


Chinese Herbal Medicine, Jian Pi Li Gan Decoction, Improved Survival of Nonresectable Hepatocellular Cancer After Radiofrequency Ablation: A Retrospective Study

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Abstract

Objective: To observe the effect of Jian Pi Li Gan Decoction (JPLGD) on long-term survival of nonresectable hepatocellular cancer (HCC) after radiofrequency ablation (RFA). **Methods:** Between January 2010 and February 2013, 95 patients with nonresectable HCC treated by RFA in our hospital were enrolled, of whom 47 patients received JPLGD accompanying RFA (JPLGD group), and 48 patients received RFA alone (control group). Medical records of these patients were retrospectively analyzed. Long-term survival, complication, and treatment event were compared. **Results:** Baseline characteristics did not differ between the 2 groups. No significant adverse effects or toxicities related to herbal medicine were found. The JPLGD group had significantly less liver failure (3/47 vs 10/48, $P = .0405$) and a higher treatment success rate than the control group (44/47 vs 37/48, $P = .0230$). The 3-year overall survival probability was significantly higher in the JPLGD group ($P = .0175$). **Conclusion:** JPLGD has the potential to effectively and safely improve long-term survival of nonresectable HCC by increasing treatment success of RFA.

Keywords

hepatocellular cancer, radiofrequency ablation, traditional Chinese medicine, overall survival, complication

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Introduction

Hepatocellular cancer (HCC) causes 690 000 deaths around the world yearly, and more than half of those deaths are in China, which makes it the second most fatal cancer in our country.¹ Radical hepatectomy and liver transplantation are recognized as curative therapies for HCC, but more than 70% of HCC patients lose the opportunity for curative therapy because of disease advancement, insufficient liver function reserve, or severe hepatocirrhosis.^{2,3} Therefore, new strategies to cure HCC are urgently needed. Radiofrequency ablation (RFA) has been utilized as an emerging local treatment and as adjuvant treatment during the waiting period for liver transplantation.^{4,5} Furthermore, RFA is proved to be an appropriate treatment for uninodular and even for medium and large HCCs.^{6,7} However, the RFA procedure usually causes severe complications, including hepatic failure, pleural effusion, hemorrhage, and hepatic abscess. RFA is terminated or postponed if life-threatening

complications occur, which harms the long-term survival. As a result, the overall efficacy of RFA is unfavorable and 5-year survival probability is still less than 10%.^{8,9} Thus, a systematic approach to preventing and treating the complications caused by RFA is necessary.

Traditional Chinese medicine (TCM) has been commonly used as adjuvant therapy in treating cancers with significant beneficial effects, but with few adverse effects reported.^{10,11} In our clinical practice, we observed that the Jian Pi Li Gan Decoction (JPLGD) could relieve RFA-related complications. In this retrospective study, we aimed

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to determine whether JPLGD could improve the prognosis of patients with nonresectable HCC treated by RFA.

Methods

Patients

Between January 2010 and February 2013, 95 patients with nonresectable HCC treated by RFA in our hospital were enrolled, of whom 47 patients received JPLGD accompanying RFA (JPLGD group), and 48 patients received RFA alone (control group). Before RFA treatment, all patients accepted percutaneous liver biopsy to confirm the HCC diagnosis. Eligibility criteria were the following: (1) age from 18 to 75 years; (2) Karnofsky performance score (KPS) ≥ 70 ; (3) no indication for radical operation; (4) number of lesions ≤ 3 , diameter of single lesion > 3 cm but greatest diameter ≤ 10.0 cm; (5) distance ≥ 0.5 cm from lesions to the hepatic hilum, gallbladder, or the common bile duct and ≥ 1 cm to the intestine; (6) no previous anticancer therapy; (7) Child-Pugh class A or B; (8) no portal thrombus or systemic metastasis; (9) no refractory ascites or organ dysfunction; (10) no diffuse or infiltrative tumors; and (11) full follow-up data.

This study was approved by the institutional research ethics committee of the First People's Hospital affiliated to Huzhou Normal College and complied with the principles of the Declaration of Helsinki and "Good Clinical Practice" guidelines. All patients signed the informed consent.

RFA Treatment

All patients accepted ultrasound-guided percutaneous RFA under moderate sedation anesthesia and local infiltration anesthesia. A commercially available RFA system (S-1500 Radiofrequency Ablation System; Medsphere International, Shanghai, China) was used to generate up to 150 W of energy to cause adequate coagulation necrosis of the target tissue and a 0.5- to 1.0-cm margin. Expandable electrodes (Medsphere International, Shanghai, China) with an outer insulated needle and a core needle with multiple small umbrella-shaped electrodes were advanced under ultrasound supervision. The core needles were expanded at a diameter ranged from 3.0 to 5.0 cm and retracted by a movable handle. Selecting an electrode diameter size depends on the size of the target tumor. Treatment began at a 50-W level, with wattage increasing 10 W every 2 minutes until tissue impedance increased and the prevention of further current flow or for 10 minutes. During the procedure, we monitored the real-time echo changes in the ablated region. For some larger lesions, additional overlapping RF ablation treatments were performed when needed to attain adequate ablation margins by changes in the radial position of the umbrella-shaped electrodes. The needle track was ablated

Table 1. Components of Jianpi Ligan Decoction With Latin and English Names.

Name in Latin	Name in English	Dose
<i>Radix Codonopsis</i>	Pilose Asiabell Root	20 g
<i>Rhizoma Atractylodis Macrocephalae</i>	Largehead Atractylodes Rhizome	10 g
<i>Poria Cocos</i>	Fu-ling	15 g
<i>Radix Glycyrrhizae</i>	Liquorice Root	5 g
<i>Rhizoma Dioscoreae</i>	Common Yam Rhizome	15 g
<i>Rhizoma Pinelliae</i>	Pinellia Tuber	10 g
<i>Fructus Crataegi</i>	Hawthorn Fruit	15 g
<i>Lotus Seed</i>	Semen Nelumbinis	20 g
<i>Herba Artemisiae Scopariae</i>	Virgate Wormwood Herb	50 g
<i>Pericarpium Arecae</i>	Areca Peel	25 g

while withdrawing the RFA electrode in all cases. Patients' vital signs were continuously supervised during the RFA procedure.

Within 2 to 4 hours after RFA, an ultrasound scan was performed to detect active bleeding and patients were transferred to an inpatient ward. Patients were monitored in hospital for 1 to 3 days after RFA procedure and hospital stay was prolonged in patients with large tumors, organ failures, or major complications. Antibiotics were not prophylactically used before or after RFA procedure.

Contrast-enhanced computed tomography (CECT) was applied to evaluate the efficacy of RFA within 14 days after the procedure. Treatment success was confirmed until no residual tumor in the liver was revealed by follow-up CECT. Patients underwent RFA every 2 to 4 weeks before treatment success was achieved. The treatment was discontinued if insufficient liver function or any contraindication was observed or patient request.

Administration of Chinese Herbal Medicine

The use of the herbal medicine was chosen by patients themselves after discussions with doctors, and the cost of the herbal medicine was covered by medical insurance. Patients who chose to accept the herbal medicine received 100 mL of the JPLGD orally once per day, 30 minutes after meals. Administration of the JPLGD was begun on the same day of RFA onset and continued for 1 week after RFA.

The composition of the JPLGD (Table 1) is as follows: Pilose Asiabell Root 20 g, Largehead Atractylodes Rhizome 10 g, Fu-ling 15g, Liquorice Root 5 g, Common Yam Rhizome 15 g, Pinellia Tuber 10 g, Hawthorn Fruit 15 g, Semen Nelumbinis 20 g, Virgate Wormwood Herb 50 g, and Areca Peel 25 g. The JPLGD was decocted in the hospital and aseptically packaged for patients as discharge medicine.

Outcome Measurements and Follow-up

The medical records of the enrolled patients were retrospectively analyzed. Complications, overall survival, and intrahepatic relapse-free survival were compared according to medical records and follow-up data. After the last treatment session, patients were followed up every 3 months for the first 2 years and every 6 months after that until last follow-up or death. Overall survival was counted from RFA onset to death or the last follow-up. Intrahepatic relapse-free survival was performed among those who accomplished treatment success and was counted from RFA onset to intrahepatic relapse, death or last follow-up, whichever occurred earliest. Intrahepatic relapse included newly developed tumor nodules distant from the primary tumors and relapse in situ, and was diagnosed by imaging and, if possible, cytological test or biopsy. In accordance with our ethical principles, optimal therapies (such as repeated RFA, transarterial chemoembolization, supportive care, etc) were performed as soon as possible after detection of tumor progression or relapse.

Statistical Analysis

All continuous variables were expressed as mean \pm SD. Pearson χ^2 tests with Fisher exact probability were used to analyze the frequency distributions of categorical variables between the 2 groups. One-way analysis of variance was utilized to compare the differences in means of continuous variables between the 2 groups. Kaplan-Meier method was used to compare long-term survival and log-rank test was performed to analyze survival curves. *P* value $<.05$ was considered statistically significant.

Results

Baseline Characteristics

No statistical difference was found in baseline characteristics, in terms of age, gender, KPS, α -fetoprotein (AFP) level, quantity of tumors, Child-Pugh class, main tumor size, and hepatitis virus infection between the two groups (Table 2).

Complication and Treatment Success

No RFA-related death or hepatic coma was observed. No significant adverse effects or toxicities related to herbal medicine were found in the JPLGD group. Complications were shown in Table 3. All complications were carefully supervised and controlled by conservative treatment. Five patients experienced moderate intraperitoneal hemorrhage (3 from the control group and 2 from the JPLGD group, *P* = .9807) and 4 patients experienced moderate gastrointestinal hemorrhage (3 from the control group and 1 from the JPLGD group, *P* = .6246). Liver failure (Child-Pugh class

Table 2. Baseline Characteristics.

Characteristics	Control Group (n = 48)	Combination Group (n = 47)	<i>P</i>
Age, y, mean \pm SD	50.74 \pm 10.45	51.38 \pm 11.86	.7807
Main tumor size, cm, mean \pm SD	6.45 \pm 1.47	6.88 \pm 1.64	.1815
Gender, n			
Male	39	37	.7582
Female	9	10	
Child-Pugh class, n			
A	30	32	.5676
B	18	15	
No. of tumors			
1	15	13	.4314
2	19	16	
3	14	18	
KPS, n			
70	12	14	.8227
80	14	13	
90	16	12	
100	6	8	
Background liver disease, n			
HBV	34	31	.8665
HCV	10	11	
Other	4	5	
AFP level (ng/mL), n			
<100	13	15	.8692
100-400	18	16	
>400	17	16	

Abbreviations: AFP, α -fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; KPS, Karnofsky performance score.

C) was found in 3 cases of the JPLGD group and in 10 of the control group. Therefore, fewer patients from the JPLGD group developed liver failure, which led to discontinuation of RFA (3/47 vs 10/48, odds ratio = 3.86, *P* = .0405). Due to patient wishes, RFA was discontinued in 1 patient of the control group. In the JPLGD group, treatment success was accomplished in 44 patients: after 3 RFA courses in 20 patients, 4 RFA courses in 15 patients, and 5 RFA courses in 9 patients. In the control group, treatment success was accomplished in 37 patients: after 3 RFA courses in 15 patients, 4 RFA courses in 12 patients, and 5 RFA courses in 10 patients. The JPLGD group had a significantly higher rate of treatment success than the control group (44/47 vs 37/48, *P* = .0230) (Table 4). The number of RFA courses until treatment success showed no difference between the 2 groups (*P* = .5351) (Table 4).

The 14 patients who discontinued RFA treatment received symptomatic and supportive therapy after RFA discontinuation and were followed up until death or last follow-up.

Table 3. Complications.

Complication	Control Group (n = 48), (No. of Cases)	Combination Group (n = 47) (No. of Cases)	P
Fever	14	8	.1606
Pleural effusion	10	6	.2935
Liver abscess	2	1	.5699
Spontaneous bacterial peritonitis	4	3	.9769
Abdominal pain	12	9	.4920
Liver failure (Child-Pugh class C)	10	3	.0405
Intraperitoneal hemorrhage	3	2	.9807
Gastrointestinal hemorrhage	3	1	.6246

Table 4. Treatment Success.

Treatment Event	Control Group (n = 48) (No. of Cases)	Combination Group (n = 47) (No. of Cases)	P
Treatment success	37	44	.0230
Treatment discontinuation	11	3	
Sessions of radiofrequency ablation until treatment success			
3	15	20	.5351
4	12	15	
5	10	9	

Overall Survival

A total of 64 patients died within the first 3 years after RFA onset (35 of the control group and 29 of the JPLGD group). Among those patients, 24 patients of the control group and 22 patients of the JPLGD group died of tumor progression. Other mortalities resulted from hepatic failure. A significantly higher 3-year overall survival probability was observed in the JPLGD group (38.30% vs 27.08%; hazard ratio [HR] = 1.7772; 95% CI = 1.0788-2.9277; P = .0175 by log-rank test) (Figure 1). However, among the patients who accomplished treatment success, 24 of 37 patients from the control group and 27 of 44 patients from the JPLGD group died within the first 3 years after RFA onset (38.64% vs 35.14%; HR = 1.3876; 95% CI = 0.7906-2.4354; P = .2309 by log-rank test) (Figure 2).

Intrahepatic Relapse-Free Survival

Intrahepatic relapse-free survival was analyzed among patients who accomplished treatment success. Within the

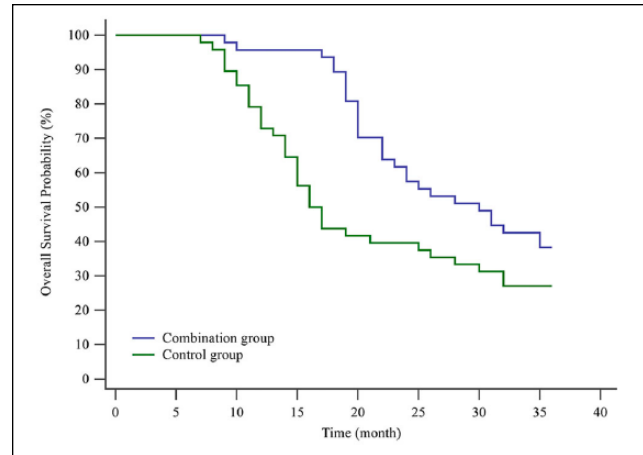


Figure 1. Kaplan-Meier curves of 3-year overall survival. During the first 3 years after radiofrequency ablation (RFA) onset, 35 patients from the control group and 29 patients from the Jian Pi Li Gan Decoction (JPLGD) group died. The 3-year overall survival probability was significantly higher in the JPLGD group than in the control group (38.30% vs 27.08%; hazard ratio [HR] = 1.7772; 95% CI = 1.0788-2.9277; P = .0175 by log-rank test).

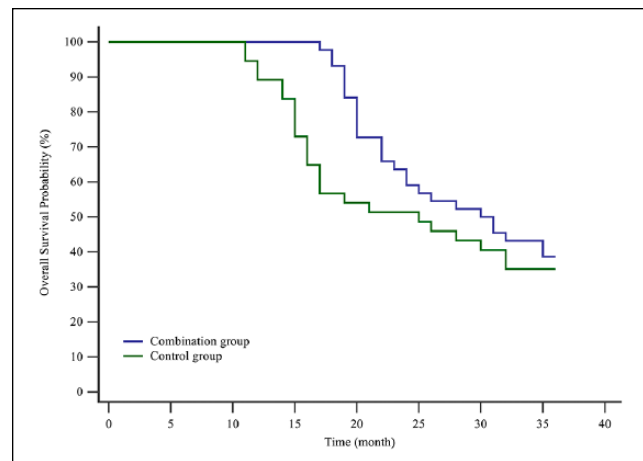


Figure 2. Kaplan-Meier curves of 3-year overall survival of patients who achieved treatment success. Treatment success was achieved in 44 patients in the Jian Pi Li Gan Decoction (JPLGD) group and 37 patients in the control group. Among those patients, 24 patients from the control group and 27 patients from the JPLGD group died during the first 3 years after radiofrequency ablation (RFA) onset. There was no significant difference in 3-year overall survival probability of patients who achieved treatment success between the 2 groups (38.64% vs 35.14%; HR = 1.3876; 95% CI = 0.7906-2.4354; P = .2309 by log-rank test).

first 3 years after RFA onset, 26 of 37 cases from the control group and 30 of 44 cases from the JPLGD group were found to develop intrahepatic relapse. Therefore, no significant difference was found in the 3-year intrahepatic relapse-free

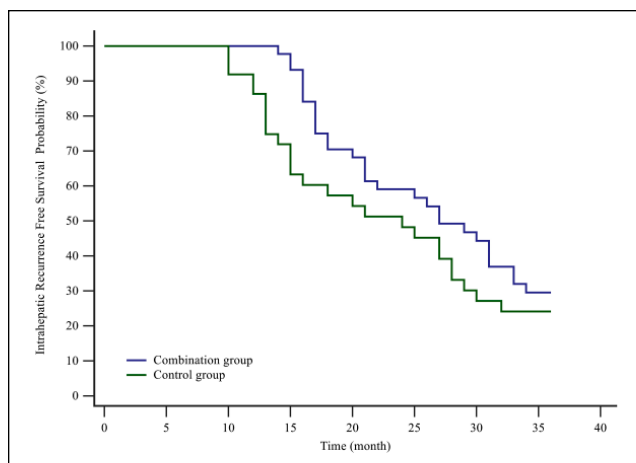


Figure 3. Kaplan-Meier curves of 3-year intrahepatic relapse-free survival of patients achieved treatment success. Treatment success was achieved in 44 patients in the Jian Pi Li Gan Decoction (JPLGD) group and 37 patients in the control group. Among those patients, 26 patients from the control group and 30 patients from the JPLGD group developed intrahepatic relapse. No significant difference between the 2 groups was found in 3-year intrahepatic relapse-free survival probability in patients who achieved treatment success (31.82% vs 29.73%; HR = 1.4264; 95% CI = 0.8311-2.4481; $P = .1722$ by log-rank test).

survival between the 2 groups (31.82% vs 29.73%; HR = 1.4264; 95% CI = 0.8311-2.4481; $P = .1722$ by log-rank test) (Figure 3).

Discussion

HCC has become the fifth most fatal cancer around the world with approximate 1,000,000 new cases every year.¹² However, most HCCs are not detected until intermediate or even advanced stages, and only 30% of HCCs are candidates for curative treatments.

For nonresectable HCCs, RFA was commonly used as a palliative treatment for disease control. In 1996, percutaneous RFA was first utilized to cure primary liver cancer or liver metastatic malignancies.¹³ Subsequently, further research suggested the merits of RFA in treating HCCs.¹⁴⁻¹⁶ However, the high incidence of complications of RFA greatly restricts its application¹⁷ and may lead to discontinuation of treatment with adverse effects on patients' prognosis.¹⁸ Various strategies have been used to alleviate RFA-related complications, but few of them were successful. Traditional Chinese medicine, characterized by its unique theoretical system, has been applied to cure diseases in our country for thousands of years. As an important part of TCM, Chinese herbal medicines were administered along with transarterial chemoembolization, RFA, or surgery to relieve treatment-related complications.^{19,20} JPLGD in this study has been used to improve tolerance of patients with

nonresectable HCC to anticancer therapies during our clinical practice for a long period. In its composition, Pilose Asiabell Root primarily regulates spleen and enhances immunity, complemented by Largehead Atractylodes Rhizome and Pinellia Tuber.²¹⁻²³ Hawthorn Fruit and Common Yam Rhizome coordinate intestines and stomach, promote digestion, and eliminate constipation.^{24,25} Fu-ling and Areca Peel improve urination and reduce ascites.^{26,27} Semen Nelumbinis helps expel internal heat and tranquilize.^{28,29} Licorice Root protects the liver and accelerates detoxification.³⁰ Virgate Wormwood Herb decreases jaundice and restores liver function.³¹

The present study showed that fewer patients from the JPLGD group developed liver failure (Child-Pugh class C) leading to discontinuation of RFA (3/47 vs 10/48, odds ratio = 3.86, $P = .0405$). Therefore, the JPLGD group had more patients accomplishing treatment success than the control group (44/47 vs 37/48, $P = .0230$).

As a result, JPLGD group obtained a significantly higher 3-year overall survival probability than the control group (38.30% vs 27.08%; HR = 1.7772; 95% CI = 1.0788-2.9277; $P = .0175$ by log-rank test). However, among all patients who achieved treatment success no differential benefit between groups was observed in 3-year overall survival probability (38.64% vs 35.14%; HR = 1.3876; 95% CI = 0.7906-2.4354; $P = .2309$ by log-rank test) or 3-year intrahepatic relapse-free survival probability (31.82% vs 29.73%; HR = 1.4264; 95% CI = 0.8311-2.4481; $P = .1722$ by log-rank test).

Conclusions

We could conclude that JPLGD has the potential to effectively and safely improve long-term survival of nonresectable HCC by increasing treatment success of RFA. However, there are some limitations to our study. Because of the retrospective nature and the small sample capacity, further prospective research with larger sample capacity is required to verify our results. Moreover, the herbal medicine was administered according to patients' choice, rather random assignment, though no significant difference was found in baseline characteristics between the 2 groups. Additionally, more investigation is needed to determine the potential mechanisms of therapeutic effects of JPLGD.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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