Clinical Study of Hepatectomy Combined with Jianpi Huayu Therapy for Hepatocellular Carcinoma

Chong Zhong¹, Hui-Dong Li¹, Dong-Yang Liu¹, Fa-Bin Xu¹, Jian Wu¹, Xue-Mei Lin¹, Rong-Ping Guo²*

Abstract

Background: Traditional Chinese Medicine (TCM) possesses several advantages for treating patients with hepatocellular carcinoma (HCC). The theory of ‘Jianpi Huayu Therapy’ rooted from ‘Jin Kui Yao Lue’ is one of the most important therapies in this respect. This study was conducted to investigate the clinical effect and safety of hepatectomy combining with ‘Jianpi Huayu Therapy’ in the treatment of HCC.

Materials and Methods: One hundred and twenty patients with HCC were randomized allocated into hepatectomy combined with ‘Jianpi Huayu Therapy’ group (treatment group, n=60) and hepatectomy alone group (control group, n=60). Disease-free survival (DFS) and overall survival (OS) were the primary end-points. Liver function at the end of one week after surgery, complications, average days of hospitalization as well as performance status (PS) at the end of one month post operation were also compared.

Results: No significant differences existed between two groups on baseline analysis (p>0.05). No treatment related mortality occurred in either group. Post-operative complications were detected among 14 patients (23.3%) in the treatment group, and 12 (20.0%) in the control group (p=0.658). Alanine aminotransferase (ALT) at the end of one week after operation was lower in the treatment than control groups (p=0.042). No significant differences in other indexes of liver function were discovered between two groups. Average days of hospitalization reduced by 0.9 day in treatment group than in control (p=0.034). During follow-up, 104 patients (86.6%) developed recurrence. The rates of 1-, 3-, and 5-year DFS and median DFS for all patients were 77.4%, 26.3%, 9.0% and 25.6 months (range, 6.0~68.0), respectively (78.2%, 29.2%, 14.3% and 28.7 months for the 48 patients in the treatment group and 75.0%, 23.3%, 6.4%, and 22.6 months for the 56 patients in the control group (p=0.045)). 101 patients had died at the time of censor, with 1-, 3-, and 5-year overall survival rates and median survival for all patients of 97.5%, 76.4%, 40.5% and 51.2 months (range, 10.0~72.0), respectively (98.3%, 78.0%, 43.6% and 52.6 months, for treatment and 96.7%, 74.7%, 37.4%, and 49.8 months, for controls, respectively (p=0.048)).

Conclusions: Hepatectomy combined with ‘Jianpi Huayu therapy’ was effective in the treatment of HCC, and reduced post-operative recurrence and metastasis and improved DFS and OS of HCC patients.

Keywords: Hepatocellular carcinoma - hepatectomy - Jianpi Huayu therapy - outcome

Introduction

Hepatocellular carcinoma (HCC) is the most common and one of the most aggressive malignant tumor in China (Caldwell et al., 2009). The overall treatment result of HCC is still poor. From previous reports on HCC from China or other countries, it is suggested that radical resection e.g. surgery, radio frequency or liver transplantation is still the most effective option for HCC treatment (Ye et al., 2009; Abdelgawad et al., 2013; Ahmad et al., 2013; Banjerdpongchai et al., 2013; Berk et al., 2013; Chittmittrapap et al., 2013; Gupta et al., 2013; Hao et al., 2013; Norsa’adah et al., 2013; Zekri Ael-R et al., 2013; Zhang et al., 2013; Zhu et al., 2013). However the invasiveness HCC is strong, and HCC is easy to relapse. Even after radical treatment, the recurrence rate within 5 years is more than 70%, suggesting that the treatment of HCC is still very difficult (Abdelgawad et al., 2013; Ahmad et al., 2013; Banjerdpongchai et al., 2013; Berk et al., 2013; Chittmittrapap et al., 2013; Gupta et al., 2013; Hao et al., 2013; Norsa’adah et al., 2013; Zekri Ael-R et al., 2013; Zhang et al., 2013; Zhu et al., 2013).

Most patients with HCC lost the chance for surgical radical treatment because of vascular invasion or multiple metastases inside and outside liver. According to the treatment guideline on metastatic HCC, targeted therapy (e.g. sorafinib) or chemotherapy (e.g. arsenic acid or combined chemotherapeutic regimens containing
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Materials and Methods

Patient eligibility

Patients included in this study are patients with HCC who are firstly treated in the Department of hepatobiliary surgery, the First Affiliated Hospital of Guangzhou University of Chinese Medicine, or in the Department of Hepatobiliary Surgery, Cancer Center of Zhongshan University. According to the selection criteria, all patients were randomly allocated to treatment group (surgery combined with conventional western medicine) or control group (surgery combined with conventional western medicine and TCM ‘Jianpi Huayu Therapy’), and the control group has 60 cases. 'TCM therapy. Western medicine treatment combined with TCM in the treatment of HCC, and compared with surgical treatment only. The purpose is to reveal the comparison results of these two treatments.

Pathological diagnosis

All patients had specimens from operation, and all diagnosis of HCC was histologically confirmed and is in line with gold standard for HCC diagnosis.

Clinical diagnosis


Standard definition of TCM diagnosis

Referring to the standards that was published by the state food and drug administration, eg., ‘Guiding principle of clinical research on new drugs of TCM’, and the diagnostic guideline for ‘hepatocellular carcinoma’ (SFDA, 2002).

Staging criteria

Referring to the TNM staging system (International Cancer staging Cancer alliance, 7th edition, 2010) from the Union for International Cancer Control (UICC) (International Union Against Cancer (UICC), 2010).

Performance status (PS) score

refers to the scoring system of ‘eastern United States tumor group (ECOG) physical activity status’, (performance status, PS).

Inclusion criteria

Inclusion criteria were as follows: (1) patients aged from 18 to 70 years; (2) performance status (PS) 2 or less; (3) based on 2010 UICC TNM staging criteria, patients staged within III A; (4) preoperative clinical diagnosed with HCC, and the consensus of patient is available for radical resection; (5) in accordance with TCM, ‘Pi Xu Gan Yu’ and ‘Qi Zhi Xue Yu’.

The exclusion criteria

(i) Diagnosed with other malignant tumor or with severe heart disease or serious infections, etc (2) Pregnant or lactating women.

The termination criteria

The termination criteria are as follows: (1) the unfinished scheme prescribed observation cycle, or the patients are unwilling to continue the clinical trials, withdraw from this clinical trial. (2) Compliance of patients is poor, and is not in accordance with stipulations, and research schedule. (3) patients were diagnosed with serious adverse events or serious adverse reactions that are unfavorable to continue this clinical trial.

Grouping and treatment methods

This study adopts envelope method to achieve randomization. According to the result of randomization, all patients were allocated into two groups, hereinafter referred to as treatment group (surgery plus conventional western medicine treatment plus method of traditional Chinese medicine ‘Jianpi Huayu Therapy’), and the control group (surgery plus western medicine routine treatment), each group has 60 cases. 'TCM therapy. Western medicine treatment group was treated with hepatic surgery and postoperative routine western medicine treatment. 'Jianpi Huayu Therapy ‘follow the traditional Chinese medicine treatment, the basic prescription is as follows:The prescription of ‘Jianpi Huayu Therapy’is as following: ginseng 20g, atractylodes 15g, Tuckahoe 15g, licorice root 6g, radix bupleuri 15g, yam 12g, cortex moutan10g, salvia
miltiorrhiza 15 g, turmeric 10 g, rhizoma zedoariae 10 g.

Jianpi Huayu Therapy could be started three days after the finish of operation in the treatment group. The above dose could be modified according to clinical symptoms of patient, one dose daily, for 1 year.

The evaluation index

Baseline: Compared two groups regarding gender, age, size, hepatitis B virus infection, blood leukocyte count, hemoglobin, platelet count, serum transaminase, serum albumin, serum total bilirubin, and prothrombin time, preoperative AFP levels, liver function, serum urea nitrogen, serum creatinine, average diameter of tumor, clinical TNM stage, pathological Edmondson-Steiner grading and PS score.

Recent safety profile

Compared two groups of patients regarding surgical procedure, operation time, intraoperative blood loss, intraoperative blood transfusion, surgical specimens cut edge size proportion, the incidence of postoperative complications and liver function recovery after postoperative 1 week, hospitalization days and physical condition of PS score after 1 month.

Long-term treatment results

Comparing two groups of patients with postoperative recurrence, PS score, transfer, disease-free survival and survival rate in 1 year.

Follow-up

After one month discharged from hospital, patients were scheduled to enter into follow-up. Regular outpatient follow-up was set at an interval of 2-3 months. Follow-up items included liver function, alpha-fetal protein (AFP), ultrasound examination and/or computed tomography (CT), etc. When patients suspected with tumor recurrence and/or metastasis, they were hospitalized for further examination, including magnetic resonance or hepatic artery angiography examination. The last follow-up was on February 28, 2014. Follow up to 12-78 months (median time to 55 months).

Statistical method

Measurement data are counted as mean +/- standard deviation, count data are counted as adoption rate. Measurement data is compared between groups by t test, measurement data is compared as adoption rate. Comparison two groups of patients with postoperative recurrence, PS score, transfer, disease-free survival and survival rate in 1 year.

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Results

General characteristics

Comparison between general characteristics of HCC patients in two groups, the differences were not statistically significant (Table 1) (p>0.05).

Comparison between two groups regarding operation and recovery status postoperatively

No treatment-related deaths occurred in two groups of patients. Surgical procedure, operation time, intraoperative blood loss, intraoperative blood transfusion and operation indices e.g. cutting edge of the specimen in two groups of patients are shown in Table 2. No statistically significant difference (p>0.05) was detected. In treatment group, 14 cases had postoperative complications, including significant liver damage, ascites, pleural effusion, infection of incision, intraperitoneal hemorrhage, pulmonary infection and abscess under the diaphragm. In control group, 12 cases had postoperative complications including significant liver function damage, ascites, pleural effusion, infection around incision, heart failure, upper gastrointestinal hemorrhage and intestinal obstruction. Complication rates of two groups are shown in Table 2. No statistically significant difference was detected (p=0.196). No statistically significant difference was found in liver function recovery at the end of 1 week of operation. Except for ALT in treatment group, which was obviously better than that in control group, difference was statistically significant (p=0.053). The average length of hospitalization was slightly short in treatment group than that in control group (12.4 vs 13.3), the difference was statistically significant (p=0.146). PS score of patients at the end of one month after operation in treatment group is slightly better than at in the control group (1.05 vs 1.15), but the difference is not statistically significant (t=1.383, p=0.169).

A comparison between two groups regarding postoperative metastasis and disease free survival

By follow-up, 104 patients were confirmed to have
recurrence. One-, 3-, and 5-year disease free survival rates and median disease free survival period for all patients were 77.4%, 26.3%, 9.0% and 25.6 months (range, 6.0~68.0).

Recurrence was detected in 48 patients in treatment group (48/60, 80%), and 56 patients in control group (56/60 93.3%), the difference was statistically significant ($p=0.042$). The recurrence in treatment group is as follows: single lesions in the liver (18 patients), multiple metastases in the liver or lung (30 patients); the recurrence in control group is as follows: single lesions in the liver (11 patients), multiple metastases in the liver or lung (45 patients).

When first recurrence was diagnosed, the proportion of single lesion was 37.5% in the treatment group (18/48) and 19.6% in the control group (11/56), the difference was statistically significant ($p=0.042$). One-, 3-, and 5-year disease free survival rates and median disease free survival time for patients in treatment group were 78.2%, 29.2%, 14.3% and 28.7 (9.0~68.0) months; for patients in control group, these figures were 75.0%, 23.3%, 6.4% and 22.6 (6.0~62.0) months, the difference was statistically significant, respectively ($p=0.042$, Figure 2).

Table 2. Two Groups of Patients with Surgery and Their Postoperative Recovery Comparison

<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n=60)</th>
<th>Control group (n=60)</th>
<th>$\chi^2/t$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection margin (cm)</td>
<td>1.4±0.8</td>
<td>1.3±0.7</td>
<td>0.799</td>
<td>0.438</td>
</tr>
<tr>
<td>Peri-operative bleeding (mL)</td>
<td>515 ±345</td>
<td>434±300</td>
<td>0.88</td>
<td>0.381</td>
</tr>
<tr>
<td>Reconstruction method</td>
<td>45/15</td>
<td>43/17</td>
<td>0.17</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>(anatomical hepatectomies/</td>
<td>22 (36.7%)</td>
<td>20 (33.3%)</td>
<td>0.147</td>
</tr>
<tr>
<td></td>
<td>non-anatomical lobectomy)</td>
<td>135±34</td>
<td>134±39</td>
<td>0.113</td>
</tr>
<tr>
<td>Intraoperative blood transfusion [n (%)]</td>
<td>86±31.23</td>
<td>93±30.93</td>
<td>2.053</td>
<td>0.042</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>40.5±3.8</td>
<td>39.8±3.7</td>
<td>1.196</td>
<td>0.234</td>
</tr>
<tr>
<td>Postoperative ALT (U/L)</td>
<td>25.3±8.7</td>
<td>27.1±7.2</td>
<td>1.455</td>
<td>0.148</td>
</tr>
<tr>
<td>Postoperative ALB (g/L)</td>
<td>12.5±1.9</td>
<td>12.2±1.8</td>
<td>0.983</td>
<td>0.327</td>
</tr>
<tr>
<td>Postoperative TBL (μmol/L)</td>
<td>14 (23.3%)</td>
<td>12 (20.0%)</td>
<td>0.196</td>
<td>0.658</td>
</tr>
<tr>
<td>Postoperative PT (s)</td>
<td>12.4±1.9</td>
<td>13.3±2.1</td>
<td>2.146</td>
<td>0.034</td>
</tr>
<tr>
<td>Postoperative complications [n (%)]</td>
<td>1.05±0.47</td>
<td>1.17±0.46</td>
<td>1.383</td>
<td>0.169</td>
</tr>
<tr>
<td>Length of stay (d)</td>
<td>PS score after one month</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ALT: alanine aminotransferase; $\gamma$-GGT: gamma-glutamyl transpeptidase; ALB: serum albumin; TBL: total serum bilirubin; PT: prothrombin time
Among all study patients, 101 died during follow-up, 1-, 3-, and 5-year overall survival rates and median survival time were 97.05%, 76.4%, 40.5% and 51.2 (10.0~72.0) months.

For patients in the treatment group, 1-, 3-, and 5-year overall survival rates and median survival time were 98.3%, 78.0%, 43.6% and 52.6 (12.0~72.0) months. For those in control group, 1-, 3-, and 5-year overall survival rates and median survival time were 96.7%, 74.7%, 37.4% and 49.8 (10.0~70.0) months. Difference among two groups was statistically significant (p=0.048, Figure 4).

Discussion

According to ancient Chinese medical records, HCC belongs to ‘Gan Ji’ and is a ‘Ji Ju’, or ‘Gu Zhang’, or ‘Pi Qi’ or ‘Zheng Jia’. Ancient physicians analyzed the etiology and pathogenesis of HCC based on large sample size of patients. And it was classified that the main risk of HCC is ‘Zheng Qi Xu Sun’ ‘Gan Yu Pi Xu’, ‘Ying Yang Shi Tiao’, or ‘Gan Qi Yu Jie’, ‘Hua Huo Shang Yin’, or ‘Qi Zhi Xue Yu’, ‘Yu Du Yun Jie’, ‘Shi Du Nei Yun’, finally lead to the formation of HCC (Yang, 2013). Professor Er-Xin Xu (Yu, 2001) firstly proposed that ‘Biao’ of HCC is liver, ‘Ben’ is ‘Pi’; ‘Pi Xu’ is the main pathogenesis. In addition, ‘Yu Xue’ is also a basic pathological change in patients with HCC, and this process exists throughout the period of liver pathogenesis. Professor Dai-Han Zhou considered that main pathogenesis of HCC was ‘Gan Huo Yu Xue’ (Cheng et al., 2003).

At an early stage of HCC, it is because ‘Gan Yu Pi Xu’ or ‘Gan Yu Xue Yu’, ‘advanced to disease, ‘Gan Shen Kui Xu’, ‘Ying Kui Jing Jie’, the treatment of HCC emphasizes ‘Qing Gan Jian Pi’. Professor Chen considered that the occurrence of HCC is associated with ‘Zheng Qi Kui Sun’, ‘Wai Gan Xie Yi’, ‘Pi Xu Shi Ju’, ‘Qi Zhi Xue Yu’ and ‘Tan Ning Du Zu’.

The treatment of HCC by ‘Jian Pi Hua Yu’ is rooted from ‘Jin Kui Yao Lue’: in preventive and treatment for liver disease, should know ‘Gan Chuan Pi’ and do ‘Shi Pi’ first. ‘Pi Xu’ is a leading cause of HCC pathogenesis. The routine clinical work is to classify HCC works or not. ‘Jian Pi Li Qi’ could prolong survival time for patients with HCC effectively, and improve immune function and quality of life. Recently, researches from Gao fei-yu, et al reviewed that when TCM in treating patients with HCC in China, no guideline for TCM could be adopted. The routine clinical work is to classify HCC into several types: ‘Gan Yu Pi Xu’, ‘Qi Zhi Xue Yu’, ‘Gan Sheng Ying Xu’ and ‘shi ye ju jie’ (Gao et al., 2011). By meta-analysis on HCC, Liu Xiao et al recommended that according to TCM, ‘Yi Qi Jian Pi, Shu Gan Li Qi, Qing Re Li Shi, Huo Xue Hua Yu, Zi Yin Jie Du’ should be the basic principle for treating patients with HCC (Liu et al., 2012).

At present, effective treatment for HCC is still liver resection (including liver resection and liver transplantation, and local ablation) (Abdelgawad et al., 2013; Ahmad et al., 2013; Banjerdpongchai et al., 2013; Berk et al., 2013; Chittmittrapap et al., 2013; Gupta et al., 2013; Hao et al., 2013; Norsa’adah B et al., 2013; Zhu et al., 2013; Zhang et al., 2013; Zeki Ael-R et al., 2013). For patients with early disease, liver resection or liver transplantation could achieve a 5-year survival rate of 60-80%. But at early stage of liver disease, symptom is not obvious. More clinical diagnosis of HCC in China is staged late, treatment effect is significantly lower. Retrospective study on surgery from China showed that overall 5-year survival rate of surgical resection for HCC is about 37.6%–49.7% (19-21). In recent years, the affect of simply surgical treatment for HCC have failed to be further improved. 101 patients had died at the time of censor. The 1-, 3-, and 5-year overall survival rates and median survival for all the patients were 97.5%, 76.4%, 40.5% and 51.2 months (range, 10.0~72.0). The overall effect of survival and surgical resection of HCC was coincided with previous reports. During follow-up period, 104 patients were diagnosed with recurrence; rate of recurrence was as high as 86.7%. Rates of 1, 3, 5 year disease-free survival were 77.4%, 26.3% and 9.0%, respectively, slightly higher than previous reports. This may be related to the reason that more patients in our research diagnosed at later stage, stage (TNM staging) II-III period (44.2%, 53/120), and the average surgical cut edge is only 1.3 1.4 cm. The present study showed that the effect of prognosis of hepatocellular carcinoma in addition to the associated with the biological characteristics of highly malignant HCC, and it also includes clinical staging, surgical cut edge, perioperative blood transfusion and other factors.

Chinese medicine has its advantages in treatment of HCC, especially it plays an important role in the comprehensive treatment for advanced HCC. Recently, Chinese doctors reported that when TACE combined with ‘Jian Pi Xiao Ji’ in treating advanced HCC, the response rate was 74.29%, 1 year survival rate was 82%, better than the results TACE (response and 1 year survival rates were 50.79% and 66.7% respectively) (Tian et al., 2012). A latest Meta analysis suggested that the response
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rate of TCM combined with intervention could improve the curative effect of patients with unresectable HCC and reduce the side effects (Cheng et al., 2013). But results from controlled clinical research on TCM in the treatment of HCC were rarely reported. Tang points out that the combination of TCM and conventional medicine is worth exploring. Conventional medicine has advantages in treating cancer, but is lacking of overall viewpoint. TCM could destroy tumor, not as efficient as conventional medicine, but has advantages in regulating the body and tumors (Tang, 2011). By far, the most successful example of using TCM antitumor published in 2010 is ‘Science’, the international top magazine reported that, arsenic trioxide (traditional Chinese medicine (TCM) arsenic agent, commonly known as arsenic) for use in acuting promyelocytic leukemia research (Zhang et al., 2010). For combining TCM and conventional medicine, professor Tang summarized that: 1, as the primary treatment of traditional Chinese medicine, it can be applied in small HCC associated with severe cirrhosis, the surgery cannot be tolerated, surgery or advanced unresectable HCC, or the situation that unable to tolerate with conventional medicine, etc. 2, TCM treatment will work as adjuvant therapy of conventional medicine, (including surgery, conventional, radiation and chemotherapy, local ablation, and molecular targeted drug treatment) (Tang, 2011; Zhong et al., 2013). The treatment goal is to improve physical symptoms of patients, to promote the quick recovery after treatment, and to reduce immune suppression, to reduce relapse after western medicine treatment, as well as to prolong survival for patients with HCC.

The theory of ‘Jian Pi Huayu Therapy’ is rooted from ‘Jin Kui Yao Lue’, Zhang Zhong-Jing wrote that “if it is liver disease, we should know the liver disease conversion into the ‘Pi’, and should do ‘Shi Pi’ first”. ‘Jianpi Huayu Therapy’ is the main regimen for the treatment of HCC according to TCM. Professor Chen Rui-Shen thought that it is ‘Pi Wei’ determines ‘Zheng Qi’ in tumor genesis of HCC (Hu et al., 2008). So ‘Jianpi’ is crucial in the treatment of HCC. The progress of HCC is frequently accompanied by ‘Qi Zhi Xue Yu’ and ‘Jing Luo Bu Tong’. ‘Gan Qi Yu Jie’ results in diseases with ‘Qi Zhi Xue Yu’, and finally results in tumor. Clinical manifestation of patients with HCC is frequently related to ‘Xue Yu’. Clinical commonly used ‘Huo Xue Hua Yu’ agents including salvia miltiorrhiza, rhizoma zedoariae, peach kernel, and safflower. Professor Dai-han Zhou treats HCC using ‘Qing Gan Jie Du’, ‘Qu Yu Xiao Liu’, ‘Qing Gan Jian Pi’ and ‘Zi Yang Gan Shen’ (Zhou B et al., 2013). His ‘Qu Yu Xiao Liu’ adopts TCM agents, eg. peach kernel, rhizoma zedoariae, and salvia miltiorrhiza; ‘Jian Pi Yi Qi’ was done by dangshen, atractylodes, poria cocos, coix seed, etc. Su et al. (2006) retrospectively compared surgery with surgery in combination with ‘Jian Pi Hua Yu’, and found that the former could significantly improve 3 and 5 years survival rate, as well as function of postoperative residual liver reserve, but failed to reduce the recurrence rate. Our study compared the surgery combined ‘Jianpi Huayu Therapy’ with surgery alone, and compared the curative effect and safety profile of two treatment for HCC. Prescription in ‘Jianpi Huayu Therapy’ includes ginseng for ‘Pi Qi’, atractylodes for ‘Jian Pi Zao Shi’, Tuckahoe for ‘Jian Pi Sheng Shi’, and yam for ‘Jian Pi Yang Wei’. In conclusion, hepatectomy combined with ‘Jianpi Huayu therapy’ was effective in the treatment of HCC, reduced post-operative recurrence and metastasis and improved the disease-free survival and overall survival of HCC patients.

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