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● *Original Contribution*

HIGH-INTENSITY FOCUSED ULTRASOUND TREATMENT OF LATE-STAGE PANCREATIC BODY CARCINOMA: OPTIMAL TUMOR DEPTH FOR SAFE ABLATION

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Abstract—Objective criteria are currently not available for assessing the extent of ablation by high-intensity focused ultrasound (HIFU). A retrospective review was conducted in Chinese patients with late-stage pancreatic body carcinoma treated with 1 h/d intermittent HIFU at a single center. Clinical and procedure-related characteristics were examined in relation to tumor posterior depth. Clinically, tumor ablation was negatively correlated with posterior tumor depth, with a 1-cm increase in depth decreasing ablation by 30.7%. At a computed tomography (CT)-determined 7-cm posterior tumor depth (considered the critical value for the procedure), ablation sensitivity and specificity were 77.8% and 72.7%, respectively. Tumor ablation >30% in patients with a CT-determined posterior tumor depth ≤7 cm was 9.333 times better than that in patients with a CT-determined posterior tumor depth >7 cm. Adverse effects did not affect the efficacy of HIFU. Tumors with posterior depths <7 cm may effectively be treated with HIFU-induced ablation with minimal adverse events. (E-mail: ghyzmw@163.com or huiyugemedsci@163.com and xiongliulin@sina.com)

Key Words: **High-intensity focused ultrasound, Ultrasound, Computed tomography, Depth, Pancreatic cancer, Carcinoma, Ablation, Safety profile.**

INTRODUCTION

Pancreatic cancer, which is most commonly diagnosed during its late stages, is responsible for 200,000 deaths worldwide each year—an extremely high mortality rate virtually equal to its incidence rate (Michaud 2004). In developed countries, approved pancreatic cancer treatments include invasive pancreatectomy or gastric bypass surgery; radiation therapy, chemotherapy and chemoradiation therapy; and targeted therapies. However, novel therapeutics still in clinical trials are openly recommended as the best treatment alternative for many pancreatic cancer patients by the U.S. National Institutes of Health (NIH 2013). Thus, there is an urgent need to advance our knowledge of the safety profile, efficacy and best practices for pancreatic cancer treatment modalities that have so far been successful in pre-clinical trials.

High-intensity focused ultrasound (HIFU) is a novel therapeutic modality used successfully in pre-clinical trials that allows the non-surgical treatment of various benign and malignant solid tumors, including unresectable pancreatic cancer (Horner et al. 2009; Wu et al. 2005; Xiong et al. 2009; Zhao et al. 2010). Moreover, HIFU remains the only effective non-surgical alternative for treatment of late-stage pancreatic cancer (Dubinsky et al. 2008). HIFU destroys tumor cells by raising local tissue temperatures as high as 60°C with converging ultrasound waves that can penetrate tissues, resulting in effective tissue ablation without the need for surgical incisions. However, there is a relatively high risk of damage to adjacent tissues (He et al. 1999; Jang et al. 2010). In addition, no comprehensive experimental data sets or mathematical models have been generated

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that objectively predict the extent of effective ablation and HIFU parameters in humans.

In the past year, a number of pre-clinical studies have used computed tomography (CT)-guided techniques to increase the precision and reliability of HIFU treatment (Cao and Jiang 2013; Jensen et al. 2012; Lee et al. 2013), a critical first step in achieving reliable clinical results. CT perfusion (CTP) data for use in HIFU have been extensively reported for animal models (Cao and Jiang 2013). Initial efforts have also been made to automate CT-guided assessment of eligible human patients using single-photon-emission computed tomography, generating data reliably equivalent to expert CT drawings and accurate to <2 mm (Lee et al. 2013). Furthermore, the important parameters of incident acoustic energy (power), depth-related acoustic attenuation and tissue perfusion have recently been considered for use in passive acoustic monitoring systems for HIFU coupled with B-mode ultrasound and CT images (Jensen et al. 2012).

As CT-guided HIFU systems are becoming more widely available, thereby increasing reliability and reducing the operator expertise required, accurate assessment of the extent of ablation and potential adverse events associated with ablation at various tumor depths becomes increasingly critical as a component of these systems and best practice guidelines. The present study reports experimental clinical findings and a resultant mathematical model for predicting the relationship between tumor depth and ablation extent in patients with unresectable carcinoma of the pancreatic body treated with HIFU. This work is essential for advancement and wide standardization of HIFU systems, which may lead to wider HIFU approval and implementation worldwide, thereby improving the treatment of cancer patients.

METHODS

Study design

A retrospective study was conducted in 20 patients with late-stage carcinoma of the pancreatic body treated with HIFU at a single center from March 2007 to December 2009. Six of these 20 patients were included in the study by Xiong et al. (2009); the remaining 14 were not included in any other report. The study protocol was approved by the ethics committee of the Peking University People's Hospital (Beijing, China). All patients provided written informed consent after being made aware of the potential benefits and risks of HIFU therapy by their treating physician.

Patients

To be included, patients had to have (i) been of advanced age (>50 y) at the time of treatment; (ii) been diagnosed with late-stage carcinoma of the pancreatic body confirmed by pathologic diagnosis, CT images or magnetic resonance images; (iii) had a single tumor; (iv) had tumors considered unresectable or otherwise considered ineligible for conventional pancreatectomy, gastric bypass or other recommended conventional surgery; (v) discontinued conventional anti-tumor therapies because of ineffectiveness or poor tolerability ≥ 1 mo before HIFU; (vi) undergone CT-guided HIFU ablation; and (vii) had complete medical histories, including relevant CT and other imaging reports indicating tumor size and dimensions and the tumor node metastasis (TNM) classification according to the International Union Against Cancer criteria (Sobin et al. 2009). Patients were excluded if they (1) were in poor physical condition indicating the likelihood of poor toleration of HIFU therapy; (2) had an estimated survival time of ≤ 3 mo; or (3) did not exhibit proper ultrasound channels for tolerable HIFU treatment, as determined by the investigators.

HIFU therapy

Patients were instructed to fast for 6–8 h before HIFU therapy and were treated with simethicone (2 mL) to reduce gastric gas several hours before the procedure. Patients were placed in the supine position, with the ribs covered with an acoustic protector, and treated with 1 h/d intermittent accumulative longitudinal ultrasound therapy without anesthesia using a FEP-BY02 HIFU system (Beijing Yuande Bio-medical Engineering, Beijing, China) with a single concave, spherical focusing element with real-time ultrasound localization and monitoring, as previously described (Xiong et al. 2009). The number of treatments was determined by the size of the tumor. Applied ultrasound had a frequency of 1.04 MHz. According to the system's built-in options, the –6–dB focal point had an oval shape and measured 3×8 mm. Each pulse had an emission time (T1) of 150 ms, interval time (T2) of 150–300 ms, width of 300–450 ms, duty factor of 33.3%–50.0% and single-point emission frequency of 60–80 Hz (some patients required many focus points to treat their lesion). The distance between spots was 4 mm in the x- and y-axes and 6 mm in the z-axis (Xiong et al. 2009). Acoustic energy per spot was 700–1200 J, approximately 1000–1200 J in most treatments. HIFU was always administered with a margin of 0.5 cm from the tumor surface to prevent pancreatic leakage and thermal damage to adjacent organs and tissues. Ambulatory electrocardiograms and blood pressure were monitored throughout each therapy session.

CT scanning

All patients were examined by CT (GE LightSpeed 16 Slice CT, Chicago, IL, USA) 1 wk before initiation of HIFU therapy, to determine appropriate treatment locations and margins, and 1 mo after HIFU therapy for