Pain management of pancreatic cancer patients with high-intensity focused ultrasound therapy

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Abstract: This study was performed to evaluate cancer pain control of high-Intensity focused ultrasound ablation (HIFU) and to manage the HIFU treatment pain in advanced pancreatic cancer patients with analgesics. We collected 71 locally advanced pancreatic cancer patients treated with HIFU from 2013 March to 2014 January in our hospital. The cancer pain (pre-HIFU and two weeks after HIFU) and HIFU treatment pain were evaluated respectively. The numeric rating scale (NRS) was used as the tool of pain evaluation. The related factors with pains were analyzed. The 70.42% cancer painless rate before HIFU was improved to 92.96% ($P<0.05$) 2 weeks after HIFU in 71 advanced pancreatic cancer patents without analgesics adjustment. The HIFU treatment pain occurred in 42 of 71 treated patients (59.15 %). The average duration was 3.93 days and pain score was 3.22. HIFU can improve cancer pain relief further in the advanced pancreatic cancer patients with third ladder analgesics, meanwhile HIFU treatment pain can be managed easy because of its short duration and low pain score.

Keywords: Pancreatic Neoplasm; Analgesics, Pain management; High-Intensity Focused Ultrasound Ablation (HIFU).

INTRODUCTION

The incidence of pancreatic cancer ranked seventh and the mortality ranked sixth in all malignancy of China (National Cancer Center, 2012). Only 10%-20% of the pancreatic cancers had the opportunity to accept resection (Loos *et al*., 2008). Prolonging of life, relieving of symptoms and improving of life quality are the major goals in the treatment of advanced pancreatic cancer patients (Hussain *et al*., 2004; Sung *et al*., 2011). Severe pain appeared in 90% of the advanced pancreatic cancers. The cancer pain relief was very important in these patients (Lindsay *et al*., 2005; Van Geenen *et al*., 2002). The analgesics to control the cancer pain were applied widely in advanced pancreatic cancer patients with the guide of World Health Organization (WHO) analgesic ladder for cancer pain management (Wolfgang *et al*., 2013; Erdek *et al*., 2013). However, the cancer pain relief was still not completely satisfactory in those patients.

High-intensity focused ultrasound ablation (HIFU) is a non-invasive treatment of malignant solid tumor and other diseases (Sofuni *et al*., 2014; Forslund *et al*., 2006; Hu *et al*., 2013). Clinical studies have reported the good results of tumor local control and cancer pain relief in advanced pancreatic cancer patients treated with HIFU (Schueller *et al*., 2003; McKenna *et al*., 2003). But there were few evidences of cancer pain relief further and treatment pain management of HIFU in advanced pancreatic cancer patients with analgesics.

Because of the anatomical location of the pancreas, the ultrasound beams are easy to meet the ribs during the therapy. The amplitude attenuation coefficient of ultrasound is about 10–20 times higher in bone than in soft tissues, a factor that causes the ultrasound beams to be absorbed rapidly within the bone (Tempany *et al*., 2011). The ribs were easy to be injured and that induce rib pain. At soft tissue–bone interfaces, approximately one-third of the incident energy is reflected back to cause skin burning pain with subcutaneous tissue and skin injury. Ultrasound beams focus on the target region inducing high temperature ablation. The thermal damage to target tissues of pancreas would cause the visceral pain. These treatment pains often occur in pancreatic patients treated with HIFU. Through this study, we want to find the effects of cancer pain control with HIFU in advanced pancreatic cancer patients with analgesics. We also want to find the characteristics and management methods of HIFU treatment pain.

MATERIAL AND METHODS

Study population

The HIFU treatment was performed on 71 patients with locally advanced pancreatic cancer (stage III) in The Second Affiliated Hospital, Zhejiang University School of Medicine from 2013 March to 2014 January. All patients were diagnosed by pathology. There were 46 males and 25 females. Age ranged from43 to 85 years with median age 65. Thirty five carcinomas were located at the head of pancreas, 30 at body and 7 at tail, 1 at both head and tail. All 71 patients had pain history and had taken the third ladder analgesics with the guide of WHO analgesic ladder for cancer pain management.

The research was approved with the approval number

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2013-R-042 by the institute ethics committee. The written informed consent was obtained from each patient.

HIFU treatment

The HIFU procedures were performed with an FEPBY02 HIFU system (Yuande Biomedical Engineering Co. Ltd, Beijing, China). A vertical scanning mode was chosen with a slice thickness of 2mm. The ultrasonic transmitter worked at a frequency of 1.1 MHz and 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 analgesics were not interrupted on the treatment day.

Cancer pain assessment and management Pre-HIFU and 2 Weeks after HIFU

The cancer pain intensities were evaluated according to numeric rating scales (NRS) 0-10.The pain assessments were performed the day before HIFU and 2 weeks after HIFU. All pains were managed with the WHO analgesic ladder for cancer pain management. There is no analgesic adjustment before and after HIFU treatment. The cancer painless rate two weeks after HIFU was compared with that before HIFU.

Pain management during the HIFU treatment

HIFU treatment was performed under general anesthesia with intubation.

HIFU treatment pain assessment and management

After the HIFU treatment, the pain assessments were performed according NRS when the patients woke from the anesthesia, then repeated again every 60 minutes within 12 hours, per 4h between 12h-24h, once a day after 24h. The skin, rib and visceral pains at treatment area were evaluated and recorded respectively. The highest pain score of three regions and different times was taken to calculate the average pain score. The data of treatment pain including pain region, onset time, duration and intensities were also obtained for analyses. The patients with NRS $\geq$ 4 after treatment were given Flurbiprofen Axetil 50mg intravenous injection to control the pain. Flurbiprofen Axetil could be repeated if the NRS was still $\geq$ 4.

STATISTICAL ANALYSIS

The data were analyzed with SPSS version 16.0. P-value <0.05 was considered as statistically significant.

RESULTS

Cancer pain comparison Pre-HIFU and 2 weeks after HIFU

Before HIFU treatment, fifty patients were painless with NRS 0 and other 21 patients were still with pain under analgesics, 14 patients with NRS 1-3 and 7 patients with NRS 4-6. None of our patients was above NRS 6 under the analgesics. The cancer painless rate was 70.42% (50/71) with 95% CI 59.80-81.04%.

Two weeks after HIFU treatment 66 patients were painless with NRS 0 and other 5 patients were still with pain NRS 1-3 without analgesics adjustment. The cancer painless rate increased to 92.96% (66/71) with 95% CI 87.03-98.89%. The difference of cancer painless rate before and after HIFU treatment was statistically significant (P<0.05, table 1).

HIFU treatment pain

The HIFU treatment pain occurred in 42 of 71 patients (59.15%). There were 4 patients with NRS 5, 13 patients with NRS 4, 3 patients with NRS 3, 12 patients with NRS 2 and 10 patients with NRS 1. The region, onset time and duration of treatment pain were showed in table 3. Skin burning pain, rib pain, and visceral pain were 42 patients, 30 patients and 29 patients respectively. Most patients suffered from more than one region of pain. The onset time of treatment pain was 0.20 to 26 hours after anesthesia with mean 0.57 hours. All treatment pain occurred at the same day of treatment except one patient at the following treatment day. The mean duration of treatment pain was 3.93 days. No patient was beyond 5 days. 17 patients were given Flurbiprofen Axetil 50mg intravenous injection because of treatment pain score $\geq$4 and 3 of them needed repeated injection of Flurbiprofen Axetil 50mg one hour later due to persisting treatment pain score $\geq$ 4.

The factors related with HIFU treatment pain were showed in table 4. The significant factor related with HIFU treatment pain was age. The patients with age $\leq$ 55 were higher treatment pain. The gender, KPS and location of the tumor had no relationship with HIFU treatment pain.

DISCUSSION

Abdominal or back pain appeared in 30 -73% of the pancreatic cancer patients at the first diagnosis and severe pain appeared in 90% advanced pancreatic cancer patients. The analgesic drugs were applied to control the pain in those patients. However, in our 71 advanced pancreatic cancer patients, there still were 21 patients with pain under the third ladder analgesics.

During the HIFU therapy, the ultrasound beams are focused on diseased tissue .The temperature within targeted tissue would rise to 65 to 85°C due to the significant energy deposition at the focus. The rising temperature would induce coagulation necrosis and destroy the targeted tissue (Orsi *et al*., 2010). It could ablate tumor to control cancer growth and eliminate the

Table 1: Comparison of cancer pain pre-HIFU with2 weeks after HIFU

NRS	Pre-HIFU			2weeks after HIFU			P-value
	N	%	95%CI (%)	N	%	95%CI (%)	
0 (painless)	50	70.42	59.80-81.04	66	92.96	87.03-98.89	<0.05
1-3	14	19.72	10.46-28.98	5	7.04	1.07-12.93	<0.05
4-6	7	9.86	2.93-16.79	0			<0.05
Total	71			71			

The factors related with cancer pain relief 2 weeks after HIFU were showed in table 2. The pain relief was greater in female, age ≤ 55. There was no difference based on Karnofsky Performance Scale (KPS) and tumor location.

Table 2: Factors related with cancer pain relief 2 weeks after HIFU

	N 71	Before HIFU (NRS)	After HIFU (NRS)	P-value
Gender				0.04
male	46	0.54	0.20	
Female	25	1.24	0.08	
Age(year)				0.01
≤55	13	1.62	0.00	
>55	58	0.60	0.19	
KPS				0.07
<80	31	0.45	0.13	
80-100	40	1.23	0.19	
Primary tumor location				0.29
Head	35	0.60	0.17	
Body and tail	37	1.00	0.14	

tumor compression to relieve pain. Another mechanism of pancreatic cancer pain relief of HIFU was that HIFU treatment can cause injury of the peri-pancreatic nerve plexus to block the pain nerve impulses (Wang *et al*., 2011). HIFU can offer palliative care in advanced pancreatic cancer (Wu *et al*., 2005; Jang *et al*., 2010; Xiong *et al*., 2009; Xiaoping *et al*., 2013). The cancer pain control effect of HIFU on advanced pancreatic cancer had been reported in literatures (Orgera *et al*., 2011). In our patients with the third ladder analgesics, a higher cancer painless rate was observed two weeks after HIFU. This was the new finding that HIFU still has the effect of cancer pain relief in the patients with the third ladder analgesics.

When the ultrasound beams pass through tissue, some incident energy was reflected back at soft tissue–bone interfaces to cause skin burning pain. The ultrasound beams could be absorbed rapidly within the bone to cause the rib pain (Tempany *et al*., 2011). The thermal damage to diseased tissues of pancreas would cause the visceral pain. During the HIFU treatment, general anesthesia with intubation could control the severe pain caused by high temperature. After HIFU treatment, we observed 42 patients with treatment pain. The control of treatment pain after waking from anesthesia can improve comfort in those patients.

Management of HIFU treatment pain would depend on the pain region and pain score. It is necessary to make the patients understand the details of the treatment pain such as the pain mechanism and pain management methods. According to our observation the HIFU treatment pain started at half hour after the patients waking from anesthesia and the pain score were less than 4 in most patients. If the treatment pain score was above 4 the patient would need injective analgesics. The skin burning pain could be relieved with cold compress or medical cream. The HIFU treatment pain might last for 2-3 days and would decline gradually. There was no treatment pain more than 5 days. Cancer pain assessment was performed at 2 weeks after HIFU treatment in order to avoid the interference of treatment pain.

HIFU was safe in most clinical reports of pancreatic cancer patients and a few complications were reported (Jang *et al*., 2010; Orgera *et al*., 2011). No serious complications were observed in this study except treatment pain. The long term cancer pain relief and analgesic adjustment need to be observed in our future research.

CONCLUSION

HIFU can improve cancer pain relief further in the advanced pancreatic cancer patients with opioid analgesics. Meanwhile the treatment pain caused by HIFU could be managed easy because of its short duration and low pain score.

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Table 3: Region, onset time, duration and score of HIFU treatment pain

	N (%)	Mean	95%CI
HIFU treatment pain	42(59.15)	3.22(NRS)	2.90, 3.60
Skin burning pain	42(59.15)	2.74(NRS)	2.31, 3.17
Rib pain	30(42.90)	3.30(NRS)	2.85, 3.75
Visceral pain	29(40.80)	3.41(NRS)	3.00, 3.83
Onset time	42(59.15)	0.57(hour)	0.00, 2.02
Duration	42(59.15)	3.93(day)	3.46, 4.39

Table 4: Factors related with HIFU treatment pain

	N=71	Score of treatment pain	P-value
Gender			0.72
male	46	1.57	
Female	25	1.72	
Age(year)			0.01
≤55	13	2.69	
>55	58	1.38	
KPS			0.56
<80	31	1.48	
80-100	40	1.73	
Primary tumor location			0.65
Head	35	1.71	
Body and tail	37	1.57	

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