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### **Ultrasonics Sonochemistry**

journal homepage: www.elsevier.com/locate/ultson



# Preoperative ultrasound ablation for borderline resectable pancreatic cancer: A report of 30 cases



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#### ARTICLE INFO

Article history: Received 30 April 2015 Accepted 13 May 2015 Available online 9 June 2015

Keywords:
Pancreatic cancer
Borderline resectability
High-intensity focused ultrasound
RO resection

#### ABSTRACT

Background and objectives: Currently, extended resection and preoperative neoadjuvant chemotherapy are the two main modalities for improvement of the resection rate and R0 resection rate of borderline resectable pancreatic cancer. The past few years, however, have witnessed some progress in the treatment of unresectable pancreatic cancer with high intensity focused ultrasound (HIFU). The aim of this study is twofold: first, to evaluate the feasibility and safety of HIFU ablation as a preoperative adjuvant therapy for borderline resectable pancreatic cancer, and second, to conduct pathological analyses to verify the safety and effectiveness of HIFU treatment of pancreatic cancer.

Methods: From January 2011 to December 2012, 30 patients with borderline resectable pancreatic cancer underwent HIFU ablation by Haifu Model-JC200 Focused Ultrasound Tumor Therapeutic System prior to radical surgery. The effect of pre-operative HIFU ablation was evaluated by post-HIFU functional imaging results, operation time of radical surgery, blood loss volume, R0 resection rate, postoperative 1-year survival rate and Ca199 curve. Postoperative pathological specimens were obtained for histological examination.

*Results:* All 30 patients with borderline resectable pancreatic cancer had completed the treatments and follow-ups. Functional image assessment after HIFU treatment showed a mean tumor ablation rate of  $(61.5 \pm 24.3)$ %. 28 patients underwent radical resection of pancreatic cancer 7–9 days after HIFU treatment (23 cases underwent pancreaticoduodenectomy. 4 patients underwent pancreatectomy and 1 patient had total pancreatectomy). 7 patients underwent combined resection and reconstruction of portal-superior mesenteric vein (23.3%), with the resectability rate of 93.3%, the R0 resection rate of 92.7%, and the 1-year survival rate of 96.7%. The biological coagulative necrosis regions identified by the postoperative pathological examination matched well with the necrosis foci identified by post-operative functional imaging.

Conclusion: The effectiveness of HIFU ablation of pancreatic tumors, as well as interstitial tissues within he main vascular spaces was confirmed by post-operative pathological examinations. Based on these observations, we conclude that preoperative HIFU ablation of borderline resectable pancreatic cancer can significantly improve the resection rate, RO resection rate, and reduce the difficulty and risk of surgery. Therefore, HIFU may be a valuable pre-operative adjunct therapy for resectable pancreatic cancer. However, the safety and the efficacy on the improvement of the surgery need to established with future multicenter, randomized studies.

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#### 1. Introduction

Pancreatic cancer is one of the most common malignancies with the poorest prognosis. More than 200,000 people all over the world die of it each year, with the high mortality/incidence ratio of 0.91 and a 5-year survival rate of less than 5% in the United States [1]. Surgical resection remains to be the only modality with an intent

of cure, however, only 10–20% of patients with pancreatic cancer of all stages are eligible for surgical resection [6] and the postoperative 5-year survival rate is only at 15–25% [2–5]. While vascular invasion is the main obstacle for operability, it is not the absolute contraindication for surgical resection. The assessment of operability of pancreas is mainly based on the imaging examinations, among which thin-section contrast-enhanced CT and three-dimensional reconstruction are currently the most optimal method [7,8]. A portion of pancreatic carcinomas that present invasion of the peripancreatic blood vessels have posted an uncertain for

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resectability, and have gradually raised clinical attention. The criteria for borderline resectable pancreatic cancer based on CT anatomy were outlined: the common hepatic artery is circumvoluted by small tumor segment; celiac trunk has no tumor infiltration and after tumor resection, the tract can be reconstructed; the superior mesenteric artery involvement is less than semirevolution (≤180); the proximal part of the superior mesenteric vein or the portal confluence is obstructed, with blood vessels above and below suitable for reconstruction [9,10]. The portal venous system is often invaded by borderline resectable pancreatic cancer located at pancreatic head. A combined resection and reconstruction of portal-superior mesenteric vein system is a feasible way to improve the RO resection rate, with a reasonable level of safety [11]. According to the report of Tseng et al., the median survival time of patients with pancreatic cancer suitable for a combined vein resection was longer than that of those who did not receive the surgery due to local vascular invasion [12.13].

More centers preferred to perform a neo-adjuvant therapy, mostly, radiotherapy and chemotherapy for borderline resectable pancreatic cancer prior to a resectability evaluation, which, combined with surgery, have prolonged the median survival time for patients, when compared with those received no surgery [14], and increased the R0 resection rate [15]. Meta analysis showed that about 1/3 of the patients with borderline resectable pancreatic cancer could receive radical resection after neo-adjuvant therapy, with no difference in their postoperative survival time than that of patients with resectable pancreatic cancer [16]. However, neo-adjuvant radiotherapy and chemotherapy have some adverse effects. Therefore, clinical scientists have been seeking alternative adjunctive therapies.

HIFU is an emerging non-invasive local modality for cancer therapy. It can induce instantaneous coagulative necrosis of tumor cells in the target area due to the collective thermal, mechanical, and cavitation effects caused by the instant heat generated after high intensity ultrasound has penetrated into the body and is focused on the target, achieving in situ ablation of tumors. Good penetration and safety of ultrasonic energy through the large vessels [17], and the safety of conducting ultrasound ablation in pancreas tissues [18] have been established. Few medical centers have deployed HIFU in the treatment of unresectable pancreatic carcinoma, mainly to alleviate symptoms and to improve the quality of life. Enhanced treatment efficacy has been observed by CBR evaluation [19]. However, the safety and effectiveness of HIFU are yet to be verified by histological examinations.

In the current study, HIFU was employed as the palliative treatment of the advanced stage of pancreatic carcinoma, and was used as a preoperative adjuvant therapy for borderline resectable pancreatic carcinoma. A retrospective analysis was conducted on thirty cases of borderline resectable pancreatic carcinoma due to local vascular invasion, in which preoperative HIFU ablation combined with radical excision was performed between January 2011 and December 2012.

#### 2. Materials and methods

#### 2.1. Inclusion criteria

All cases enrolled in the treatment group met all of the following five criteria: 1. Pancreatic cancer was confirmed by diagnostic imaging or biopsy; 2. Distant metastasis was excluded by PET-CT or abdomen-thorax CT; 3. The circularity and invasion of the peripheral vessels were assessed with thin-section contrast-enhanced CT (2 mm), according to the standards of resectable borderline pancreatic cancer set by M.D. Anderson Cancer Center, and had met at least one of the following criteria:

common hepatic artery is circumvoluted by small tumor segments; celiac trunk is not infiltrated, tumor can be resected and the digestive tract reconstructed; the superior mesenteric artery involvement is less than semirevolution ( $\leq$ 180); the proximal part of the superior mesenteric vein or the portal confluence is obstructed, with blood vessels above and below suitable for reconstruction; 4. The patient was able to endure general anesthesia for operation during hospitalization; 5. The patient and his/her family were fully informed of and consented to the new comprehensive tumor treatment based on surgical excision. The treatment protocol was approved by the local ethics committee.

#### 2.2. HIFU therapy

High-intensity focused ultrasound therapy system IC200 (Chongging Haifu Technology Co., Ltd) was used for the HIFU treatment in this study, with the built-in two-dimensional ultrasound imaging to locate and monitor the treatment process. Obstruction of acoustic path was eliminated by ultrasound pre-positioning before treatment. The patient was placed in prone position after general anesthesia intubation, with the abdomen submerged in a water balloon filled with degassed water. Another adjustable degassed water balloon was placed between the head and abdomen and to press against the upper abdomen. During the treatment, 200-400 ml degassed water was injected into indwelling gastric tube (extracted after operation), so as to improve the acoustic path, to reduce gas interference in intestinal tract, and to expose the pancreatic tumor clearly. The major parameters of ultrasonic probe of JC200 system were as follows: ultrasonic frequency delivered at 0.8 MHz focal length of 130-150 mm. The probe monitor was in sagittal view. The solid region of tumor was divided into different treatment planes with an interval of 3-5 mm. Spot scanning was used in treatment with its scanned area limited strictly within the tumor, being 0.5-1.0 cm apart from the tumor margin detected by ultrasonic image, and the distance increased accordingly in the high-risk areas. The selection of acoustical power and frequency followed a gradual process. starting with a low dosage of 150-200 w with a single treatment time of 1 s and the interval time of 3 s and were increased gradually thereafter. Two-dimensional ultrasound image changes in focal area were monitored for determining the maximum acoustical power where echogenicity was significantly enhanced or a high echogenic mass was detected in focal area. For cases in which the characteristic echogenic changes were absent, the swept-focus was limited within the absolutely safe area, with the total treatment power lower than 280 w and the total treatment time less than 500 s/cm<sup>3</sup>. High power and high frequency were used for the tumor segment near the blood vessel in the early phase of the operation. Ultrasound findings of enhanced echogenicity in the entire tumor area or high echogenic mass covered from deep to shallow tissues indicated the onset of coagulative necrosis in the targeted region and thus the treatment could be terminated. Tumors that had rich blood supply showed in pre-operative CT were imaged and compared by ultrasonography before and after the treatment to confirm the effectiveness of HIFU.

#### 2.3. Post-HIFU procedure and evaluation

All of the 30 patients undergoing HIFU were exuberated in the operation room, and observed in ICU for 12 h before returning to the general ward. Postoperative procedures included routine fasting for 72 h, analgesia, acid suppression, and gastrointestinal mucosa protection. Pancreatin was measured at 1 d and 3 d to record adverse reactions like gastrointestinal injury and acute pancreatitis. Thin-section contrast-enhanced CT was performed 5 days

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