing pain relief, reducing tumor size, and extending survival rates [12,13].

In the current study, we conducted a retrospective analysis to compare the efficacy and safety of HIFU and surgical resection in the treatment of non-metastatic pancreatic cancer. This study, which represents the first comparison of these two treatments, aims to provide clinical insights for the application of HIFU in PC treatment and reliable evidence for the individualized treatment of PC.

Methods

Eligibility criteria

This retrospective study included patients diagnosed with pancreatic cancer who underwent HIFU or surgical resection

at the Third Xiangya Hospital of Central South University from January 2020 to December 2021. All cases enrolled in this study met the following criteria: (1) age \geq 18 years old; (2) PC was confirmed by histopathology or typical imaging findings accompanied by increased peripheral blood CA19-9; (3) distant metastasis was excluded by PET-CT or thoracic-abdominal contrast-enhanced CT; (4) the patient was able to endure general anesthesia; (5) the patient received HIFU treatment or radical surgical resection at our hospital. Exclusion criteria: (1) patients who had received prior systemic or local anti-tumor therapy; (2) patients who had undergone both HIFU and surgical resection; (3) patients with concurrent malignancies. The specific patient selection process is shown in Figure 1. A total of 89 patients were included, with 43 patients receiving HIFU therapy and 46 patients undergoing radical surgical resection.

This trial was approved by the ethics committee and institutional review board of the Third Xiangya Hospital of Central South University (ethics approval number 22047), and all patients provided written informed consent.

Treatment

HIFU treatment was performed utilizing the JC200 high-intensity focused ultrasound tumor treatment system (Chongqing HAIFU Medical Technology Co., Ltd). Prior to the HIFU treatment, the patient underwent catharsis 16h before the procedure and fasted for 8h with water deprivation. Before the procedure, the skin in the treatment area was cleaned. The patient was positioned either prone or in a left lateral position. The HIFU therapeutic energy was delivered in a pulsed mode with energy levels ranging from 200W to 400W depending on adjacent risk structures. Real-time ultrasound was used to comprehensively detect tumor

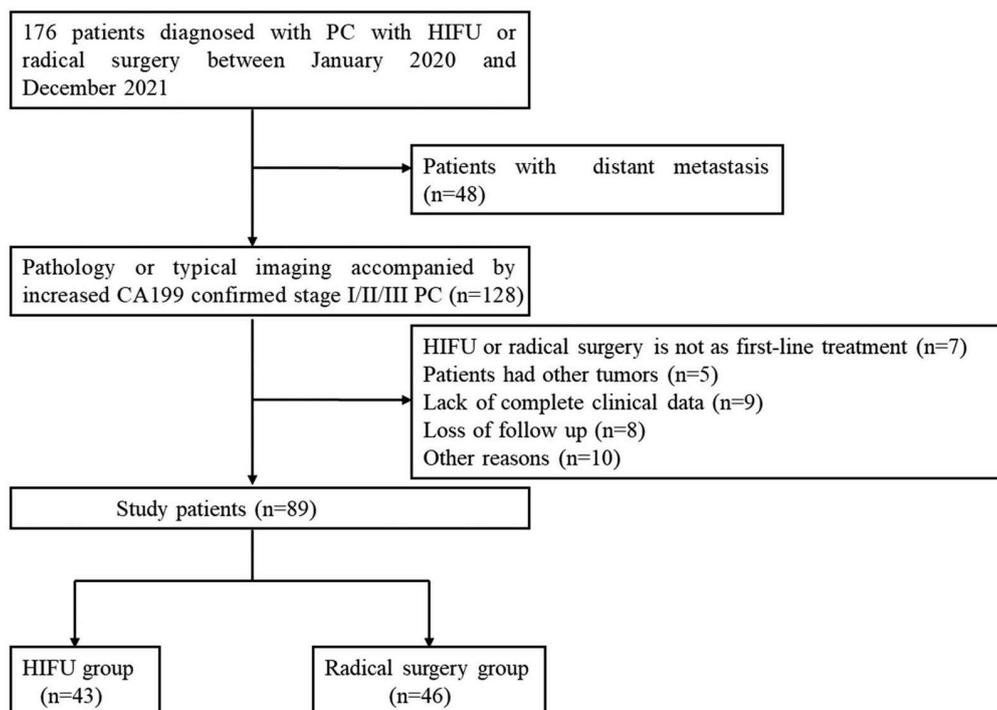


Figure 1. Patient selection. PC: pancreatic cancer; HIFU: High-intensity focused ultrasound.

targets. The target area was scanned with a continuous high-intensity focused ultrasound beam to achieve the largest ablation volume. All procedures were performed under general anesthesia. All patients in the HIFU group received adjuvant chemotherapy within 3 days following HIFU treatment, with the exception of one patient who experienced a grade III skin burn; this particular patient underwent adjuvant chemotherapy 23 days post-HIFU. The adjuvant chemotherapy regime consisted of Nab-paclitaxel/Gemcitabine (AG) or S-1 monotherapy.

Surgical procedures, including pancreatoduodenectomy (PD) and distal pancreatectomy (DP), were performed in a laparoscopic, robotic, or open manner. Adjuvant chemotherapy was administered post-surgery, following a minimum recovery period of 14 days, with the chemotherapy regimen comprising Nab-paclitaxel/Gemcitabine (AG) or S-1 monotherapy.

Data collection

The baseline characteristics of patients included gender, age, CA199 levels, tumor location, maximum tumor diameter, and TNM stage according to the 8th edition of the American Joint Committee on Cancer (AJCC 8th Edition). Pain relief was evaluated using the visual analogue scale (VAS), ranging from 0 to 10, with 0 representing 'absolute painlessness' and 10 indicating 'unbearable pain'. Functional status was evaluated using Karnofsky Performance Scale (KPS), which ranges from 0 to 100 (higher scores indicating better functional status). Pain and functional status were evaluated 3 days before HIFU/surgery treatment and 30 days after treatment. Patients were followed up monthly until death, 31 December 2022, or failing to follow-up, whichever came first. Overall survival (OS) was defined as the time from treatment to death or the last follow-up before 31 December 2022. Complications related to HIFU and surgery were recorded and evaluated in accordance with the Clavien–Dindo classification [14]. A grade I complication is defined as any deviation from the normal post-operative course without the need for intervention, or any non-life-threatening complication not requiring therapy. A grade II complication is defined as any complication that requires pharmacological treatment (including blood transfusions and total parenteral nutrition). A grade III complication is defined as any complication requiring surgical, endoscopic, or radiological intervention. A grade IV complication is defined as any life-threatening complication requiring IC/ICU management. A grade V complication is defined as any complication resulting in the death of the patient.

Statistical analysis

All statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as $x \pm s$, and categorical variables were presented as counts and percentages. The baseline characteristics of patients in the HIFU group and radical operation group were compared using the Chi-square, Fisher's exact test or the Wilcoxon test. Pain score and functional status score were expressed as median (range), and the rank sum test was applied for comparison. The pain relief rate, as well as 6-month and 12-month

survival rates, were compared using the χ^2 test. The Kaplan–Meier method was used to compare the survival curves of the two groups, and Cox regression analysis was used to evaluate the effect of multiple factors on survival. Variables with statistical significance in the single factor analysis were included in the multiple-factor analysis. Differences with $p < 0.05$ were considered statistically significant.

Results

Patient characteristics

A total of 89 patients were included in the study, with 43 being treated with HIFU and 46 undergoing radical surgical resection. The baseline characteristics were showed in Table 1. There were more patients with III stage in the HIFU group (79.07%) compared with the surgery group (39.13%). There were no significant differences in gender, age, tumor location, or maximum tumor diameter between the two groups ($p > 0.05$), with the exception of CA199 levels, KPS and VAS. The patients in the HIFU group with higher baseline CA199 levels ($p < 0.001$), lower baseline KPS ($p = 0.043$), and higher baseline VAS ($p = 0.042$) than that in the surgery group. At the time of data cutoff, the mean duration of follow-up was 11.42 months in the HIFU group and 17.17 months in the surgery group ($p = 0.002$).

Table 1. Characteristics of patients in HIFU group and surgery group.

Variables	HIFU (n=43)	Surgery (n=46)	P (Wilcoxon*/ Chisq**)
Age (year), Mean \pm SD	61.21 \pm 9.28	58.13 \pm 9.40	0.0913*
Age, n(%)			0.1619**
<60	17 (39.53)	25 (54.35)	
≥ 60	26 (60.47)	21 (45.65)	
Gender, n(%)			0.7836**
Male	24 (55.81)	27 (58.70)	
Female	19 (44.19)	19 (41.30)	
Maximum diameter of tumor (cm), Mean \pm SD	4.26 \pm 1.52	3.70 \pm 0.93	0.0880*
CA199 (U/ml), Mean \pm SD	5540.23 \pm 13426.97	564.29 \pm 1384.02	0.0002*
CA199, n(%)			0.3392**
≤ 34	6 (13.95)	10 (21.74)	
> 34	37 (86.05)	36 (78.26)	
KPS, Mean \pm SD	72.79 \pm 12.41	78.48 \pm 12.29	0.0432*
KPS, n(%)			0.1124**
<80	25 (58.14)	19 (41.30)	
≥ 80	18 (41.86)	27 (58.70)	
VAS, Mean \pm SD	4.07 \pm 1.68	3.41 \pm 1.50	0.0418*
VAS, n(%)			0.0384**
<4	14 (32.56)	25 (54.35)	
≥ 4	29 (67.44)	21 (45.65)	
Tumor_location, n(%)			0.0745**
Head or neck of pancreas	19 (44.19)	29 (63.04)	
Body or tail of pancreas	24 (55.81)	17 (36.96)	
TNM, n(%)			0.0001**
I/II stage	9 (20.93)	28 (60.87)	
III stage	34 (79.07)	18 (39.13)	
OS Follow up time (month), Mean \pm SD	11.42 \pm 4.95	17.17 \pm 8.66	0.0024*

KPS: Karnofsky Performance Scale; VAS: Visual Analog Scale; OS: overall survival; Statistical differences ($p < 0.05$) are indicated in bold.

Table 2. VAS evaluation in the HIFU group and surgery group.

Group	Before treatment		Post-treatment		P value
	VAS	Mean rank	VAS	Mean rank	
HIFU group	4(3–8)	40.64	2(0–8)	31.09	<0.001
Surgery group	4(3–6)	32.13	2(1–5)	42.21	<0.001
P value	0.074		0.019		

VAS, visual analog scale; HIFU, High-intensity focused ultrasound; Statistical differences ($p < 0.05$) are indicated in bold.

Table 3. Pain relief rate post-treatment in the HIFU group and surgery group.

Group	Pain relief (n)		Pain relief rate	P value
	Yes	No		
HIFU group	33	4	89.19%	0.100
Surgery group	26	9	74.29%	

HIFU: high-intensity focused ultrasound.

Table 4. KPS evaluation in the HIFU group and surgery group.

Subgroup	Before treatment	Post-treatment	P value
HIFU group	70(40–100)	80(40–100)	0.024
Surgery group	80(50–100)	70(60–90)	0.015
P value	0.043	0.005	

KPS: Karnofsky Performance Scale; HIFU: High-intensity focused ultrasound; Statistical differences ($p < 0.05$) are indicated in bold.

Pain relief

Of the 43 patients in the HIFU group, 37 had pain symptoms, while 35 of the 46 patients in the radical operation group had pain symptoms. There were more patients with moderate-severe pain (VAS ≥ 4) in the HIFU group compared with the surgery group (67.44% vs 45.65%; $p = 0.038$; Table 1). The VAS score 30 days post-treatment was significantly lower than that of pretreatment in the HIFU group (median VAS score, 2 vs 4; $p < 0.001$; Table 2). A similar result was observed in the surgery group (median VAS score, 2 vs 4; $p < 0.001$; Table 2). There was no significant difference in pretreatment VAS score between the HIFU group and the surgery group (median VAS score, 4 vs 4; $p = 0.074$; Table 2). However, a significant difference was observed in post-treatment VAS scores between these two groups (median VAS score, 2 vs 2; $p = 0.019$; Table 2), with the HIFU group exhibiting a lower mean rank of post-treatment VAS scores compared to the surgery group (31.09 vs 42.21). There was no significant difference in the pain relief rate at 30 days post-treatment between the HIFU group and surgery group (89.19% vs 74.29%; $p = 0.1$; Table 3).

Functional status

The median baseline KPS score in the HIFU group was significantly lower compared to that in the radical surgery group (70 vs 80; $p = 0.043$; Table 4), while the KPS score at 30 days post-treatment in the HIFU group was significantly higher than that in the radical surgery group (80 vs 70; $p = 0.005$; Table 4). The KPS score showed a significant improvement 30 days post-HIFU treatment ($p = 0.024$), while in the radical surgery group, the KPS score 30 days post-treatment significantly decreased ($p = 0.015$). These results indicate that HIFU therapy is more likely to improve the functional status of patients with pancreatic cancer, while radical surgery could lead to a decline in postoperative functional status of patients with pancreatic cancer at least in the short term.

Table 5. Clavien-Dindo Classification of complications after HIFU treatment (n(%)).

Complications	Grade I	Grade II	Grade III	Grade IV	Total
Pain	26(30.23)	0	0	0	26(32.20)
Skin burns	4(5.00)	0	1(1.25)	0	5 (6.25)
Fever	7(8.75)	0	0	0	7(8.75)
Amylase elevation	4(5.00)	0	0	0	4(5.00)
Nausea and vomiting	12(15.00)	0	0	0	12(15.00)
Sinus bradycardia	6(7.50)	0	0	0	6(7.50)

Table 6. Clavien-Dindo Classification of complications after surgery (n(%)).

Complication	Grade I	Grade II	Grade III	Grade IV	Total
Bleeding	0	4(8.70)	1(2.17)	3(6.52)	8(17.40)
Pancreatic fistula	13	4(8.70)	1(2.17)	3(6.52)	21(45.65)
Biliary fistula	4(8.70)	0	1(2.17)	0	5(10.87)
Intestinal fistula	0	2(4.35)	0	0	2(4.35)
Incision infection	6(13.04)	0	3(6.52)	0	9(19.57)
Abdominal infection	4(8.70)	0	0	3(6.52)	7(15.22)
Gastric paralysis	2(4.35)	3(6.52)	0	0	5(10.87)

Complications

The most common complications after HIFU treatment were pain in the treated area (30.23%) and nausea and vomiting (9.30%). All complication in the HIFU group were grade I except for one patient who experienced a grade III skin burn (Table 5). In the radical surgery group, the most common complications were pancreatic fistula (45.65%), incision infection (19.57%), postoperative hemorrhage (17.40%), and abdominal infection (15.22%) (Table 6). The rate of complications \geq grade III in the HIFU group and surgery group was 2.33% and 32.6%, respectively.

Survival analysis

The median overall survival in patients in the HIFU group was 10 months (ranging from 2 to 26 months), with overall survival rates at 6 months and 1 year of 97.67% and 32.6%, respectively. In the radical surgery group, the median overall survival was 23 months (ranging from 3 to 33 months), with overall survival rates at 6 months and 1 year of 91.30% and 69.57%, respectively. The median OS in the HIFU group was shorter than that in the radical surgery group ($p < 0.001$; Figure 2). The 6-month OS rate did not significantly differ between the two groups ($p = 0.36$). However, the 1-year OS rate of HIFU group was significantly lower than that of the radical surgery group ($p < 0.001$).

In subgroup analysis, patients with stage I/II disease in the HIFU group exhibited a median OS of 11 months (ranging from 6 to 24 months), which was significantly shorter than the surgery group's median OS of 24 months (ranging from 4 to 33 months) ($p = 0.002$). Although the 1-year OS rate for stage I/II PC in the HIFU group was significantly lower compared to that of the surgery group (22.22% vs 82.14%, $p = 0.002$), there was no significant difference in the 6-month OS rate between the two groups (100% vs 96.43%, $p = 1$).

Remarkably, there were no statistically significant differences in overall survival, 6-month survival rate (97.06% vs 83.33%, $p = 0.222$), or 1-year survival rate (35.29% vs 50%,

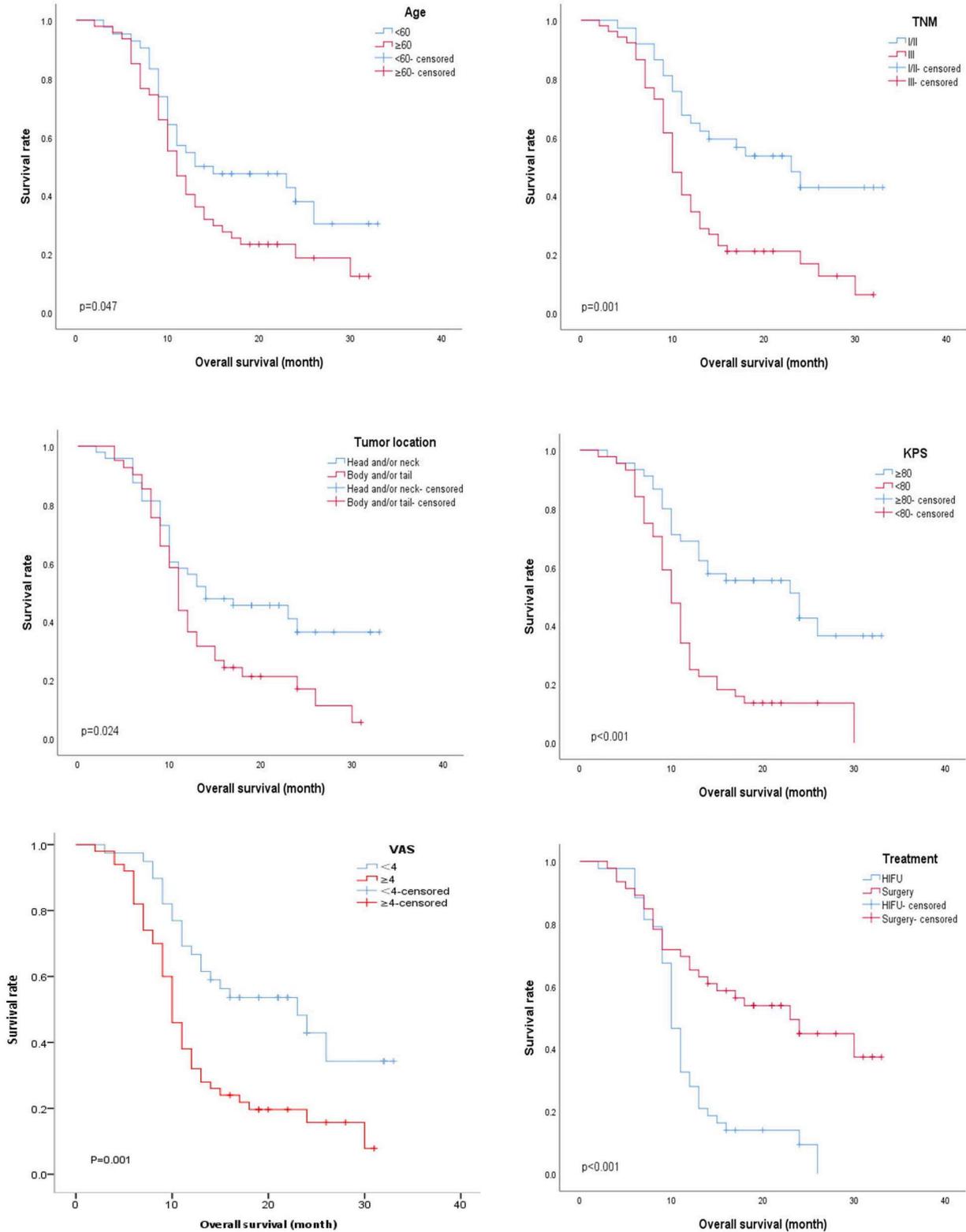


Figure 2. The Kaplan–Meier survival curves for overall survival according to age, tumor location, TNM, KPS score pretreatment, VAS score pretreatment and treatment method in stage I/II/III pancreatic cancer patients.

$p=0.304$) between the HIFU and surgery groups among stage III patients. The median overall survivals were observed to be 10 months (range: 2–26 months) and 11 months (range: 3–32 months), respectively ($p=0.177$).

In univariate analysis, age, tumor location, TNM stage, KPS score, VAS score, and treatment method were significantly associated with OS (Table 7). The Kaplan–Meier survival analysis showed that age ≥ 60 years old, tumors located at the

Table 7. Univariate cox regression analyses of risk factors in pancreatic cancer patients with stage I/II/III.

Variables	N	Median OS(months)	P value
Gender			
Male	51	12	0.561
Female	38	11.5	
Age (years)			
<60	42	13.5	0.047
≥60	47	11	
Tumor location			
Head or neck of pancreas	48	14	0.024
Body or tail of pancreas	41	11	
Maximum diameter of tumor (cm)			
<4	38	14	0.079
≥4	51	11	
TNM stage			
I/II	37	18	0.001
III	52	10	
CA199			
≤34	15	19	0.166
>34	74	11.5	
KPS score			
≥80	45	16	<0.001
<80	44	10	
VAS score			
<4	39	21	0.001
≥4	50	13	
Treatment method			
HIFU	43	10	<0.001
Surgery	46	23	

KPS: Karnofsky Performance Scale; VAS: visual analog scale; HIFU: high-intensity focused ultrasound; Statistically significant ($p < 0.05$) values are in bold.

Table 8. Multivariate cox regression of risk factors in pancreatic cancer patients with stage I/II/III.

Variables	B	BE	Wald	df	Sig
Age	0.044	0.284	0.024	1	0.013
Tumor location	-0.166	0.288	0.330	1	0.566
TNM stage	0.544	0.327	2.771	1	0.096
KPS score	-0.822	0.331	6.149	1	0.013
VAS score	0.396	0.436	0.827	1	0.363
Treatment method	-0.801	0.322	6.187	1	0.013

KPS: Karnofsky Performance Scale; VAS: visual analog scale; Statistically significant ($p < 0.05$) values are in bold.

body or tail of the pancreas, high TNM stage, KPS score pretreatment < 80, and VAS score pretreatment ≥ 4 were significantly associated with poor OS, as shown in Figure 2. Multivariate Cox regression analysis was conducted with the above six significant variables, and the results showed that age, KPS score, and treatment method were independent prognostic factors for OS (Table 8). These results indicated that radical surgery confers a survival advantage over HIFU in patients with pancreatic cancer; while for stage III disease, HIFU demonstrates comparable overall survival to surgery.

Discussion

Radical surgical resection remains the only method that potentially cures PC. However, even for those who receive radical surgery therapy, the 5-year survival rate is less than 20% [3, 4]. Despite advancements in surgical instruments, techniques, and perioperative management, the incidence of serious complications and perioperative mortality in pancreatic surgery has not

decreased significantly over the past five decades. Due to the unsatisfactory survival benefits, some patients are hesitant to undergo radical surgery. As a result, medical researchers have been working to develop less invasive therapies that can improve the length and quality of life for patients with PC. In this context, HIFU, an emerging noninvasive ablation therapy, may be a suitable option for patients with PC. As reported by numerous studies, HIFU can be used in patients with advanced pancreatic carcinoma safely and effectively [15,16]. However, there is currently no data comparing the effect and safety of HIFU with those of radical surgery. In this study, we aimed to compare the outcomes of these two methods in the treatment of non-metastatic PC by retrospectively analyzing 89 patients with stages I-III PC.

Patients with pancreatic cancer often experience serious pain and a decrease in performance due to disease progression or treatment. It has been reported that more than 80% of PC patients suffer from pain during the disease progression, and severe or chronic pain can significantly impact their quality of life and survival [17]. Pain management in patients with PC is a challenging task in clinical practice. The pain associated with pancreatic cancer can be caused by the compression of the tumor, the direct invasion of the abdominal and mesenteric plexus, or a combination of both factors [18]. Opioid analgesics and nonsteroidal anti-inflammatory drugs are commonly used to relieve pain in these patients. However, long-term use of opioids can lead to addiction and gastrointestinal reactions such as nausea and vomiting, affecting patients' quality of life [19], while prolonged use of nonsteroidal anti-inflammatory drugs may lead to gastrointestinal ulcers, bleeding, or even perforation [20]. As the disease progresses and patients develop tolerance to pain medications, their effectiveness may diminish. In cases where medication is not sufficient for pain relief, interventional therapy may be considered to block or destroy the celiac plexus [21]. However, the duration of pain relief from this therapy may be limited. In addition to local tumor ablation, HIFU can target the celiac plexus near the tumor, not only controlling tumor growth but also blocking nerve conduction to achieve analgesic effects [22,23].

In this study, we evaluated the effects of HIFU and radical surgery on pain relief and functional status of patients with PC using VAS and KPS scores, respectively. The results showed that both HIFU and radical surgical resection significantly reduced the pain related to pancreatic cancer. The pain relief rate at 30 days post-treatment showed no significant difference between the HIFU group and surgery group. However, when the pretreatment VAS scores were not significantly different between the two groups, a significant difference was observed in the post-treatment VAS scores. Specifically, the mean rank of the post-treatment VAS in the HIFU group was lower than that of the surgery group, indicating superior pain control performance with HIFU therapy. In terms of functional status, the KPS score 30 days post-HIFU treatment significantly improved compared to pretreatment, while the surgery group's score significantly decreased. These results demonstrated that HIFU has a significant advantage over surgery in terms of pain relief and postoperative recovery. Performance status has long been recognized as an important prognostic factor to predict PC patient outcome and evaluate whether they can benefit from anti-tumor therapy. It has been shown to be an independent prognostic factor for DFS, PFS, and OS in PC patients after surgery and other

therapies [24,25]. A European multicenter study conducted by Marinova et al. evaluated the effect of HIFU on the functional status of pancreatic cancer patients. The study collected quality of life and symptom data from 80 patients at baseline, as well as 1, 3, and 6 months post-treatment. Compared to baseline, patients' functional status, global health, and symptoms at 6 months significantly improved after HIFU treatment [26]. Though radical surgical resection can offer a potential cure for PC, patients often experience a significant decline in physical, social, and overall quality of life within 30 days after surgery [27].

Improving patients' prognosis and prolonging their survival has always been the main goal in anti-tumor treatment. Currently, radical resection remains the most effective method for extending the survival of pancreatic cancer patients. We compared the OS between the HIFU group and the radical surgery group, revealing that the OS of patients in the radical surgery group was significantly better than that in the HIFU group ($p < 0.001$), with overall one-year survival rates of 69.57% and 32.6%, respectively. Interestingly, the 6-month OS rate of the HIFU group and radical surgery group has no significant difference (97.67% vs 91.30%; $p = 0.36$), and for III stage patients, there were no statistically significant differences in overall survival ($p = 0.177$), 6-month survival rate ($p = 0.222$), and 1-year survival rate ($p = 0.304$) between the HIFU and surgery groups. These results indicated that the short-term prognosis of HIFU is comparable to radical surgery. Moreover, in patients with stage III disease, HIFU demonstrates comparable overall survival to surgery, potentially attributed to delayed administration of post-surgery adjuvant therapy due to operative complications. In this study, all patients in the HIFU group received adjuvant chemotherapy within 3 days following HIFU treatment, with the exception of one patient who experienced a grade III skin burn. Conversely, in the surgery group, adjuvant chemotherapy was administered at least 14 days post-surgery based on patients' recovery status. Post-operative adjuvant chemotherapy is crucial for pancreatic cancer, as it is considered the most effective way to prevent or delay tumor recurrence, especially in cases of locally advanced disease [28]. Many trials have demonstrated that postoperative adjuvant chemotherapy can significantly improve recurrence-free survival and overall survival in PC patients, with multi-agent chemotherapy regimens showing better outcomes than single-agent therapy [29,30]. Therefore, post-operative adjuvant chemotherapy with multi-agent regimens should be recommended unless contraindicated. In contrast, patients who undergo HIFU treatment can typically start systemic chemotherapy immediately or the following day, highlighting a unique advantage of HIFU in treating patients with pancreatic cancer [31,32]. In addition, our study identified tumor location, TNM stage, and VAS score as prognostic factors for OS, while age and KPS score were found to be independent prognostic factors for OS. These findings are consistent with previous studies [24,33,34].

In this study, we documented the complications of the two treatments. In general, the incidence of severe complications from pancreatic surgery was relatively high, with post-operative pancreatic fistula (POPF) being the most common complication in our experience (45.65%), consistent with previous literature [35]. POPF is the leading cause of postoperative mortality in pancreatic surgery, presenting a significant challenge for pancreatic surgeons despite great efforts to

prevent and mitigate its occurrence. Currently, there is a lack of a specific surgical technique capable of eliminating or drastically reducing the development of clinically relevant POPF [36,37]. In the surgery group, nine patients experienced complications rated as grade 4, including postoperative bleeding (3 cases), pancreatic fistula (3 cases), and abdominal infection (3 cases). In contrast, HIFU is a noninvasive therapy with few complications. Among the 43 patients treated with HIFU, only one patient experienced a skin burn rated as grade 3, while the rest had grade 1 complications. Common adverse events included pain in the treated area, nausea, and vomiting, most of which resolved on their own without requiring special treatment, consistent with previous reports [15,38]. In conclusion, HIFU offers a significant safety advantage over radical surgery.

Overall, radical surgical resection provides superior tumor control and long-term survival benefits compared to HIFU in patients with non-metastatic PC. However, HIFU offers advantages in pain relief, performance status improvement and safety. Besides, for III-stage disease, HIFU was noninferior to surgery in overall survival. Therefore, for patients who decline or are not suitable for surgery, especially those experiencing intense pain or with a poor performance status, HIFU may serve as an effective alternative treatment option.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author, Yu Xiao. The data are not publicly available due to their containing information that could compromise the privacy of research participants

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