

The current potential of high-intensity focused ultrasound for pancreatic carcinoma

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Abstract

Introduction Pancreatic carcinoma has one of the poorest prognoses among malignant tumors. Many pancreatic carcinoma patients who undergo common treatments, such as surgery, radio-chemotherapy and chemotherapy, gained little benefit because of the histological characteristics.

Materials and methods HIFU is a new technique of noninvasive treatment for unresectable pancreatic carcinoma. HIFU has the ability to ablate the deep tissues inside body from an external source using high-intensity focused ultrasound. The effects of HIFU can result in cell destruction and tissue necrosis.

Results Results from study in China in 251 patients with advanced pancreatic carcinoma suggested that HIFU treatment could reduce the size of tumors without causing complications and prolong survival. Moreover, according to some reports from China, HIFU treatment is suggested to be useful as the one of palliative treatments for unresectable pancreatic carcinoma. Our case of HIFU therapy for pancreatic carcinoma is presented including pathological findings in this paper. The results suggested that HIFU treatment might be effective in controlling local tumor.

Conclusion HIFU therapy may have the possibility of becoming one of the combination therapies for treating pancreatic carcinoma in the future.

Keywords High-intensity focused ultrasound (HIFU) · Pancreatic carcinoma

Introduction

The yearly mortality due to pancreatic carcinoma exceeds 200,000 [1] worldwide and is increasing. Even with recent advances in diagnostic imaging technology, most cases of pancreatic carcinoma are only discovered at an unresectable stage, when the prognosis is poor and the 5-year survival rate is <1% [1]. To date, multimodality therapy, consisting of chemotherapy with 5-fluorouracil (5-FU) [2] and radiotherapy [3], has been the standard treatment for unresectable pancreatic carcinoma. Since the results of these treatments were unsatisfactory, gemcitabine (GEM) (Eli Lilly Japan, Kobe, Japan) has recently become the standard chemotherapy medication for unresectable pancreatic carcinoma, and GEM is expected to both increase antitumor efficacy [4] and improve clinical benefit response (CBR) [4]. However, it cannot be said that the results of chemotherapy are sufficient for unresectable pancreatic carcinoma. Therefore, new advances in therapy are required for these patients.

Recently, the technique of ultrasound has been developed. Its use has spread not only to diagnostic imaging and needle guidance or biopsy for percutaneous procedures but also to directed therapy for tumors. Ultrasound technology has been developed to use focused ultrasound energy for therapeutic purposes, such as tissue ablation. High-intensity focused ultrasound (HIFU) is being promoted as a method to ablate the tumor and achieve pain relief in unresectable pancreatic carcinoma. HIFU therapy is regarded as minimally invasive or noninvasive therapy and has few side effects, unlike radiofrequency therapy. Therefore, it may be possible to combine HIFU with chemotherapy as a minimally invasive combination therapy.

This article provides a summary of HIFU, that is, the principles, method, effects, cases of HIFU therapy, and current clinical application for pancreatic carcinoma.

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The principles of HIFU

HIFU has the ability to deliver high-intensity focused ultrasound from an external source into deep tissues, with a large convergence angle. The combination of thermal, mechanical (cavitation), and biological effects can result in cell death and tissue necrosis [5]. The device is used clinically to treat both benign and malignant solid tumors [5]. HIFU differs from the traditional hyperthermal therapy. The results of previous animal experiments have shown that transient temperatures were 70–100°C at the focal point inside the body [6]. Results presented in this paper showed that HIFU can destroy tumors or restrain the growth of tumor tissue. The hyperthermia due to HIFU (which can reach temperatures higher than 70°C in the targeted area) causes necrosis, liquefaction, absorption, and fibrosis of tissues [5], which could bring about the effects of HIFU thermal therapy.

Clinical history of HIFU

Lindstrom [7] and Fry et al. [8] investigated the possibility of using high-intensity ultrasound for therapy of neurological disorders in the 1950s. Subsequently, ultrasonic therapy for tumors was investigated in the 1970s, although using only low-intensity ultrasound [9]. The concept was to produce hyperthermia within the tumor, maintaining the elevated temperature for a certain period of time. However, this method lacked sufficient control to reach and maintain a consistent temperature within the tumor. The first clinical application which used high-intensity ultrasound was in the treatment of kidney stones using extracorporeal shockwave lithotripsy (ESWL) in the 1980s [10]. The development of technology such as magnetic resonance thermometry brought about the innovation of HIFU for the treatment of tumors in the 1990s. Moreover, it has been recognized that HIFU can give rise to almost immediate cell death by coagulation necrosis in selected regions of tissue, raising the possibility of a new treatment for tumors [11–13].

New kinds of HIFU systems have been developed by several companies recently. HIFU systems fall into two types of method: bombardment from outside the body and transendothelial rectum bombardment.

Those systems using bombardment from outside the body include Haifa (Insightec, Ltd, Israel), CZ901 (Mianyang Sonic Electronic, China), Chongqing HIFU (Chongqing HIFU, China), Sonablate 500 (Focus Surgery, Inc., USA), FEB-BY Series HIFU System (China Medical Technologies, Inc., China). Transendothelial rectum bombardment is used by EDAP (Edap Technomed Inc., France). Of these, it is expected that the FEB-BY Serial HIFU System (China Medical Technologies, Inc., China) is the HIFU system which will receive the most attention.

Characteristics of the FEB-BY Series HIFU therapy system

The CMT FEP-BY Series HIFU therapy system (Fig. 1) has the capacity to deliver high-intensity focused ultrasound from an external source deep into tissues, with a large convergence angle. The focus is oval in shape and is approximately 3 mm in diameter and 10 mm in length. The combination of thermal and mechanical (cavitation) biological effects can result in cell death and tissue necrosis. The device is clinically used to treat both benign and malignant solid tumors.

The main characteristics of this system are as follows: (1) Noninvasive procedure: treatment performed with this HIFU therapy system does not require incisions or transfusions, thus minimizing the risks and complications associated with invasive procedures. (2) Minimal side-effects: the large aperture of the transducer produces less intense ultrasound waves at the point of skin penetration, significantly reducing the likelihood of skin burns and collateral damage to healthy body tissue. (3) High degree of safety: treatment can be performed without anesthesia and does not cause significant discomfort, skin-burn, or hemorrhage. (4) Treatment for a broad range of tumors: the two-transducer system enables the HIFU therapy system to target a wide range of tumors including those of the liver, breast, kidney, pancreas and so on.

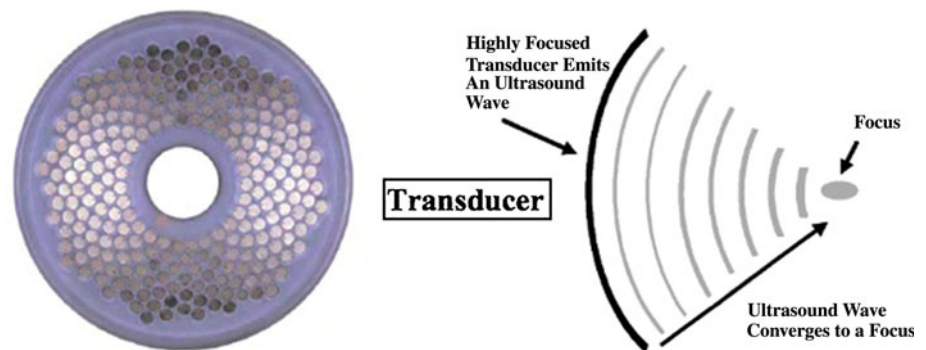
This instrument also has some advantages in comparison with those of other companies. These include ultrasound imaging guidance, no anesthesia needed, two transducers, spherical direct focus, and temperature monitoring. Furthermore, this device has been recently updated to add some new functions, such as a temperature monitoring system, a respiratory monitoring system, three-dimensional treatment planning, and real-time monitoring. Monitoring the focal temperature produces more effective therapy and is achieved by analyzing the echo signals acquired by the system before and after HIFU exposure. It reduces the targeting of unintended tissue caused by movement. The device automatically analyzes the respiratory status of the patient using real-time B-mode ultrasound images; allows consistent delivery of HIFU energy during either end expiration or inspiration; allows for accurate targeting of the tumor regardless of the geometry; and provides B-mode images of the treatment plane which are captured between pulse emissions.

The characteristics of the HIFU transducer are as follows (Fig. 2): frequency 1.1 MHz; aperture diameter 37 cm; radius of curvature 25.5 cm; and 251-element array. Each ceramic piezoelectric unit is selected from tens of thousands of units. In order to achieve high focusing accuracy and stability, each transducer is made of hundreds of elements with the same frequency. The wide angle of

Fig. 1 FEP-BY Series high-intensity focused ultrasound (HIFU) therapy system. The system includes computer control, a GE ultrasound imaging system, and a treatment table with dual transducers



Fig. 2 Principles of the HIFU therapy system. The energy level reaches 150,000 times that of normal US. Tissue temperatures reached more than 60°C within one second and coagulative necrosis occurred within a few seconds



convergence (80°) of the high-intensity ultrasound beam keeps the acoustic intensity at the skin surface below the threshold for pain and skin burns. A large-aperture transducer creates a wide convergent angle to decrease the acoustic intensity at skin level, avoiding skin burn.

The HIFU therapeutic unit has an output power of 1–2 kW, an effective treatment depth of 3.5–14.0 cm, a therapy medium of degassed water, a practical focused volume of 0.3 cm × 0.3 cm × 0.8 cm (Fig. 3), and an effective focused volume of 0.6 cm × 0.6 cm × 1.0 cm. According to one report [14], the point accumulation method was applied to form the treatment matrix. Larger tumors can be fully treated by dividing them into several treatment segments. Energy is delivered in a pulsed mode. Treatment parameters are: transmit time (t1), interval time (t2), input power, and number of pulses. Primary parameters are: output power of 1–2 kW; transmit time (t1) of 0.1–0.28 s; an interval between shots of t2, t1:t2 = 2:1; and number of treatment shots at each spot (T) of 30–80 times. All of the parameters can be properly adjusted according to the location and depth of the tumor, the density of the tumor tissue, and the attenuation of ultrasound.

Case presentation

The treatment of our first case of unresectable pancreatic carcinoma at our institution is presented below, including the practical methods.

The patient had multiple episodes of acute pancreatitis since August 2006. He also had a lower bile duct stricture, and was admitted to our institution for diagnosis. His diagnosis was autoimmune pancreatitis with related sclerosing cholangitis, and he was checked regularly. A mass of 30 mm was seen in the pancreas body on CT imaging in September 2007; no mass had been seen on CT in July. The mass was diagnosed as pancreatic carcinoma by percutaneous biopsy. The tumor was inoperable because of invasion of the superior mesenteric artery (SMA). After adequate intensive care, chemotherapy in combination with HIFU was performed.

Chemotherapy began on November 7, 2008. HIFU therapy was performed on December 1, 2008.

None of the patient's laboratory data were abnormal apart from minimal tumor marker elevation. Physical findings were normal. The ultrasound (US) images (B-mode and contrast-enhanced ultrasonography; CE-US)

Fig. 3 Principles of the HIFU therapy system. The CMT FEP-BY Series system has the ability to deliver high-intensity focused ultrasound from an external source into deep tissues, with a large convergence angle. The focus is oval in shape and is approximately 3 mm in diameter and 10 mm in length. Transducers have multi-element array and concave focusing. The patented multi-element array technology ensures an even acoustic field. The angle of convergence is 80° and the size of the focal point is smaller than $3\text{ mm} \times 3\text{ mm} \times 10\text{ mm}$

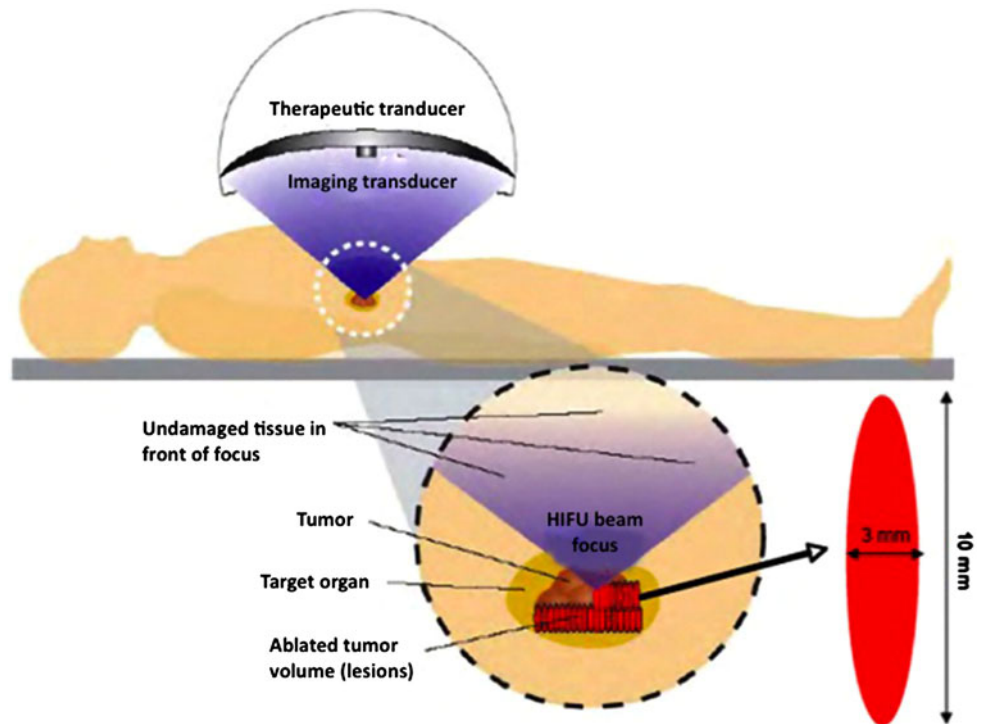
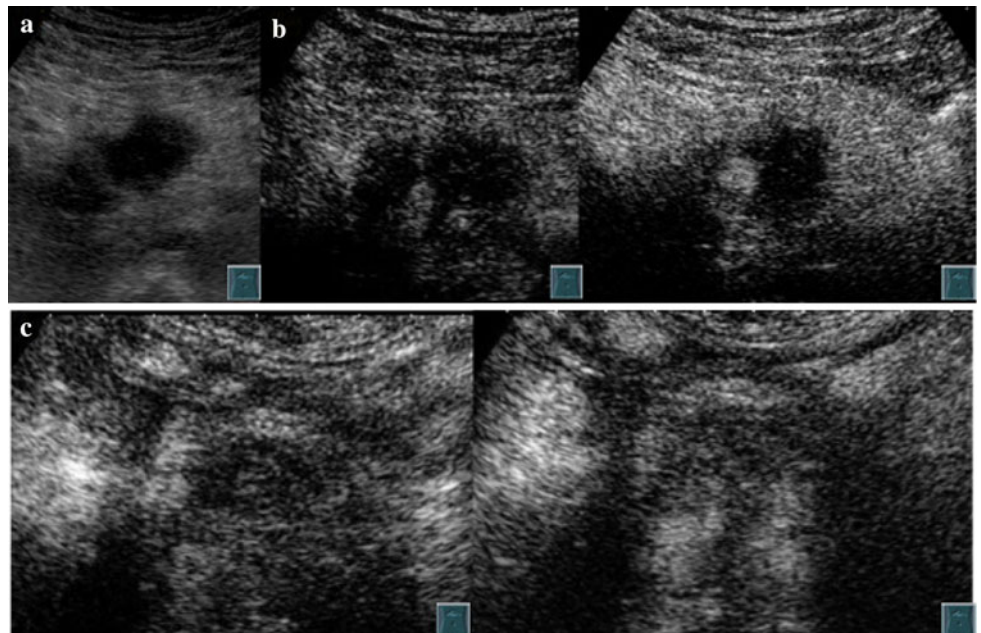


Fig. 4 US imaging before HIFU therapy. **a** The tumor before chemotherapy was visualized as a hypo-echoic mass near the SMV in B-mode US. **b** CE-US imaging before chemotherapy shows hypovascularity. **c** CE-US imaging after chemotherapy and before HIFU therapy shows increasing blood flow inside the tumor



and CT images are shown in Figs. 4 and 5. The tumor was visualized as a hypo-echoic mass near the superior mesenteric vein (SMV) in B-mode US. After chemotherapy but before HIFU therapy, CE-US showed an increase in blood flow inside the tumor though CE-US imaging had shown only hypovascularity before chemotherapy [15]. This changed image was used for comparison with the images

after HIFU therapy. CT imaging demonstrated that the tumor had low density (Fig. 5).

The position, size, and morphological aspects of the tumor, and the tumor's relationship to the adjacent organ were determined from imaging equipment before treatment. The intestinal cavity was cleaned by the patient fasting, taking oral laxative medication, and drinking

Fig. 5 CT imaging before HIFU; the tumor shows low density

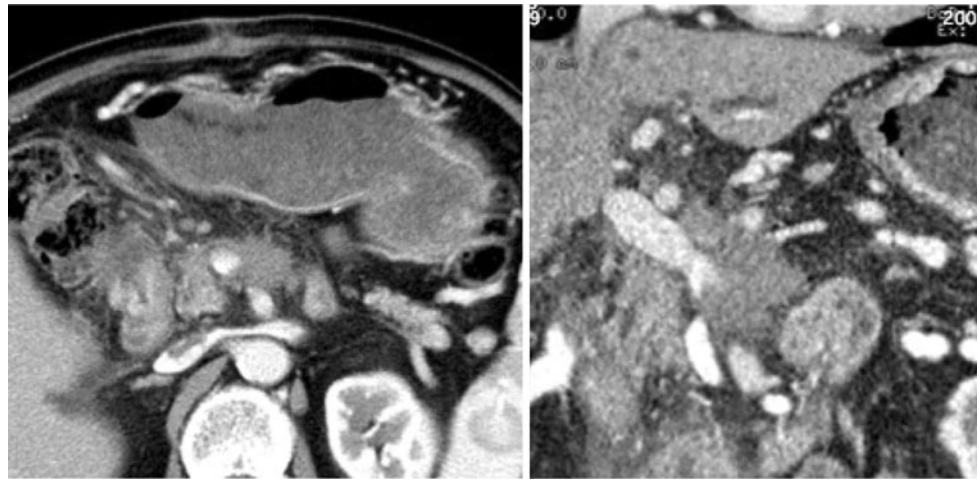
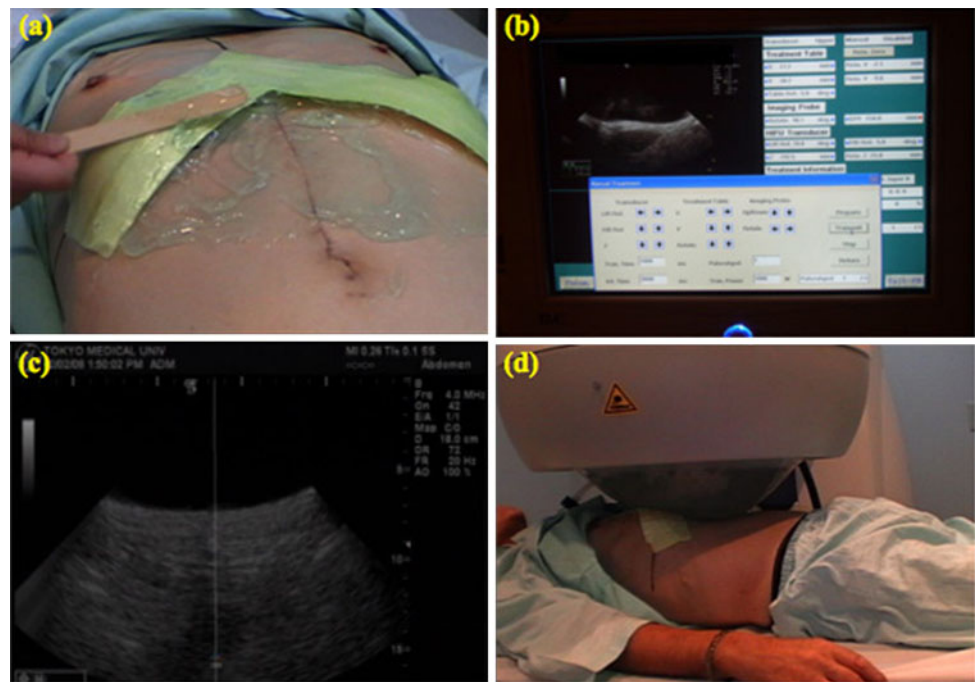


Fig. 6 Preparations for HIFU. **a** Echo jelly was painted thickly over the bombardment area. **b–d** The treatment range, treatment layers, and power were defined by a B-mode ultrasound scanner monitoring system. The treatment probe was then moved according to the planned procedure



degassed water. During treatment the patient lay on a treatment table facing down. Echo jelly was painted thickly over the bombardment area. B-mode ultrasound scanner monitoring system was used to define the treatment range, treatment layers, and power, and then the treatment probe was moved according to the planned procedure (Fig. 6).

HIFU therapy was performed four times over the course of 10 days, each treatment lasting about an hour and a half (Fig. 7). Treatment parameters were as follows: transmit power 500–1,000 W; 200 × 3–4 pulses/spot; transmit time (t_1) 150–1,000 ms; interval time (t_2) 150–3,000 ms; 47 treatment points in total. Anesthesia and analgesic drugs were not required during treatment. No accidents or complications (including skin-burn) occurred.

After HIFU therapy, no apparent change was seen on CT imaging (Fig. 8). However, B-mode US revealed hyper-echoic changes in the area of HIFU therapy (Fig. 9). CE-US imaging also revealed some more interesting changes. Isovascularity of the tumor before HIFU therapy had changed to hypovascularity in the area of HIFU therapy, that is, the blood flow of tumor inside increasing before HIFU therapy was decreased after HIFU therapy (Fig. 10).

Percutaneous biopsy was performed after treatment of HIFU about 1 month later. The results of histopathology, using HE and immunostaining imaging, revealed a few viable carcinoma cells inside the tumor. However, there was no finding of increasing in tumor and liver metastases in temporal images. Unfortunately, this patient died from

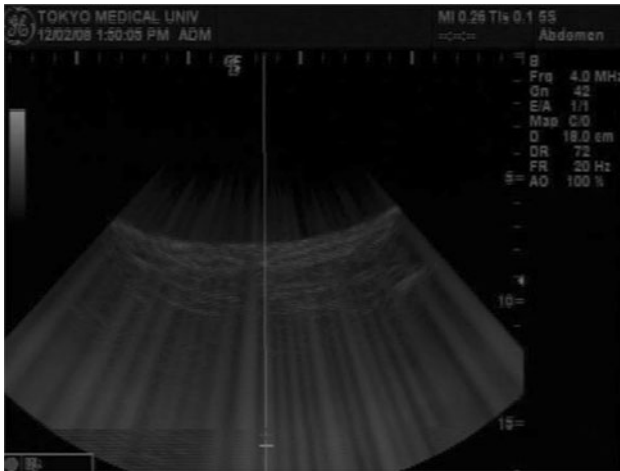


Fig. 7 US imaging during HIFU therapy

Fig. 8 CT imaging after HIFU therapy shows no apparent change

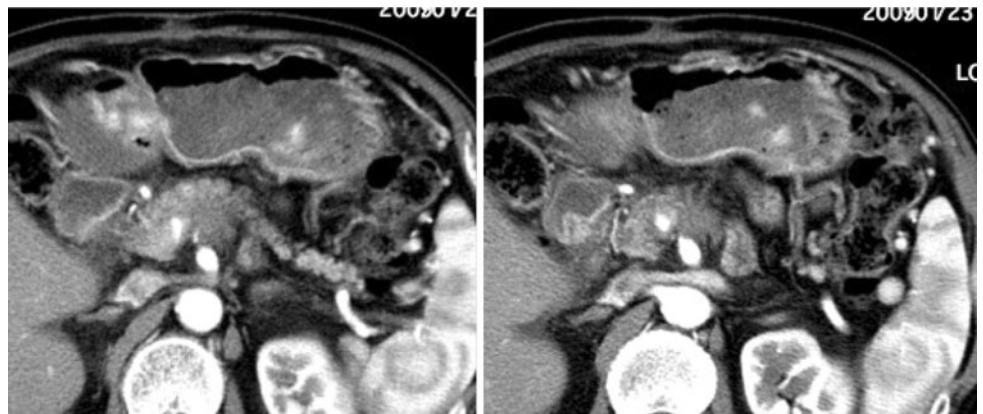
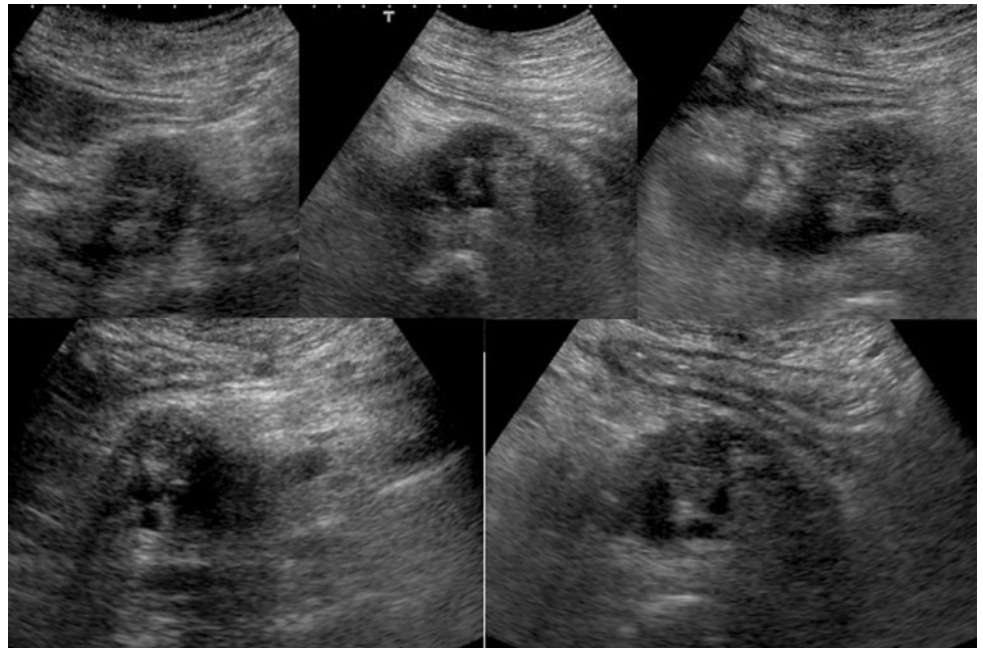


Fig. 9 B-mode US after HIFU therapy. B-mode US visualized hyper-echoic changes (except SMV) in the area of HIFU therapy

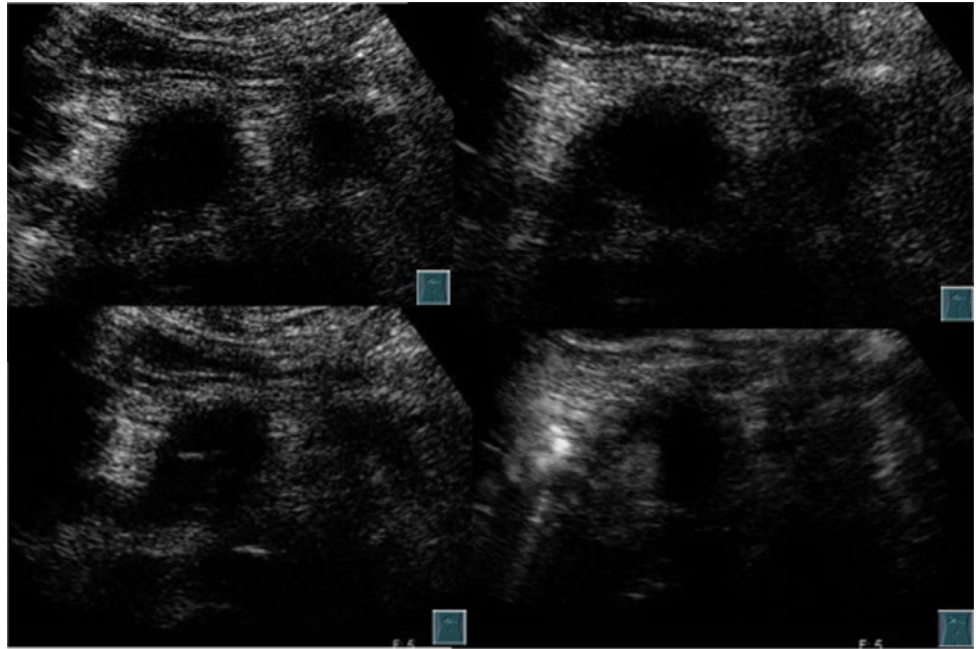


carcinomatous peritonitis in our affiliated hospital 10 months after HIFU treatment. At autopsy, the tumor which had been treated by HIFU was replaced by a scar, and there was no apparent mass lesion in the area. The branch of large vessel through the tumor had not been destroyed (Fig. 11a–c). In addition, HE and immunostaining images only showed a very few viable tumor cells which were a little scattered (Fig. 11d, e). Furthermore, the vasculature of the branch of large vessel through the tumor had remained after HIFU treatment without being destroyed (Fig. 11e).

Discussion

HIFU is a new technique of noninvasive treatment for unresectable pancreatic carcinoma. HIFU has the ability to

Fig. 10 CE-US imaging after HIFU therapy. Isovascularity imaging of the tumor before HIFU therapy changed to hypovascularity in the treated area

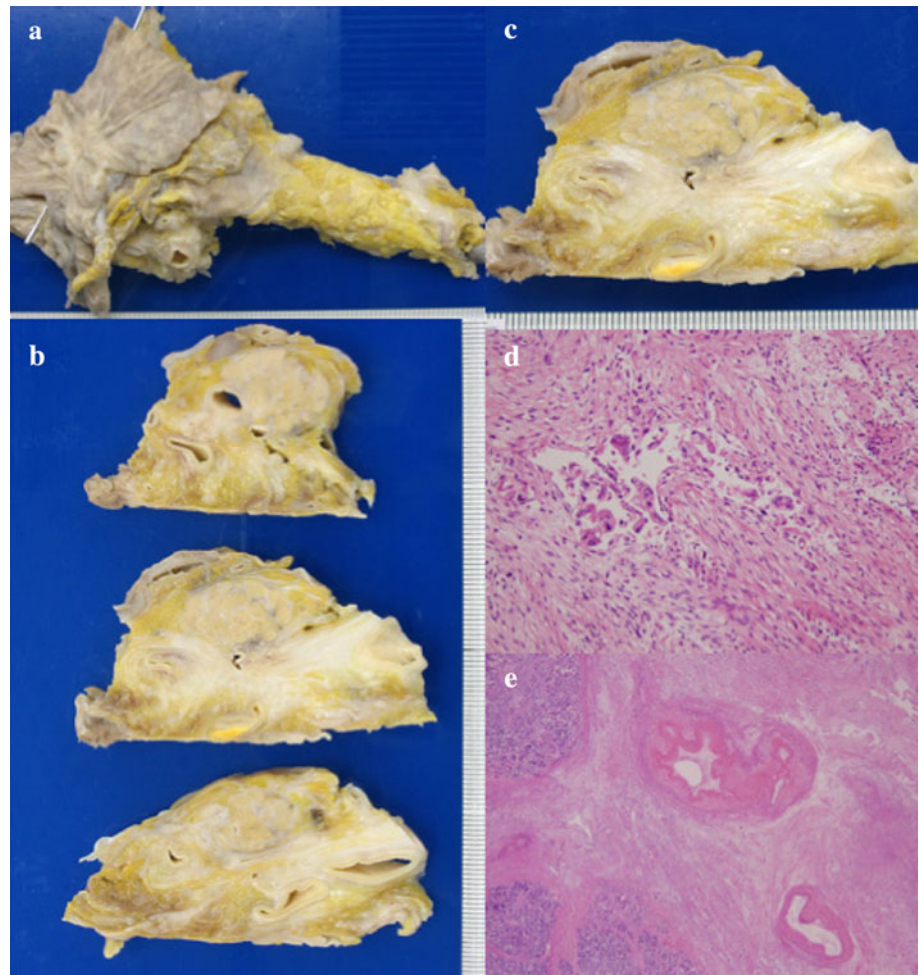


ablate deep tissues inside the body using high-intensity focused ultrasound from an external source. HIFU can cause cell destruction and tissue necrosis and differs from traditional hyperthermal therapy. Previous animal experiments have shown transient temperatures of between 70 and 100°C at the focal area inside the body [6]. According to this paper, HIFU can destroy tumors or restrain the growth of tumor tissue. Hyperthermia due to HIFU can reach temperatures higher than 70°C in the targeted area, which then causes necrosis within a few seconds, liquefaction, absorption, and fibrosis of tissues. The effects of HIFU [5] are thought to be thermal effects, mechanical effects, biological effects, coagulation necrosis, apoptosis, and non-linear effects. Mechanical effects, such as cavitation, microstreaming, and radiation forces, are associated with high intensities. At the level of biological effects, high-intensity ultrasound can result in tissue heating and necrosis, cell apoptosis, and cell lysis. Coagulation necrosis occurs in tissue exposed to high-intensity ultrasound when the temperature of the tissue is elevated to a certain level for a certain time. Moreover, although most initial cell death in tissues exposed to HIFU is caused by cell necrosis from thermal injury, HIFU can also induce apoptosis. Nonlinear effects are observed at high acoustic intensities, resulting in faster attenuation of the ultrasound energy and faster tissue heating. The pathological findings of our case showed the fibrosis change of ablated tumor. This means that HIFU therapy can bring cell necrosis and apoptosis, and progress cell destruction and fibrosis. This suggested that HIFU treatment could be useful for local tumor control.

Pancreatic carcinoma is one of the most common malignant tumors. Treatment is difficult due to its fast progression. The median survival with pancreatic carcinoma is about 6 months. In addition, many pancreatic carcinoma patients who undergo common treatments, such as surgery, radio-chemotherapy, and chemotherapy, receive little benefit because of the histological characteristics. It seems that HIFU therapy may benefit local tumor control, as in our case. Treatment with HIFU will be useful for those patients who develop symptoms, and may become a palliative treatment for pancreatic carcinoma. Results of a study in China of 251 patients with advanced pancreatic carcinoma have suggested that HIFU treatment could reduce tumor size without causing complications, and prolong survival [16]. An interesting finding was that 84% of patients with pain due to pancreatic carcinoma obtained significant relief of their pain after treatment with HIFU. According to some reports from China [14, 17–23], HIFU treatment may be useful as a palliative treatment for unresectable pancreatic carcinoma. HIFU may be noninvasive and effective, but is a new technique and many aspects require inspection. Therefore, HIFU treatment cases should be gathered, and randomized controlled trials should be conducted to determine the results of HIFU treatment for pancreatic carcinoma in terms of local tumor response and clinically beneficial outcomes, e.g. by improving pain, functional status, quality of life, or survival.

In conclusion, the clinical applications of HIFU therapy have begun a new era of noninvasive local treatment. HIFU

Fig. 11 Autopsy images. **a–c** Macro-imaging: the area of tumor which had been treated by HIFU was replaced by a scar, and no apparent mass lesion was found in the area. The branch of large vessel through the tumor had not been destroyed. **d, e** Micro-imaging; HE images showed a very few viable tumor cells, which were a little scattered. Furthermore, the vasculature of the branch of large vessel running through the tumor was not destroyed



therapy may become one of the combination therapies for pancreatic carcinoma in the future.

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