High Intensity Focused Ultrasound Therapy Combined Gemcitabine for Treating Unresectable Pancreatic Carcinoma
W Lv, T Yan, G Wang, W Zhao, T Zhang, D Zhou

ABSTRACT

Objective: To study therapeutic effect and safety of high intensity focused ultrasound (HIFU) combined Gemcitabine on unresectable pancreatic carcinoma (PC).

Methods: Total 45 PC patients were randomly divided into 2 groups: experimental group (treating with HIFUT and gemcitabine, n=23), control group (treating with gemcitabine only, n=22). The therapeutic effects and clinical benefit rates in two groups were compared by using the Kaplan-Meier and Log-Rank tests, including the median survival time (MST), 6-month and 12-month survival rates.

Results: Our results showed that MST and 6-month survival rates of experimental patients were significantly higher than that of control patients (8.91 vs 5.53 mths, 73.9 vs 40.9%, p<0.05). For the 12-month survival rates, no statistically difference was observed between the two groups (13.0 vs 4.5%, p>0.05). The clinical benefit rates in experimental group and control group were 69.6% and 36.3%, respectively (p<0.05). The pain remission rate in experimental group was significantly higher than in control group (65.2 vs. 31.8%, p<0.05).

Conclusions: For treating pancreatic carcinoma, HIFUT combined gemcitabine is better than gemcitabine only. The former treatment (HIFUT combined gemcitabine) may become a better effective treatment strategy for treating unresectable pancreatic carcinoma.

Keywords: Combined therapy, gemcitabine, high intensity focused ultrasound, pancreatic carcinoma/treatment

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INTRODUCTION
Pancreatic cancer is one of the most common digestive tract malignant tumors with an increasing morbidity in the whole world. Because of the absent of signs and symptoms in the early state, 80% of the patients are in the late state of pancreatic cancer when figured out which excision rate was low. During this state, the median survive time is only 3-6 months (1). In China, the currently annual incidence of pancreatic cancer is around 5.1/1000 00 which is three times larger than twenty years ago (2). Recently, overall survival rate and quality of living are the goal of pancreatic cancer patients and pain management is the key point. Gemcitabine as the main drug of chemotherapy cannot relieve pain and so it is not useful to make the patients live a better life, palliative treatment of pancreatic cancer is a big problem in medical science.

In order to improve the patient general condition and to improve the survival rate, we use HIFU surgery combined with gemcitabine static drops of chemotherapy to treat the pancreatic cancer which cannot be surgically cut off. Furthermore, we observed the efficacy and safety of this combined therapy, which supplied an essential scientific research basis for using this strategy to treat pancreatic cancer in clinical.

SUBJECTS AND METHODS
Subjects
We chose 45 pancreatic cancer patients which cannot be surgically cut off from March 2008 to January 2011 in our hospital. Among them, there are 28 males and 17 females from 26 to 71 years old. The median age of these patients are 59.3 years old and there are 22 pancreatic head carcinomas and 23 carcinomas of pancreatic body and tail. From the abdomen CT/MRI, we can know that the smallest tumor is 2.6cm×2.5cm×1.8cm, and the largest tumor is
8.1cm × 7.5cm × 5.8cm. From the UICC staging criteria, 29 cases are in III period and 16 cases are in IV period. Subjects selection criteria are following: 1) Confirmed by pathological histology or cytology, or with typical clinical manifestations combined with imageological examination and tumor marker CA-199 test; 2) Patients have the measurable and valuable lesions on the imaging such as abdominal pain and (or) waist pain, loss of appetite, weight loss (>15%); 3) Lost opportunities or surgery contraindications; 4) Physical condition (KPS scores > 70) is well, no obvious ascites and jaundice, expected survival time > 3 months; 5) Routine blood and kidney function well; there are no significant different between the two group patients (p>0.05). Expected observation and follow-up time is at least 12 months.

**Therapeutic Method**

*Application equipment and treatment parameters*

The experimental group patients received HIFU treatment and the equipment was produced by Chong Qing Hai Fu Company. This equipment is JC200 type high intensity focused ultrasound tumor treatment system. We can identify body surface location and develop a plan of treatment according to the image of the tumor. During the surgery, we can compare the target image and gray value and observe the lesions echo to identify the coagulation necrosis. Treatment parameters: Frequency 0.97MHz, Focus 147mm, Layer number of treatment 20–30, Treatment layer spacing 5mm, Therapeutic range 80%~100%, Average total treatment time 1560s, Average power 350W, Overall average energy 725000J. Experimental group patients were expected to accept a single treatment, additional treatment can be added when necessary.

*Gemcitabine application solutions*

Gemzar (Domestic gemcitabine booster injection, Lilly Suzhou pharmaceutical company) 1000mg/m², static 30 minutes, once a week, three weeks total, 28 days to 1 cycle. The two
groups of patients were accepted at least 2 cycles of chemotherapy. In the experimental group, patients were observed for three days after HIFU surgery. If there is no special complication, Static drops of gemcitabine chemotherapy would be used.

**Curative effect valuation standard**

*Disease related symptom improvement (DRSI)*

DRSI is the comprehensive assessments of pain, performance status and weight change. It is also same as clinical benefit response (CBR), and the evaluation criteria was following: 1) The daily decreased dosage of analgesic drugs \( \geq 50\% \); 2) Relieve pain \( \geq 50\% \), and the MPAC was used to do weekly summary; 3) Physical conditions improvement \( \geq 20\) scores, and the Karnofsky was used to do the daily assessment; 4) The above three evaluation indicator were stable, weight gain \( \geq 7\% \). If more than one index above was improved for more than 4 weeks and there is no other deterioration indicator, we considered that the patient is the clinical benefit case.

*Objective curative effect of tumor*

According to the RECIST curative effect evaluation standard, it can be divide into: 1) complete remission (CR, All tumor lesions disappeared for more than 4 weeks), 2) partial remission (PR, The max tumor diameter reduced 30\% for more than 4 weeks), 3) stable disease (SD, changes between PR and PD) and 4) progression of disease (PD the sum of the single largest diameter increased by 20\%, or a new lesions). Disease Control Rate (DCR) = CR + PR + SD.

*Survival time*

Median survival time (MST) is the median time from treatment to dead; survival time is the date from treatment to dead or the second day after dead. During the follow-up period, we use the whole data of the survival patients and part of the data which only reached the dead day
for the dead patients.

HIFU Complications and chemotherapy toxicity

We separated the adverse reaction of chemotherapy to I-IV degrees according to the WHO and did safety assessment to the experiment groups HIFU ablation.

Statistical analysis

All the data were analyzed by SPSS 17.0. The Kaplan-Meier was used to analysis the survival analysis, the survival rate of 6 months and 12 months, and the median survival time, and the Log-Rank was used to analysis the difference in different groups. Enumeration data were tested by $\chi^2$ test, and $p<0.05$ means significant difference.

RESULTS

Clinical benefit rate

The total effective rate of experiment group (23 patients) was 69.6%, while the control group (22 patients) was 36.3%. There is significance difference between the two groups ($\chi^2 = 4.98$, $p<0.05$). Analysis showed that the pain relief rate of experiment groups was 65.2%, and it is better than only Gemcitabin treated patients which pain relief rate was 31.8%. There is significant difference between the two groups ($\chi^2 = 5.01$, $p<0.05$).

Table 1. CBR comparison after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pain Relief</th>
<th>Painkillers to Reduce</th>
<th>Physical Strength to Improve</th>
<th>Weight Gain</th>
<th>Effective Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group</td>
<td>15</td>
<td>16</td>
<td>8</td>
<td>0</td>
<td>69.6</td>
</tr>
<tr>
<td>Control group</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>36.3</td>
</tr>
</tbody>
</table>
**Disease control rate**

Among the 45 patients, there is no CR. For the experiment groups, there are 10 patients reached PR, and 8 patients reached SD. Disease control rate was 78.2%. For the control groups, there are 4 patients reached PR and there are 9 patients reached SD among the total 22 patients. Disease control rate was 59.0%. There are no significant different between the two groups ($\chi^2 = 1.92$, p $>$ 0.05).

**Survival analysis of patients with pancreatic cancer**

The MST of the experimental group was 8.91 mths, and the accumulative survival rate of 6 months and 12 mths is 73.9% and 13.0%, respectively. The MST of the control group was 5.53 mths, and the accumulative survival rate of 6 months and 12 mths is 40.9% and 4.5%, respectively. There is significant difference between the two groups in the 6 months survival time ($\chi^2 = 5.10$, p $<$ 0.05), while there is no significance difference between the two groups in the 12 mths survival time ($\chi^2 = 0.22$, p $>$ 0.05). The survival rate and compare and survival curves are shown in Table 2 & Figure 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
<th>6 months survival</th>
<th>12 months survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cases</td>
<td>Survival rate (%)</td>
</tr>
<tr>
<td>Experimental group</td>
<td>23</td>
<td>17</td>
<td>73.9</td>
</tr>
<tr>
<td>Control group</td>
<td>22</td>
<td>9</td>
<td>40.9</td>
</tr>
</tbody>
</table>
Adverse reaction and safety observation

HIFU dependent adverse reaction

All the 23 patients in experiment group accepted HIFU presented skin warm feeling which disappeared in 3~4 days. No obvious skin burn, pancreatic fistula, gastrointestinal perforation, pancreatitis and other serious complications was observed.

Chemotherapy related adverse reactions

Blood system toxicities and gastrointestinal reactions are the mainly adverse reactions observed. Among the 23 patients in experiment group, 8 patients showed I leukopenia, 3 patients showed II leukopenia and 4 patients showed III leukopenia. In the control group, 5 patients showed I leukopenia, 4 patients showed II leukopenia and 4 patients showed III leukopenia. Both the two groups did not show IV degree adverse reactions and there was significant difference between the two groups ($\chi^2=0.179$, p>0.05). Gastrointestinal reaction mainly presented severe nausea and vomiting, and overall the patient can tolerate. In our investigation, no patients quit during chemotherapy.
DISCUSSION

Application of ultrasonic to treat tumor has a history over than 50 years. Currently, it has developed as the ultrasonic surgical techniques - high intensity focused ultrasound technology (3,4). HIFU could produce heat effect in tumor area via the penetrability and focusability of ultrasonic. It will make the target area to get 65 ~100 00 in a short time, leading to protein denaturation and coagulation necrosis in the tumor area (5). Besides, HIFU can also produce mechanical effect and cavitation effect. Because the tumor invade the superior mesenteric vein and portal vein which will make the surgery face great risk, most patients would lose the chance to get well by surgery. Previous researches revealed that HIFU would not affect blood vessels with a diameter larger than 200 μm, and it only blocked the vasa vasorum with a diameter smaller than 200 μm (6,7). These properties became the foundation of ablation therapy to advanced pancreatic cancer. Severe back pain is thought to be associated with tumor invasion to abdominal and retroperitoneal plexus around (8). The mechanism of HIFU relief pain is that HIFU could make damage to the pancreas and solar plexus around when treat pancreatic tumors. In addition, early results also showed that HIFU can stimulate the body's immune system (9).

Gemcitabine is the only antitumor drug approved by the FDA to treat advanced pancreatic cancer. Gemcitabine currently has become the first-line agent to kill pancreatic cancer both in China and abroad (10,11). The III period test showed that there is no difference between the Gemcitabine treatment with or without cisplatin (12). The efficiency of Gemcitabine for pancreatic cancer treatment is 20~30%, median survival time is 4.2~5.5 mths and 1 year survival rate was below 16~19% (13-15). HIFU could also enhance the concentrations of antitumor drug in tumor tissues and improve the drugs’ therapeutic efficacy theoretically. There is a synergy between heat treatment and chemotherapy, and the specific mechanism may be that HIFU could increase the local temperature and membrane
permeability of tumor cells. The results of the study showed that HIFU ablation combined gemcitabine static drop after chemotherapy can significantly improve the survival rate of 6 months compared with gemcitabine chemotherapy alone. The two groups were significant differences in abdominal pain remission rate, showing that HIFU is better than that of pure gemcitabine chemotherapy group in improving patients' quality of life. In terms of safety, the experimental group patients after HIFU ablation just has warm feeling but not serious complications.

In conclusion, HIFU combined gemcitabine chemotherapy is better than gemcitabine alone for treating inoperable pancreatic cancer. It can improve the life quality and prolong survival time. When taking HIFU, there is no serious adverse reaction.
REFERENCES


