Influence of high intensity focused ultrasound (HIFU) treatment to the pancreatic function in pancreatic cancer patients

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Abstract: Present study was designed to investigate the pancreatic endocrine and exocrine function damage after High Intensity Focused Ultrasound (HIFU) therapy in patients with advanced pancreatic cancer. It was a retrospective analysis of blood glucose and amylase changes in 59 advanced pancreatic cancer patients treated with HIFU from 2010 February to 2014 January. The mean glucose and amylase before HIFU treatment were 6.02mmol/L and 59.17 U/L respectively. After HIFU treatment, it was shown that the mean glucose and amylase levels were 5.66mmol/L and 57.86/L respectively. There was no statistical significance between them. No acute pancreatitis was observed. The endocrine and exocrine function of pancreatic cancer patients was not damaged by HIFU treatment. HIFU treatment for the pancreatic cancer patients seems to be safe.

Keywords: Pancreatic cancer, Focused Ultrasound (HIFU), endocrine, exocrine.

INTRODUCTION

Pancreatic cancer is one of the most aggressive and highly lethal cancer. In the United States, It is the fourth leading cause of cancer death second to lung cancer, colon cancer and breast cancer. The mortality rate of pancreatic cancer is very high. Its 1 -year survival rate is only 25%, with the 5 -year survival rate being only less than 5% (Loos *et al.*,2008). According to "2012 China Annual Report of Cancer Registration", the incidence of pancreatic cancer was ranked the seventh, with the mortality rate being the sixth in China (National Cancer Center., 2012). It's hard to be diagnosed at the early stage. Most of patients were locally advanced or with distant metastasis when diagnosed.

High intensity focused ultrasound (HIFU) is a non-invasive treatment for malignant solid tumor which was developed at the end of twentieth Century. Many clinical studies have published the results of HIFU treatment for pancreatic cancer both in east and west and showed good clinical benefit (Schueller *et al.,* 2003; Sung, *et al.*, 2011).

During the HIFU therapy, by focusing ultrasound beams on the lesion, the energy deposited. The temperature in the lesion would rise to 65-85°C, which cause the coagulation necrosis of the lesion (Franco Orsi, *et al.*,2010). The ultrasound energy would not accumulate in the path of the beam (Akash Yadav, *et al.*, 2011). HIFU is expected to have less damage to the adjacent tissue and less influence to the pancreas endocrine and exocrine function compared with other forms of energy-focused treatment. It is critically important to find out whether the HIFU treatment would keep the normal functions of both endocrine and exocrine glands in pancreas.

Hyperglycemia is a common and very important clinical feature of the pancreas damage. Insulin is a hormone secreted by B cell in pancreas, and is central to regulate the blood glucose. Therefore, monitoring the blood glucose level would be helpful to observe the damage HIFU caused to the endocrine function. The level of amylase reflected the exocrine function of pancreatic tissue. It is another index should be monitored during the HIFU treatment for pancreatic cancer.

However, the research of HIFU caused damage on human pancreas is rare. The data about the safety of HIFU to the tissue adjacent the pancreatic cancer is also insufficiency.

In this paper, we collected the data of 59 pancreatic patients treated with HIFU. The level of blood glucose and amylase before and after treatment were recorded to evaluate the damage of pancreatic tissue adjacent to the tumor and the safety of HIFU.

MATERIAL AND METHODS

Patients

We collected 59 pancreatic patients who treated with HIFU between February 2010 to January 2014 in our department. All cases were diagnosed pathologically. 35 of them are males, 24 are females. The mean age is 66 years (range from 43-79 years). 26 of them with the tumors located in head of pancreas and 33 in the body or

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tail. 14 cases were in stage III and 45 cases were in stage IV according to the Union for International Cancer Control (UICC) classification. The total ablation of the lesions of all the cases was achieved 30 days after treatment according to magnetic resonance imaging (MRI). The research was approved by the ethics committee of our hospital. The informed consent was obtained from each patient.

Instrumentation and measures

The HIFU procedure was performed with an FEPBY02 HIFU system (Yuande Biomedical Engineering Co. Ltd, Beijing, China). A vertical scanning mode was chosen with a slice thickness of 2 mm. The ultrasonic transmitter worked at a frequency of 1.1 MHz and 11.0 MHz. GELOGIQ 400CL was used for real-time monitoring during the therapy. The ultrasonic power was 130 W. Detailed therapeutic parameters were as follows: T1/T2 990 ms/10 ms; 40 transmissions per therapeutic point with a distance of 2 mm between adjacent therapeutic points; treatment of each unit (five therapeutic points) for 200 seconds with an interval of 2 minutes between each unit; a spacing of 5 mm between adjacent treatment slices. The ablation effect was measured by magnetic resonance imaging (MRI) after the HIFU procedure. All HIFU treatments were performed under monitored sedative anesthesia. The serum glucose and amylase were obtained at the same day before HIFU treatment and 3 days after the treatment. All data were analyzed using a Pair T test for the determination of statistical significance with a threshold for significance set at *p* values less than 0.05.

RESULTS

Blood glucose before and after HIFU treatment

Fifty-nine pancreatic patients were treated with HIFU. The mean blood glucose of them before HIFU treatment was 6.02mmol/L. After HIFU treatment, the mean blood glucose was 5.66mmol/L. The difference between them was 0.36mmol/L with SD of 1.94mmol/L (95%CI:(-0.14,0.87), P=0.15), which was no obvious statistic difference.

Thirty-nine cases' blood glucoses (66%, 39/59) were in normal level before HIFU treatment. 4 of them (10%,4/39) had temporary hyperglycemia (mean blood glucose was 7.18mmol/L) and 5 of them(12.8%, 5/39) had slight hypoglycemia (mean blood glucose was 3.47mmol/L) after HIFU treatment. 18 (30%) cases had hyperglycemia (mean blood glucose was 7.44mmol/L) and 2 cases had slight hypoglycemia (mean blood glucose was 3.47mmol/L) before HIFU treatment. All of them returned to the normal level in 3 days after the HIFU treatment without medication.

The changes of blood glucose according to the gender, age, tumor location are showed in table 1.

Serum amylase after HIFU treatment

Fifty-nine patients had normal amylase before and after HIFU treatment. The mean value was 59.17 and 57.86 U/L. The difference was 1.31 with SD of13.56 (95%CI: (-4.84, 2.23), P=0.46).

For 56 cases with normal amylase before HIFU treatment, 7 cases (12.5%, 7/56) showed a higher amylase after treatment without any pancreatitis symptom. The amylase fell to normal level in 3 days without treatment. Two cases had elevated amylase and 1 case had decreased amylase before the treatment. The amylases of them convert to normal level in 3 days, respectively the changes of serum amylase according gender, age, tumor location are shown in table 2.

DISCUSSION

In advanced pancreatic cancer, HIFU has been found as a good method for palliative care (Sung, *et al.*,2011). During the treatment of pancreatic cancer, HIFU would cause the necrosis of cancer cell, further the elimination of tumor infiltration and nerve compression, which would relief the pain. HIFU also block the pulse conduction of the pain by injury of the peripancreatic nerve plexus. When the tumor was ablated, the hidden tumor-associated antigens would be exposed, which would stimulate the patients' own immune system (Schueller *et al.*,2003).

An important difference between HIFU and many other forms of focused energy treatment, such as radiation therapy or radio surgery, is that the ultrasound energy would not accumulate in the path of the beam (Akash Yadav, *et al.,* 2011). It is important to evaluate the possibility of injure HIFU caused to adjacent normal tissue during the treatment for pancreatic cancer.

Everhart reported that the pancreatic cancer would cause elevation of blood glucose, because the expansion of the tumor would destroy the islet cells, structure and function (Everhart and Wright 1995). Meanwhile, it was confirmed that the secretion of insulin was increased rather than decreased in pancreatic cancer, which was opposite to chronic pancreatitis. The abnormal glucose metabolism in pancreatic cancer would reduce the sensitivity of insulin, suggesting the cancer was associated with insulin resistance. The most common symptoms of pancreatic cancer, such as jaundice, abdominal pain and dyspepsia, are caused by the obstruction of main pancreatic duct and the reduction of pancreatic exocrine function manifested as the decreasing lipase and trypsin (Osawa *et al.,* 2002). Effective palliative treatment for advanced pancreatic cancer should not create further damage to the endocrine and exocrine function of the pancreas. In this study, we compared the serum blood glucose and amylase before and after HIFU treatment to evaluate the safety of HIFU for the endocrine and exocrine function of the pancreas.

Table 1: The blood glucose change before and after HIFU

	N	Mean fasting plasma glucose pre HIFU (mmol/L)	Mean fasting plasma glucose post HIFU (mmol/L)	Univariate P value
Sex				0.35
Male	35	6.51	6.34	
Female	24	5.83	5.18	
Age (y)				0.53
≤55	10	5.15	5.15	
>55	49	6.45	6.01	
ECOG score				
<2	32	6.10	5.97	0.32
≥2	27	6.39	5.74	
Primary tumor localization				0.74
Head	26	5.49	5.23	
Body and tail	33	6.81	6.37	

Table 2: The serum amylase before and after HIFU

	N	Amylase Pre HIFU (U/L)	Amylase Post HIFU (U/L)	Univariate P value
Sex				
Male	35	57.97	58.29	0.272
Female	24	60.92	57.25	
Age (y)				
≤55	10	61.57	60.00	0.742
>55	49	47.40	47.40	
ECOG score				
<2	32	60.12	58.97	0.928
≥2	27	58.04	56.56	
Tumor location				
Head	26	59.81	60.38	0.349
Body and tail	33	58.67	55.88	

Our results showed that HIFU didn't affect the function of pancreas for treatment of the advanced pancreatic cancer. During the therapy, when the instantaneous coagulation necrosis occurs, the digestive enzymes and zymogen granules in the pancreatic cells were inactivated by the thermal injury. The lysis of the cells was delayed. So the acute pancreatitis would not happen. The observation of membrane and ultra structures of cells under the transmission electron microscopy proved that the cell membrane, lysosomes and other organelles were remaining intact during the HIFU ablation (Clarke and Ter Haar, 1997; McDannold *et al.*, 1999). Therefore, the digestive enzymes would not be released from the pancreatic cells, which would avoid the liquefaction necrosis and subsequent pancreatitis. The fast increased temperature in HIFU treatment would deactivate pancreatic enzymes to prevent the acute pancreatitis

According to the previous clinical reports, HIFU treatment was safe for pancreatic cancer. A few complications were reported (Sung HY, *et al.*, 2011; Orgera *et al.*, 2011). In a review about 10 years of treatment, Zhang reported some rare complications of HIFU, including gastrointestinal perforation, hemorrhage, pancreatic fistula, biliary fistula, and tumor fever. Most of the complications were observed at the early stage of HIFU application (Zhang and Wang 2010). In our research, no serious complication was observed in 59 patients, which is consisted with most of recent reports.

Slight elevates of blood glucose and amylase was observed in several cases in our research. The values returned to normal in a few days without special treatment. The monitoring of blood glucose and amylase after HIFU treatment for pancreatic cancer should be performed routinely. Sometimes, the fasting serum C peptide, which is the endogenous insulin production, and the serum trypsin, which is a valuable index for chronic pancreatitis could be used for future evaluation (Chowdhury *et al.*, 2003).

CONCLUSION

High intensity focused ultrasound for the treatment of pancreatic carcinoma did not cause any significant changes of blood glucose and blood amylase. HIFU treatment on the target pancreatic region would not cause obvious damage to the adjacent normal tissue and didn't affect the pancreatic function.

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