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Original article

CLINICAL SAFETY OF FOCUSED ULTRASOUND SURGERY IN THE TREATMENT OF ADVANCED PANCREATIC CANCER PATIENTS - SINGLE CENTER PROSPECTIVE STUDY

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SUMMARY

Purpose: Our purpose is to study the clinical safety of focused ultrasound surgery (FUS) in the treatment of patients with advanced pancreatic cancer.

Methods: A single-center prospective study was conducted in the period 02. 2013 - 06. 2018 at HIFU department at University hospital St. Marina – Pleven, Bulgaria looking at the postoperative complications after focused ultrasound surgery of advanced pancreatic cancer patients.

Results: 47 patients were included in the study with a III or IV stage pancreatic cancer. The complication rate was 10.6% and no severe complications were observed.

Conclusions: FUS seems to be a safe method of treating patients with advanced pancreatic cancer. Large randomized trials in the area are needed.

Keywords: pancreatic cancer, postoperative complications, High-intensity focused ultrasound

INTRODUCTION

Pancreatic cancer is a socially significant disease with a bad prognosis. Patient survival has not improved significantly over the past 50 years. Treating advanced pancreatic cancer remains a challenge. The golden standard nowadays is surgical resection. Approximately 80% of patients have unresectable disease at presentation [1]. The median overall survival (OS) for III stage patients is app. 6-10 months and for IV stage – 3-6 months [2]. Chemotherapy has not shown to greatly improve the OS rate for patients with advanced pancreatic cancer [2-5].

Focused ultrasound surgery (FUS) or high-intensity focused ultrasound (HIFU) treatment is a novel non-invasive method to treat advanced pancreatic cancer [6-7]. During the past decades it has proven its benefits in treating patients with this disease.

Our aim is to study the clinical safety of focused ultrasound surgery (FUS) in the treatment of patients with advanced pancreatic cancer by a single-center prospective study.

MATERIAL AND METHODS:

A single-center prospective study was conducted in the period 02. 2013 – 06. 2018 at HIFU department at University hospital St. Marina – Pleven, Bulgaria. A total of 47 patients answered the following inclusion criteria during the study period [Table 1].

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion Criteria
• Pancreatic ductadeno carcinoma, proven histologically • Patients who are not candidates for resection - locally advanced carcinoma (III stage) and metastatic	• A scar in the acoustic pathway • Uncontrolled infection • Obstructive jaundice, obstruction of the gastrointestinal tract

disease(IV stage) • ECOG - 0-2 or KPS ≥70%	• Bleeding from the gastrointestinal tract • Uncontrolled heart disease, hepatic dysfunction (Child-Pugh Class C), renal dysfunction • Complete infiltration or obstruction of the major blood vessels around the pancreas

In all patients with obstructive jaundice a metal biliary stent was placed and the procedure was carried out after bilirubin levels were in normal range.

The JC USgHIFU system (Chongqing Haifu Medical Technology Co. Ltd., Chongqing, China) was used to treat all patients. The therapeutic procedure was guided by real-time B-mode ultrasound. A DU3 US imaging device with 2.5–3.5-MHz imaging probe (Esaote, Genova, Italy) was used as the real-time imaging unit of the system. Therapeutic ultrasound energy was produced by a transducer with 0.85 MHz frequency.

Easily-digested food as a 3 days diet and fasting 10 hours before the procedure was recommended. Bowel preparation was performed on the day before FUS and an NGT and urinary catheter were placed as well as degassing and defatting of the skin was performed in the morning of the treatment day. In most of the cases anaesthesia was used. Only in patients with a short and safe acoustic pathway from skin to tumor and a low BMI were treated with moderate sedation. Patients were placed in prone position on the table. A tank containing degassed water was used in the space between the body and the transducer in order to create an airless acoustic pathway. A water balloon was placed between the abdominal wall and the transducer in order to move the bowels (potentially containing any gas) away from the acoustic pathway. The dot-line-slice-volume method was used for FUS until the hyper-echogenic changes appear in the whole targeted lesion.

To prevent edema of the front abdominal wall and to reduce the risk of skin burns we followed a safety protocol: 1. single ultrasound treatment shots were used with a pause of at least 3 seconds between them; 2. a maximum energy of 400W was not used; 3. a 5 to 7 minutes pause was made and the transducer was removed from the skin in every 300 seconds of sonication.

Sonication time, average power and total energy were studied. Sonication time is defined as the period from the first test shot to the last treatment shot. The average power and total energy were recorded and calculated by JC USgHIFU system.

After the FUS standard lab tests and vital signs were monitored. All the patients were started on gradually increased amounts of fluid and then solid food. All the patients stay in the hospital until full recovery. A computer tomography was performed up to 15th day after the procedure. The patients were followed-up for 30 days after the procedure for complications.

The clinical assessment was performed after ultrasound-guided focused ultrasound surgery (USgFUS) procedure and the complication was recorded one week post-USgFU Saccording to the Clavien-Dindo classification [8].The adjuvant chemotherapy which included 4-6 cycles was recommended to all patients. Statistical analysis was done using Stat graphics software for Windows.

RESULTS:

47 patients were included in the study with a mean age of 58.5 years. Mean tumor volume was 22.98ml and the localization was: in 34 patients (72.34%) in the head of the pancreas, in 9 patients (19.15%) in the body and in 4 patients (8.5%) in the tail. 7 of the patients have undergone previous abdominal surgery. Other patients' characteristics are shown in Table 2.

The parameters of USgFUS are shown in Table 3. The mean sonication time was 694sec.

Table 2. Patients' characteristics

Characteristics	Value
Number of patients	47
Age, mean± SD (range), y	58.5 +/-8.18 (40-76)
Sex (male/female), n	24/23
Tumor volume, mean±SD (range), ml	22.98 +/- 11.891 (4.4-56.5)
Tumor localisation(head/body/tail), n	34/9/4
TNM stage(III/IV)	20/27
Chemotherapy(YES/NO)	42/5
Metal stent placement before USgFUS (Yes/NO)	14/33
Abdominal surgery before USgFUS (Yes/No)	7/40

Table 3. The parameters of USgFUS of patients with advanced pancreatic cancer

Parameters of USgFUS	Value
Number of cases /n/	47
Number of Sessions /n/	51
Sonication time /sec/ (mean, ± SD)	694 +/-338.2
Average power /W/	262 +/-74.8
Recovery days after USgFUS (mean, ± SD)	3.9 +/-1.1

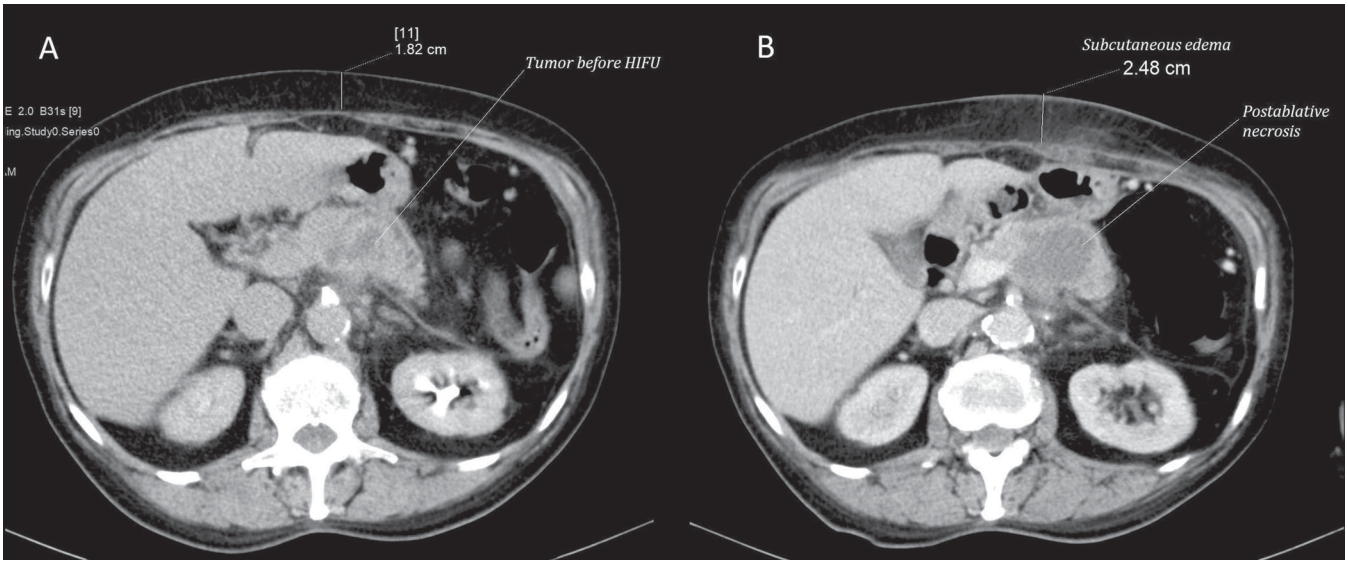
The complication rate was 10.6% and no severe complications were observed. One case of mild pancreatitis and four skin burns were seen [Fig. 1]. No therapy was needed for all of them and they resolved in a week [Table 4]. 27 cases of subcutaneous edema as side effects were detected on the CT images after the procedure. There was no clinical manifestation of these findings [Fig. 2]. In one of our patients, obstructive jaundice was recorded on the 20th post-op which required the insertion of a metal stent. The total bilirubin level before the treatment was 41 μmol/L with no clinical manifestation of jaundice.

Fig. 1. Case of 2nd degree skin burn. Burning detected immediately after USgFUS procedure.

Table 4. Number and grade of complications and outcome.

Complication	Number/Grade/	Outcome
Gastrointestinal injury	0	/-/
Vessels injury or thrombosis	0	/-/
Pancreatitis	1 /Clavien-Dindo I/	Serum-amylase level was increased. Back to normal in one week. No treatment needed.
Skin burn	4 /Clavien-Dindo I/	Due to the previous surgery scar, dressings applied, the wounds healed in one week.

Fig. 2. Case of a 64-year-old patient with pancreatic cancer treated with USgFUS A. Tumor is localized at the body of the pancreas with 1.8 cm subcutaneous fat B. The pancreatic tumor is almost completely ablated with a huge coagulative necrotic area and subcutaneous edema



There was statistically significant increase of the skin burns in the previous abdominal surgery group (p=0.039). There was no statistical significant correlation between age, sex, tumor size, localization, stage or metal stent placement on one side and complications on the other.

DISCUSSION:

Ultrasound can pass through tissues harmlessly but when focused in a certain point enough energy can be produced to form a well-defined volume of coagulation necrosis [9]. Advances in radiology and imaging devices over the past 20 years have allowed accurate focusing of the energy and thus making this technology applicable in clinical practice, although the idea was born in 1940s [10]. The most widely used system in oncology at present is the JC USgHIFU system (Chongqing Haifu Medical Technology Co. Ltd., Chongqing, China). The system allows non-invasive real-time monitored ultrasound surgery, which allows very good control, focus and orientation in difficult-to-access solid tumors such as pancreatic cancer [11-13]. Focused ultrasound surgery is still not widely used in Europe in the treatment of pancreatic cancer as only a few centers use it [14-16]. Most of the research and experience with this innovative approach comes from China [17-26]. Our team was trained by experienced Chinese colleagues 6 years ago. The selection criteria, the preparation, ablation and safety protocol were entirely borrowed from our mentors. This leads to a gentle learning curve of introducing focused ultrasound surgery.

For teams that started earlier with non-invasive ablation in pancreatic cancer more serious complications appeared. In such series severe pancreatitis, bleeding from the gastrointestinal tract and skin burns III degree requiring plastic surgery of 2 patients are reported [14]. Orsi et al. reported one case out of six difficult pancreatic cancer ablations with portal vein thrombosis as a severe complication after HIFU [16].

When studying the long-term outcome of high-intensity focused ultrasound in advanced pancreatic cancer in 46 patients Sung et al found only two cases with pancreatic duodenal fistula and one case with GI bleeding as major complications after HIFU. They also concluded that HIFU is safe and effective for pancreatic cancer [27].

In our series of patients we have seen only a few side effects which are mostly in the area of the anterior abdominal wall. In only one patient laboratory data for acute pancreatitis without fever and sepsis was reported and was controlled after conservative therapy. Possible reason as an explanation of these side effects would be edema of the pancreatic tissue and abdominal wall based on the USgFUS exposure as the secondary effect.

Although the scars in some patients were not in the acoustic pathway of the US waves, a scar in the abdomen seems to be an independent factor for increasing skin burns($p = 0.039$). In our study, two out of the four patients who wad skins burns have had previous operations on the pancreas – radical and palliative surgery. The other two were with scars from operations in the epigastrium on another occasion. This complication is directly related to the USgFUS exposure.

Strunk et al demonstrate that HIFU treatment can be safely applied to pancreatic cancers enveloping large mesenteric blood vessels with only 6% adverse events regarding vessel patency [28].

Subcutaneous edema may be due to the pressure to the abdominal wall caused by the transducer and the absorption of reflected ultrasound waves in the subcutaneous tissue. In some cases the presence of the edema worsened the ultrasound image during the procedure and necessitated its early interruption.

An open-label trial in China including 251 patients with advanced pancreatic cancer treated with FUS showed that FUS could reduce the tumor volume without a great risk of pancreatitis thus increasing the OS [29].

Radiofrequency ablation of pancreatic cancer is associated with very high morbidity rates (4-37%), overall morbidity (10% -40%) and mortality (0% -25%) [30-32]. Common complications include fluid collection, pancreatic fistula, duodenal perforation and vascular damage, gastrointestinal bleeding, infections or abscesses [30-34]. In a study of 20 patients, two patients died from severe complications - septic shock and bleeding [34].

Microwave ablation in advanced cases with pancreatic cancer has been used in some studies. It is based on the microwaves emitted from the antennas through the skin or most often intraoperatively inserted into the tumor during a palliative bypass operation under imaging guidance [35.36]. The largest study so far included 15 patients with minor complications reported in 40% of them -asymptomatic pancreatitis, ascites and minor bleeding.

Cryoablation for advanced pancreatic cancer shows prolonged survival up to 13 months at low levels of severe complications [37-39].

CONCLUSION:

FUS seems to be a safe method of treating patients with advanced pancreatic cancer. Large randomized trials in the area are needed to accurately define the risk factors for complications after USgFUS treatment for pancreatic cancer patients.

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