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SPECIAL FEATURE: REVIEW ARTICLE

Cutting-edge therapeutic ultrasound-its basic and clinical medicine; the spread of ultrasound-based theranostics

High-intensity focused ultrasound therapy for pancreatic cancer

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Abstract

Pancreatic cancer (PC) has one of the poorest prognoses among solid cancers, and its incidence has increased recently. Satisfactory outcomes are not achieved with current therapies; thus, novel treatments are urgently needed. High-intensity focused ultrasound (HIFU) is a novel therapy for ablating tissue from the outside of the body by focusing ultrasonic waves from multiple sources on the tumor. In this therapy, only the focal area is heated to 80–100 ℃, which causes coagulative necrosis of the tissue, with hardly any impact on the tissue outside the focal area. Although HIFU is a minimally invasive treatment and is expected to be useful, it is not yet generally known. Here, we discuss the usefulness of HIFU treatment for un-resectable advanced PC using the results of previous research, meta-analyses, and systematic reviews on its efficacy and safety. HIFU therapy for un-resectable PC is useful for its anti-tumor effect and pain relief, and is expected to prolong survival time and improve quality of life. Although HIFU for PC has several limitations and further study is needed, this technique can be safely performed on un-resectable advanced PC. In future, HIFU could be utilized as a minimally invasive treatment strategy for PC patients with a poor prognosis.

Keywords High-intensity focused ultrasound · Pancreatic cancer · Un-resectable

Abbreviations

HIFU	High-intensity focused ultrasound
PC	Pancreatic cancer
QOL	Quality of life
MST	Median survival time
US	Ultrasound
MRI	Magnetic resonance imaging
CEUS	Contrast-enhanced ultrasonography
GEM	Gemcitabine
RECIST	Response Evaluation Criteria in Solid Tumors
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease

Introduction

Pancreatic cancer (PC) has an increasing incidence and a 5-year overall survival rate of approximately 7%, one of the poorest prognoses among solid cancers [1]. Despite the numerous methods for early diagnosis, 60–70% of all PCs are un-resectable. Furthermore, the severe pain caused by advanced PC is extremely difficult to treat and may greatly affect the patient's quality of life (QOL). Moreover, chemotherapy and chemo-radiotherapy are the standard of care for un-resectable PC, but their outcomes are not satisfactory, with a median survival time (MST) of only 7 months. Thus, novel treatments for PC with a poor prognosis are needed. In recent years, high-intensity focused ultrasound (HIFU)—a minimally invasive treatment that does not involve radiation exposure, needles, or anesthesia—has garnered attention [2–4]. Moreover, the results of clinical trials with a large number of patients and their long-term outcomes have been published, and expectations for the clinical application of HIFU have accelerated. In this review, we discuss the principles of HIFU as well as the equipment, mechanisms of its effects, and indications of HIFU. Further, we examine HIFU for PC in general and contrast the outcomes of HIFU

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in Japan and worldwide. Lastly, we summarize systematic reviews and meta-analyses on HIFU for PC and highlight new developments in the field.

About HIFU

Principles of HIFU

While ultrasound (US) is often used in diagnostic equipment, it also has therapeutic applications in hyperthermia, HIFU, and histotripsy. Hyperthermia is the use of the thermal action of ultrasonic waves, whereas HIFU heats tissue to a greater degree and in a more focused manner to cause coagulative necrosis. Because of differences in their irradiation conditions, HIFU mainly leverages thermal and mechanical actions, whereas histotripsy uses mechanical action via cavitation. Specifically, HIFU cauterizes tissue from outside the body by focusing ultrasonic waves from a transducer with many ultrasonic sources on a single point, known as the target tumor [2–4]. This modality is groundbreaking because it only causes coagulative necrosis via thermal and non-thermal energy (mainly cavitation) to the focal area, with hardly any impact on the intervening tissue outside the focal area. Moreover, the ultrasonic waves are emitted from multiple sources inside a semicircular probe, and the vibrational energy converges on the center of the curvature or the focal region [2–4] (Fig. 1). Depending on the absorption coefficient of the tissue, the vibrational energy is converted to heat at 80.0–98.6 ℃. The temperature of the tissue in the focal region increases quickly (generally within 1 s), but there is hardly any effect on healthy tissue outside the focal area because the temperature decreases to 50 ℃ 7–8 mm away. Therefore, this technique does not require general anesthesia, epidural anesthesia, sedation, or analgesics.

Equipment

HIFU requires different equipment depending on whether it is used for external or trans-rectal irradiation, which is mainly used for treating the prostate. External irradiation devices are guided by magnetic resonance imaging (MRI) or US. MRI-guided devices are mainly used to treat the uterus and mammary glands. MRI-guided therapy is beneficial in that it is not affected by patient factors such as obesity. Additionally, this modality can be used to perform objective assessments, and it is available at many facilities. However, MRI-guided therapy has a high equipment cost, is laborious and time-consuming, and the time available for treatment may be limited because the equipment is prioritized for regular examinations. Additionally, the treatment site cannot be observed in real time, the spatial resolution is low compared with US, and the treatment site must be large to use MRI. In contrast, with US-guided therapy, the lesion can be monitored in real time, the spatial resolution is high, the treatment and displayed images are both US images facilitating the process, evaluating therapy is easy with contrast-enhanced US, and the cost is low. Additionally, US-guided therapy can be used on abdominal organs that have peristaltic movement, and treatments can be performed safely and accurately by observing the treatment site in real time.

Biological effects of ultrasonic waves and the mechanism of HIFU's effects

US is a diagnostic tool widely used worldwide with the potential to shift from the diagnostic to the therapeutic realm by changing the intensity and irradiation time of the

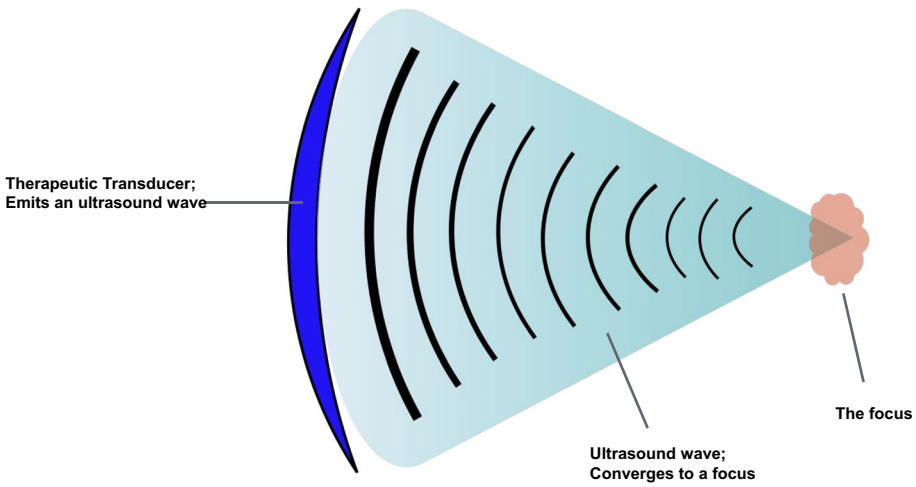

Fig. 1 Principles of HIFU. HIFU is performed by ablating tissue from outside the body by focusing ultrasonic waves on a single target tumor. The ultrasonic waves are emitted from multiple sources placed inside a semicircular probe, and this vibrational energy converges on the center of the curvature, also known as the focal region. HIFU, high-intensity focused ultrasound

ultrasonic waves [5, 6]. The energy level of HIFU is about 103 times that of ultrasonic devices used for imaging, which is much lower than that of proton beams or X-ray computed tomography. Ultrasonic waves have two biological actions: thermal (heating) and non-thermal (mainly cavitation) [5, 6]. Heating occurs when the ultrasonic waves propagate and are scattered or absorbed, by which the ultrasonic energy converts into thermal energy. If the target lesion causes severe scattering, it will generate intense heat at the site. Moreover, the biological action of ultrasonic waves is a linear correlation of irradiation intensity × time. That is, when a threshold value is exceeded, the biological actions occur, and a therapeutic effect is elicited (Fig. 2). The recommended focal temperature for HIFU is ≥ 55 ℃ with 15 s of irradiation. In practice, coagulative necrosis can be achieved by irradiation for only a few seconds at a focal temperature of ≥ 60 ℃.

The radiation pressure and vibration of ultrasonic waves also cause non-thermal effects, mainly due to cavitation. Cavitation is a phenomenon in which a vacuum is created when a high-amplitude ultrasonic vibration is applied to a liquid. The vacuum gradually grows and then collapses, causing tissue and cell damage by destroying cell membranes or rupturing capillaries. The therapeutic effects of HIFU are caused by heating and cavitation, which cause coagulative necrosis, degeneration, apoptosis, cell destruction, and fibrosis [2–4, 7–15].

Indications of HIFU

Patients should undergo HIFU (1) to achieve tumor ablation and pain relief from malignant tumors, such as PC, liver cancer, renal cancer, prostate cancer, bladder cancer, breast cancer, and soft tissue sarcoma; (2) to treat benign diseases, such as uterine myoma and prostatic hypertrophy; and (3) to treat neurological diseases, thrombolysis, arterial occlusion, bleeding, and hemostasis for vascular or organ hemorrhage.

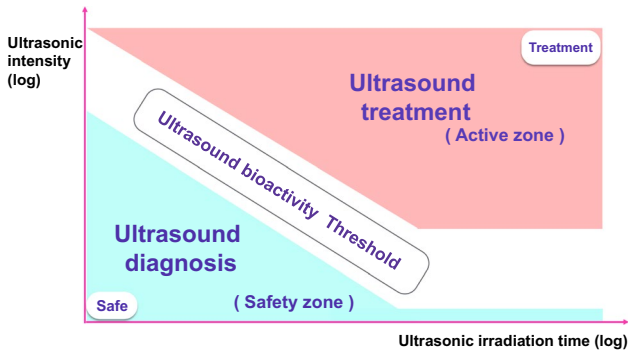

Fig. 2 Schematic diagram of the zones for ultrasound diagnosis and treatment. The biological action of ultrasonic waves is a linear correlation of irradiation intensity × time. That is, when a threshold value is exceeded, the biological action occurs, and a therapeutic effect is elicited. By increasing the intensity of the ultrasonic waves and their irradiation time, the threshold between the safety zone of ultrasound diagnosis is exceeded, and the ultrasound treatment zone is entered. Thus, HIFU is in the ultrasound treatment zone

HIFU for pancreatic cancer

Indications of HIFU for pancreatic cancer

HIFU is suitable for patients with PC with un-resectable advanced cancer that is not indicated for or does not respond to conventional local therapies or whose pain can only be controlled by increasing the dose of analgesics. Moreover, HIFU therapy is expected to improve the QOL of patients by preventing local complications such as duodenal obstruction through local control and symptom relief effects such as pain relief. In addition, it has been reported that local treatment activates the antitumor immuno-stimulatory effect (abscopal effect) and has antitumor effects on distant metastases and prolonged survival [11–16]. Therefore, the local treatment of advanced PC with distant metastasis is also an indication for HIFU therapy. However, there is a limit to where the focused ultrasonic HIFU waves can reach. The tumor depth cannot be more than approximately 10 cm from the skin surface; thus, deeper tumors are not indicated for this treatment. Therefore, cancers in the pancreatic tail are often not indicated for HIFU because of their depth, and the effects of gastrointestinal gas make these tumors difficult to visualize.

Complications

Complications of HIFU include skin burns, gastrointestinal perforation, digestive ulcers, gastrointestinal obstruction, acute pancreatitis, pancreatic pseudocysts, pancreatic leaks, obstructive jaundice, vascular obstruction, peritonitis, local infections, bleeding, hematoma formation in the lesion, and pain. Moreover, the pancreas is an extremely sensitive organ, and the effects of the heat from HIFU can cause severe inflammatory changes. No serious adverse events were reported in animal studies [2–4, 7–15]. In addition, no serious complications have been reported in clinical practice to date, and thus this modality is considered minimally invasive or noninvasive [16–68] (Table 1).

HIFU in practice

Contrast-enhanced ultrasonography (CEUS) should be performed by the day before treatment to formulate a treatment strategy with an appropriate treatment route, range, and relationship with surrounding organs. To prevent attenuation of the ultrasonic waves and enable visualization of the target tumor, patients should fast for 12 h and abstain from drinking for 4 h before treatment. Prior

Table 1 HIFU therapeutic outcomes

Author	Year	Patients (*n*)	Study design	Median survival (months)	Pain relief (%)	Adverse events
Wang et al. [16]	2002	15	HIFU monotherapy in late stage PDAC*	N/A	100	Mild abdominal pain
Xie et al. [17]	2003	41	HIFU alone vs HIFU + gemcitabine in locally advanced PDAC	N/A	66.7(HIFU), 76.6(HIFU + GEM)	None
Xu et al. [18]	2003	37	HIFU monotherapy in advanced PDAC	N/A	80	None
Yuan et al. [19]	2003	40	HIFU monotherapy in PDAC	N/A	80	None
Wu et al. [20]	2005	8	HIFU in advanced PDAC	11.25	100	None
Xiong et al. [21]	2009	89	HIFU in unresectable PDAC	26.0 (stage II), 11.2 (stage III), 5.4 (stage IV)	N/A	Skin burn, subcutaneous fat sclerosis, asymptomatic pseudocyst
Zhao et al. [22]	2010	37	Phase II study of gemcitabine + HIFU in locally advanced PDAC	12.6 (95%CI: 10.2–15.0)	78.6	Neutropenia, thrombocytopenia, nausea vomiting
Orsi et al. [24]	2010	6	HIFU in unresectable PDAC	N/A	100	Portal vein thrombosis
Sung et al. [28]	2011	46	Stage III or IV PDAC	12.4 (Overall survival at 12 mo was 30.4%)	N/A	Minor: abdominal pain, fever, nausea, major: pancreaticoduodenal fistula, gastric ulcer, skin burns
Wang et al. [29]	2011	40	Advanced PDAC	10 (stage III), 6 (stage IV)	87.5	None
Lee et al. [30]	2011	12	HIFU monotherapy in unresectable PDAC (3/12 received chemotherapy)	10.3 (HIFU alone: 9/12 pts)	N/A	Pancreatitis
Li et al. [32]	2012	25	Unresectable PDAC	10 (42% survived more than 1 year)	92(PS and pain)	Skin burn
Wang et al. [35]	2013	224	Advanced PDAC	N/A	N/A	Elevated amylase, gastrointestinal dysfunction, obstructive jaundice, vertebral injury
Gao et al. [37]	2013	39	Locally advanced PDAC	11 (30.8% survived more than one year)	79.5	None
Sofuni et al. [39]	2014	30	Unresectable advanced PDAC	N/A	66.7	Skin burn, mild pancreatitis, pseudo pancreatic cyst
Vidal-Jove et al. [45]	2015	43	Stage III and stage IV PDAC with systemic chemotherapy	13	N/A	Severe pancreatitis with GI bleeding, skin burning
Marinova et al. [50]	2016	13	Locally advanced PDAC	N/A (tumour reduction was 34.2% at 6 weeks and 63.9% at 3 months)	77	None
Li et al. [51]	2016	16	Combined application of HIFU and radiotherapy for locally advanced PDAC	14	VAS** declined (5.1 → 3.3)	None
Li et al. [52]	2016	61	HIFU in combination with S-1 and S-1 alone for metastatic PDAC	10.3 (HIFU + S-1) vs 6.6 (S-1)	57 (HIFU + S-1) vs 20 (S-1)	None
Strunk et al. [53]	2016	15	Unresectable locally advanced PDAC	N/A (average volume reduction of 63.8% after 3 months)	80	None

Table 1 (continued)

Author	Year	Patients (*n*)	Study design	Median survival (months)	Pain relief (%)	Adverse events
Ning et al. [54]	2016	436	Unresectable PDAC for HIFU and non-HIFU	7.1 (HIFU) vs 5 (non-HIFU)	N/A	Increase of serum or urinary amylase levels, incomplete intestinal obstruction, mild fever
Ji et al. [57]	2018	87	Unresectable locally advanced PDAC	12.2	64	Fatigue, abdominal pain, fever, nausea, rash
Marinova et al. [58]	2019	50	Unresectable advanced PDAC	16.2	84	None
Ning et al. [60]	2019	347	Unresectable advanced PDAC for HIFU + GEM and GEM	7.4 (HIFU + GEM) vs 6.0 (GEM)	None	Skin burn, vertebral injury, GI bleeding, elevated amylase, abdominal pain, fever, obstructive jaundice
Zhu et al. [61]	2019	86	Advanced PDAC	9.9	97.6	Fever, abdominal pain, skin burn, amylase elevation
Tao et al. [62]	2019	38	Advanced PDAC (HIFU + Gemox)	12.5	90	Upper abdominal discomfort, tolerable liver area pain or low back pain, fever, obstructive jaundice
Sofuni et al. [68]	2021	176	Unresectable advanced PDAC	21.3 (HIFU + chemotherapy) vs 9.5 (chemotherapy alone)	63.8	Skin burn, mild pancreatitis, pseudo pancreatic cyst, gastric ulcer

*PDAC: pancreatic ductal adenocarcinoma, **VAS: visual analog scale

to HIFU, the patient is placed in the supine position to identify the appropriate treatment route and relationships with surrounding organs, and US is performed in B mode. Low-viscosity US gel for HIFU is applied to the treatment site. Unclear images due to gas in the intestine can be overcome by administering degassed water, dimethicone, or butylscopolamine to the patient, or increasing the pressure of the water bag, while sedatives are not usually necessary.

There are several US-guided HIFU devices. For example, the FEP-BY02 system made by Yunde Bio-Medical Engineering Co. (Beijing, China) is a specialized device with upper and lower transducers capable of depicting the tumor in detail during therapy and assessing the therapeutic effect afterward. The transducers in this system have 251 US emitters of 1.1 MHz on a 37-cm sphere that focus on a single fixed focus. The upper transducer is used to treat PC as it can be pressed against a patient in the supine position to depict the tumor. The water sac is filled with degassed water, the transducer is lowered to the treatment site, and the target is observed with an image confirmation probe while pressed lightly with the water sac. The confirmation probe and the therapeutic oscillator are on the same axis. Moreover, the treatment plan is formulated while observing the target; however, the visualization ability of the confirmation probe declines as it is lifted up during treatment. The thickness of the abdominal wall (skin, subcutaneous fat, muscles), distance from the skin to the target, and the size and depth of the tumor are measured to calculate attenuation from the tissue and surrounding environment, which is used to calculate the therapeutic dose. The treatment plan is entered into a computer, which controls the output power, treatment position, and other aspects during HIFU. If the distance to the surrounding major organs (stomach, spleen, liver, duodenum, and bile duct) is ≥ 1 cm, and blood flow in the superior mesenteric artery is weak or the vessel is thin, the distance from this vessel should also be ≥ 1 cm. Moreover, if the target is deep, the US waves will attenuate greatly during transmission (energy attenuates by about 20% for every 1 cm of depth); thus, the energy will be low when the target is reached, which could result in ineffective treatment. Because the area ablated by a single irradiation is small ($3 \times 3 \times 10$ mm), the entire tumor is ablated in layers. In practice, if cavitation occurs, the cauterization extends widely around the site.

During HIFU, patients are checked for pain in the abdomen, back, pelvic area, or skin. If the patient complains of abdominal pain that is more severe than before treatment or if skin pain occurs, treatment can be suspended until the pain is relieved. The initial power can be used after resuming treatment, or it can be reduced by 10% after treatment or if pain is experienced.

Outcomes of HIFU for pancreatic cancer

Outcomes of HIFU for pancreatic cancer (outside of Japan)

Table 1 shows the treatment outcomes and complications of HIFU performed outside of Japan. Pain relief was reported in 57–100% of patients with a mean of 81.8%. Further, survival was shown to be prolonged in the HIFU group in a number of studies [20–22, 28–30, 32, 37, 45, 51, 52, 54, 57, 58, 60–62, 68]. Specifically, Xie et al. [17] reported a clinical efficacy rate of 66.7% with HIFU alone and 76.6% with HIFU plus chemotherapy, and a response rate of 33.3% with HIFU plus chemotherapy and 14.3% with chemotherapy alone. Meanwhile, Wang et al. [29] reported a response rate of 50.0% with HIFU plus chemotherapy and 31.3% with chemotherapy alone. Moreover, Vidal-Jove et al. [45] reported a clinical response rate of 82% for HIFU in combination with chemotherapy in 48 cases of un-resectable PC and a MST of 13 months. The main complications observed in the study were pancreatitis with gastrointestinal hemorrhage and skin burns. Furthermore, Li et al. [52] compared HIFU in combination with S-1 chemotherapy to S-1 chemotherapy alone in 120 cases of metastatic PC after gemcitabine (GEM) failure. The MST was 10.3 months in the combination group, which was significantly longer than the 6.6 months in the chemotherapy alone group. The pain relief results were also significantly improved in the combination group as compared with the chemotherapy alone group (57% vs. 20%, $P=0.000$). No serious complications were observed in this study. Ji et al. [57] reported a median overall survival of 12.2 months (95% confidence interval [CI] 11.1–12.7) for patients with HIFU therapy alone, combination with chemotherapy, and radiotherapy. The 6- and 12-month survival rates were 94.25% (95% CI 86.74–97.57%) and 50.85% (95% CI 38.17–62.21%), respectively. Complications included fatigue, abdominal pain, fever, nausea, and rash. Additionally, Marinova et al. [58] examined HIFU in 50 cases of un-resectable advanced PC and reported a median overall survival and progression-free survival of 16.2 and 16.9 months from diagnosis and 8.3 and 6.8 months from the intervention, respectively. In a study by Ning et al. [60] in 347 patients who underwent HIFU + GEM chemotherapy and 176 patients who received only GEM chemotherapy, the median overall survival was 7.4 and 6.0 months ($P=0.002$), respectively. The survival rates of the two groups at 6 months, 10 months, 1 year, and 2 years were 66.3% and 47.5% ($P=0.0001$), 31.12% and 15.9% ($P=0.0001$), 21.32% and 13.64% ($P=0.033$), and 2.89% and 2.27% ($P=0.78$), respectively. Thus, the survival rate was significantly improved in the combination group (Table 1).

Outcomes of HIFU for pancreatic cancer (Japan)

In Japan, a study to verify the safety of HIFU for advanced un-resectable PC was reported in 2014 [39]. The results of an efficacy analysis of 30 cases showed the mean number of treatments was 2.6 (2–4), and the mean treatment time was 2.4 h (1.3–4 h). The mean number of irradiations was 2285 (110–4085), the rate of sedative administration was 0%, and the rate of analgesic administration was 3.3%. The frequency of adverse events was 10%, and there were two cases of pancreatic pseudocysts, one of which was treated with endoscopic drainage, while the other case received conservative therapy. Delayed pancreatitis occurred in one case 2 weeks after treatment. There were no serious adverse events, and the authors concluded that HIFU for advanced un-resectable PC was safe and minimally invasive (Table 1).

Further, a study of 176 cases of advanced un-resectable PC reported in 2021 [68] found that the frequency of adverse events was 2.8%, none of which was serious. Early pain relief was observed in 63.8% of cases, and the therapeutic effects on the primary lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) were complete response (CR) in 0%, partial response (PR) in 20%, stable disease (SD) in 60.2%, and progressive disease (PD) in 27.8% of cases. The tumor control rate for the primary lesion was 72.2%. Regarding treatments after HIFU therapy, open surgery for PC removal could be performed in 4.5% of un-resectable PC cases. In addition, the mean post-diagnosis survival was significantly longer in 176 patients who underwent HIFU (648 days [21.3 months]) than in 100 patients who underwent chemotherapy alone (288 days [9.5 months]) ($P<0.001$). Additionally, the mean survival was significantly longer in the stage III group at 372 days (12.2 months) compared with the stage IV group at 220 days (7.2 months) ($P<0.001$). Taken together, these results suggest that HIFU contributes to prolonged survival in patients with PC (Table 1).

Meta-analyses and systematic reviews of HIFU for pancreatic cancer

To date, two meta-analyses and two systematic reviews on HIFU for PC have been reported. A 2014 meta-analysis [69] included a total of 23 studies: 19 randomized controlled trials and four clinical controlled trials. Of those studies, 14 reported on safety. The 6- and 12-month survival rates, efficacy rates, and clinical efficacy rates for the HIFU radiation chemotherapy group were significantly higher than those for radiotherapy ($P<0.05$), GEM monotherapy ($P<0.05$), GEM + cisplatin ($P<0.05$), and GEM + 5-fluorouracil ($P<0.05$). There were no serious adverse events, and the most common complications were skin burns and fever.

The other systematic review from 2014 [70] reported pain relief in 66.7–100% of patients, a MST of 11.25–12.4 months, and an overall survival time of 12.6 months (95% CI 10.2–15.0). In a 2015 systematic review [71] of 136 cases of advanced local PC from five studies, pain relief was observed in 79% of patients, and the MST was 10.0–12.6 months after HIFU alone or in combination with simultaneous chemotherapy. Another meta-analysis from 2017 [72] examined the usefulness of HIFU for pain relief in 729 cases of un-resectable PC from 23 studies. The pain-relief effect was 81% (95% CI 76–86), and the authors concluded that HIFU is an effective means of pain relief in patients with advanced PC.

In a 2018 systematic review of 581 cases from 17 studies [73], the tumor response of 120 patients from six studies was described. Complete regression was observed in 14%, ≥ 75% regression in 70%, 50–75% regression in 11%, 25–50% regression in 4%, and 0–25% regression in 1% of patients. Moreover, CR was observed in 10% and 5.1% of patients in two studies and PR in 38.5–70% of patients in six studies. Additionally, pain relief was described for 148 cases from nine studies. Complete or partial relief on a visual analog scale (75–100%) was observed in 83%, 50–75% relief in 8%, and 25–50% relief in 9% of patients.

The most recent meta-analysis from 2021 [74] examined 992 cases of un-resectable PC from seven studies. Survival was longer in the combination therapy group of HIFU plus chemotherapy compared with the chemotherapy alone group, with a hazard ratio of 0.40 (95% CI 0.28–0.58). Moreover, the 1-year survival rate was significantly higher in the combination therapy group (odds ratio 0.35, 95% CI 0.22–0.53, $P < 0.001$).

The results of these meta-analyses and systematic reviews indicate that HIFU has antitumor and pain-relieving effects on advanced PC, though higher quality evidence is needed for clinical application. Further research using standardized and unified assessment criteria is needed.

New developments in HIFU for pancreatic cancer

HIFU has many potential uses, including relieving pain and other symptoms, promoting antitumor effects, prolonging survival, enhancing drug delivery (drug penetration), and strengthening specific immunity for cancer [11–16, 22, 27, 30, 32, 43, 62, 63]. At present, the results of various other studies are awaited, including those examining the abscopal effect from the tumor immune response [16], preoperative HIFU aimed at R0 resection for un-resectable local advanced PC for which chemotherapy or chemo-radiotherapy was successful [68], low-power cumulative HIFU therapy [75, 76], drug delivery therapies [77], and sonodynamic therapy [77].

Conclusion

HIFU is a cutting-edge therapy for PC. However, further study through animal experiments and clinical research, as well as the accumulation of more cases and improved device performance, are needed. At present, HIFU is used in combination with systemic chemotherapy to achieve local antitumor effects and pain relief in patients with un-resectable PC. Unlike radiation therapy, HIFU can be performed as many times as needed. As novel chemotherapies develop, HIFU is expected to exhibit an even greater effect on prolonging survival through synergistic effects with these new regimens. Previous clinical studies have indicated that HIFU can be performed safely to treat un-resectable PC. In future, this method could be a minimally invasive addition to treatment strategies for patients with PC with a poor prognosis.

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Declarations

Conflict of interest Atsushi Sofuni, Yasutsugu Asai, and Takao Itoi declare that they have no conflicts of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

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