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Original Article

Efficacy of radiofrequency ablation plus hepatic arterial chemoembolization in primary hepatic carcinoma and its effect on serum markers

Lina Xiong[1*], Li Zhang[1*], Jing Ma[2], Jie Li[1]

[1]Department of Digestive Disease, Liyuan Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan City, Hubei Province, China; [2]Emergency Department and Intensive Care Unit, Liyuan Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan City, Hubei Province, China. [*]Equal contributors and co-first authors.

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Abstract: Objective: To investigate the efficacy of radiofrequency ablation (RFA) in combination with hepatic arterial chemoembolization (HACE) in the treatment of primary hepatic carcinoma (PHC) and its effect on the serum markers. Methods: A total of 74 patients with PHC who were admitted to our hospital from February 2013 to January 2014 were randomly allocated to the experimental group (n=37) and the control group (n=37) in terms of a random number table. The patients in the control group received HACE whereas those in the experimental group underwent RFA plus HACE. The adverse events during treatment, the efficacy 2 months after treatment, the recurrence rate, the survival rate and the degree of tumor necrosis 3 years after surgery were compared between the two groups. In addition, the changes in serum markers before and after treatment were observed in the two groups. Results: Two months after treatment, glutamyl transpeptidase (GGT) lowered significantly in the experimental group as compared with the control group (P=0.000), so was alpha fetoprotein (AFP). And the difference was significant between the two groups (P=0.000). The overall clinical response and the rate of tumor complete necrosis were significantly higher in the experimental group (P=0.017, P=0.000, respectively). The 3-year recurrence rate was markedly lower (P=0.027), but the survival rate was strikingly higher in the experimental group (P=0.006). Furthermore, no significant differences were noted in the incidence of adverse events between the two groups (P=0.662). Conclusion: The protocol of RFA in combination with HACE in PHC was associated with greatly improved serum markers, reduced recurrence rate and enhanced survival rate of patients with PHC. Therefore, it is a safe and effective alternative for treatment of PHC.

Keywords: Radiofrequency ablation, hepatic arterial chemoembolization, primary hepatic carcinoma, serum marker

Introduction

Primary hepatic carcinoma (PHC) is a common malignancy in China. The most effective method to cure PHC is surgical resection. The rates of five-year survival among the patients ranged from 27% to 42% after resection, but only 15% to 25% patients showed the exact indications to reoperation [1, 2]. The more common technique for treatment of hepatic carcinoma is hepatic arterial chemoembolization (HACE), which is an effective techniquein inhibiting postoperative tumor recurrence and prolonging the survival of patients [3]. Over the past decade, radiofrequency ablation (RFA), one of the typical local minimally invasive procedures in the treatment of PHC, has been proved to be an effective modality in treating small hepatic carcinoma [4]. Clinically, RFA or HACE alone is ineffective in the treatment of PHC [5, 6]. Accordingly, it is necessary to take a comprehensive treatment. HACE in combination with RFA has shown to exert a synergistic effect in the treatment of PHC [7, 8]. A combination of RFA with HACE can complement each other and achieve better results, but other studies have demonstrated no significant improvement in survival among patients with a combined therapy as compared with those with HACE alone [9]. Few studies have been involved in HACE plus RFA, so the effect and prognosis of the patients concerned should be evaluated com-

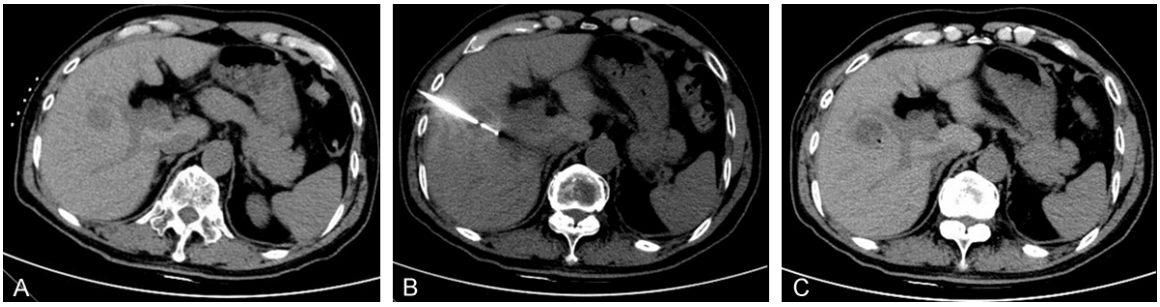

Figure 1. Radiofrequency ablation for primary hepatic carcinoma. A: Before operation; B: During operation; C: After operation.

prehensively. The present study was designed to analyze the efficacy of RFA in combination with HACE in PHC treatment and its effect on serum markers, providing experimental and clinical evidence for the treatment of PHC.

Materials and methods

Clinical data

A total of 74 patients with PHC admitted to our hospital from February 2013 to January 2014 were recruited in this study. Inclusion criteria included the patients were diagnosed in line with the Criteria for Clinical Diagnosis of Primary Hepatic Carcinoma; they were diagnosed as having PHC, as demonstrated by serum alpha fetoprotein (AFP), CT or MRI; the Karnofsky Performance Status (KPS) score ≥70; the Child-Pugh scores or TNM stages of liver function were accurate; no previous systemic chemotherapy or radiotherapy. Patients were excluded if they were associated with obvious hepatic arteriovenous fistula, had hepatic tumor exceeded 70% of the volume of the liver, had obvious cachexia, jaundice, ascites or distant metastasis or a contraindication to chemotherapy. The entire study was completed with the written informed consent of each patient and their families, and the approval of the Hospital Ethics Committee. The eligible 74 patients were allocated to the experimental group (n=37) and the control group (n=37) in terms of a random number table.

Methods

The patients in the control group were assigned to under go HACE. They were required to be anesthetized with an intramuscular injection of ketamine (10 mg) 0.5 h before surgery after fasting for 5 h. Under local anesthesia, the femoral artery was punctured and the contrast agents were injected. After the site of hepatic tumor artery was confirmed by digital subtraction angiography, a catheter was inserted into the feeding artery, into which nonionic contrast agent lipiodol (5 ml), 5-fluorouracil (2 g), and oxaliplatin (200 mg) were injected. Absorbable gelatin sponge and polyvinyl alcohol particles were also injected under the guidance of angiography and fluoroscopy. The catheter was removed, followed by pressurized bandaging at the punctured site, with the lower limbs of the patient keeping in the braking state for 12 h after surgery. The punctured site was closely observed for hematoma and blood oozing. The skin color and dermatoglyph of the lower limbs, as well as the pulses of the dorsal artery artery were also under close observation.

The patients in the experimental group underwent RFA in addition to the above-mentioned therapy assigned to the control group. The procedures of RFA were initiated at 15 d after HACE. Conventional skin disinfection was performed at the insertion site under the guidance of CT. With the patient under local anesthesia, the RF electrode was inserted into the tumor tissue under the guidance of CT, with the ablation power at 60 W for 10-15 min. Single needle ablation was administered for 1-3 bulbous focus, bilateral focal ablation for 4-6 bulbous focus, and fractional ablation for poor-tolerated patients. The RFA range can be extended to 1 cm inside the normal tissues to ensure full ablation (**Figure 1**).

Outcome measures

Primary outcomes included serum markers glutamyl transpeptidase (GGT) and alpha fetopro-

Table 1. General data of patients

Variable	Group		t/X^2	P
	Experimental	Control		
Case	37	37		
Gender (n, %)			X^2=0.5103	0.4750
Male	21 (55.76)	24 (64.86)		
Female	16 (43.24)	13 (35.14)		
Age (year)	59.45±5.34	60.06±5.41	t=0.4881	0.6269
Tumor diameter (cm)	5.08±0.84	5.09±0.86	t=0.0506	0.9598
Hepatic cancer stage (n, %)			X^2=0.8860	0.6421
I	11 (29.73)	13 (35.14)		
II	18 (48.65)	19 (51.35)		
III	8 (21.62)	5 (13.51)		
Child-Pugh class of hepatic function (n, %)			X^2=0.2372	0.6263
A	25 (67.57)	23 (62.16)		
B	12 (32.43)	14 (37.84)		

Table 2. Serum markers of the patients before and after treatment

Variable	Group		t	P
	Experimental	Control		
Case	37	37		
GGT (U/L)				
Pre-treatment	134.24±14.02	137.32±14.41	0.932	0.355
Post-treatment	98.32±9.14*	121.43±11.24	9.703	0.000
Difference	35.89±10.23*	16.04±9.76	11.765	0.000
AFP (ng/mL)				
Pre-treatment	743.21±42.15	747.43±41.03	0.436	0.664
Post-treatment	364.25±21.45*	621.51±26.32	37.098	0.000
Difference	375.69±31.21*	124.94±34.55	26.162	0.000

Note: In comparison with the pre-treatment, *P=0.000.

tein (AFP), as well as clinical response. Secondary outcomes consisted of tumor necrosis, survival, recurrence, and adverse events.

The serum markers (GGT and AFP) of the patients before treatment and at two months after treatment were compared between the two groups. After 5 mL of fasting venous blood was drawn from each patient at 1 d before treatment and 2 months after treatment, respectively, the blood was processed for anticoagulation, from which serum was isolated. The GGT levels were measured with the use of an automatic biochemical analyzer whereas the AFP levels were detected using the chemiluminescent microparticle immunoassay. The kits were provided by Kurt Backman (US). All the procedures were followed strictly after the instructions of the kits.

The treatment outcomes were followed up for 3 year in accordance with the Response Evaluation Criteria in Solid Tumors [5]. The criteria for tumor response include complete response (the disappearance of all target lesions), partial response (at least a 30% decrease in the sum of the longest diameter of target lesions at baseline), progressive disease (the appearance of new lesions or at least a 20% increase in the sum of the longest diameter of target lesionsat baseline), and stable disease (neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease in target lesions at baseline). The equation for calculation of overall response rate states: Overall response rate = (Cases of complete response + Cases of partial response)/ total number of patients * 100%.

Partial necrosis was defined as 50-89% of tumor necrosis; incomplete necrosis as 90-99% of necrosis and complete necrosis as 100% of necrosis.

The rates of survival and recurrence at 3-year follow up were compared between the two groups. The recurrence rate was defined as the probability of appearance of new lesions or

Table 3. Short-term clinical response of patients

Group	Case	Compete response	Partial response	Stable disease	Progressive disease	Overall response
Experimental	37	26 (70.27)	5 (13.51)	4 (10.81)	2 (5.41)	31 (83.78)
Control	37	7 (18.92)	12 (32.43)	11 (29.73)	7 (18.92)	19 (51.35)
X^2		9.745	8.703	9.365	8.374	8.880
P		0.007	0.018	0.010	0.024	0.017

increased primary lesions within 3-6 months after the first cycle of treatment. Adverse events (fever, nausea, vomiting, abdominal pain, cholecystitis, portal hypertensive bleeding, and ulcerated bleeding) during treatment were assessed among the patients in the two groups.

After treatment, all patients were followed by outpatient appointments and telephone calls once every 3 months for 3 years for observation of clinical outcomes of the patients.

Statistical analysis

The data analyses were performed with the use of SPSS software, version 20.0. Quantitative data including serum markers were represented as $\bar{x} \pm sd$; the independent samples t-test was used to compare serum markers before treatment with those after treatment for both groups; the differences in improvements inserum markers between the two groups were compared using the independent samples t-test; intragroup comparisons before and after treatment were made by the paired samples t-test. The count data including the rates of adverse events and clinical response of the patients were represented as n, (%); inter-group comparisons in adverse events and clinical response were performed with the use of the chi-square test. $P<0.05$ was considered as statistically significant.

Results

General data of the study patients

There were no significant differences between the two groups in such clinical data as age, gender, tumor diameter, hepatic cancer staging, so they were comparable ($P>0.05$, **Table 1**).

Serum markers

No striking differences in serum markers were found between the two groups ($P>0.05$). The levels of the serum markers GGT and AFP 2 months after treatment decreased significantly in the patients of both groups, and the differences between the two time points were significant (all $P=0.000$). Two months after treatment, the levels of GGT and AFP dropped significantly in the experimental group, as compared with the control group ($P=0.000$, **Table 2**).

Short-term clinical response

After treatment, the overall clinical response of patients in the experimental group improved significantly as compared to that of the control group ($P=0.017$, **Table 3**).

Tumor necrosis

The rate of complete tumor necrosis was significantly higher, but the rates of incomplete necrosis and partial necrosis were significantly lower in the experimental group than in the control group ($P<0.05$, **Table 4**).

Recurrence and survival

In 3-year follow-up, the recurrence rate was markedly lower ($P=0.027$), but the survival rate improved significantly in the experimental group as compared with the control group ($P=0.006$, **Table 5**).

Adverse events

Abdominal pain, nausea and vomiting occurred in one patient, respectively; mild fever occurred in 2 patients in the experimental group. Nausea, vomiting, and mild fever occurred in one patient, respectively, and abdominal pain occurred in three patients in the control group. All the patients improved after receiving symptomatic treatment. No serious adverse events such as cholecystitis, portal hypertensive bleeding and ulcerated bleeding were noted among the patients in the two groups. Furthermore, no significant difference in the rate of adverse events was observed between the two groups ($X^2=0.192$, $P=0.662$).

Discussion

Standard combined therapy is the primary effective protocol to improve the clinical response

Table 4. Tumor necrosis of the patients (n, %)

Group	Case	Complete necrosis	Incomplete necrosis	Partial necrosis
Experimental	37	32 (86.49)	4 (10.81)	1 (2.70)
Control	37	11 (29.73)	15 (40.54)	11 (29.73)
X^2		10.032	15.674	17.293
P		0.005	0.000	0.000

Table 5. Recurrence and survival of the patients (n, %)

Group	Case	Recurrence	Survival
Experimental	37	8 (21.62)	36 (97.29)
Control	37	17 (45.95)	28 (75.68)
X^2		4.893	7.400
P		0.027	0.006

in advanced hepatic carcinoma. HACE is one of the most effective techniques for palliative therapy. By injecting the mixture of antitumor agents and lipiodol into the feeding artery of hepatic tumor viathe catheter, it is effective in inducing tumor necrosis and shrinkage, remaining themaximum hepatic function, reducing the prevalence of postoperative complications, and prolonging the time for survival in patients. However, HACE alone is imperfect in treatment of hepatic carcinoma [10-13]. As far as RFA is concerned, an ablation needle is inserted into the tumor via percutaneous puncture under the guidance of adjunct imaging. With the heat generated by high frequency current, protein in the local tissues degenerates, leading to coagulative necrosis and even carbonization. Thus, the goal of tumor treatment achieves [14, 15]. RFA has shown to be characteristic of small trauma, good tolerance and rapid recovery. Its efficacy in treating small hepatocellular carcinoma is similar to that of surgery [16, 17]. However, RFA is limited in treatment of lesions adjacent to inferior vena cava, portal vein and diaphragm, with high complication rate and risk.

In recent years, increasing attention has been paid to the combined therapy of HACE and RFA due to its complementary benefits. The protocol of HACE plus RFA has shown to significantly improve the survival of hepatocellular carcinoma as compared with HACE alone [18, 19]. In addition, HACE in combination with RFA has reported to be also effective for treatment of patients unable to receive re-embolization or those with residual tumors after repeated embolization [20, 21]. Cytokine AFP is a specific marker for PHC, and GGT exists in the hepatobiliary system. GGT is also used as a sensitive marker for diagnosis of hepatobiliary diseases. The presence of hepatobiliary tumor may produce pressure to the liver or gallbladder and obstruct the bile excretion, increasing the concentration of GGT in hepatocytes [22]. In the present study, considerable reductions in the levels of AFP and GGT were observed in PHC patients after the combined treatment of RFA and HACE, as compared with HACE alone. This suggests that the patients became better and the short-term clinical response was also perfect. In addition, the rate of complete tumor necrosis was increased significantly in patients undergoing RFA plus HACE, but the rates of partial and incomplete necrosis were relatively lower. After 3 years of follow-up, a significant increase in survival rate and a striking reduction in recurrence of tumors were found in PHC patients who had undergone the combined therapy. This further indicates that the combined protocol of RFA and HACE in treatment of PHC could significantly improve the short-term clinical response, reduce the recurrence rate of tumor, enhance the necrosis of tumor and prolong the survival time of patients, contributing to better prognosis in patients. Although abdominal pain, nausea and vomiting occurred in one patient respectively, and mild fever occurred in two patients during the combined treatment, the patients were improved significantly after symptomatic treatment. No serious adverse events including cholecystitis, portal hypertension bleeding, or ulcerated bleeding occurred in the patients, suggesting the protocol is of high safety and tolerance.

In conclusion, the combined protocol of RFA and HACE for treatment of patients with PHC is proven to be effective in improving their serum markers, survival, and prognosis, reducing the rates of tumor recurrence. It is such a safe and effective method that it is worthy of extensive use in clinical practice. However, there are still some limitations in this study, such as a small sample size and a single-center study by nature. Nevertheless, the findings still warrant further validation in large-sample, multicenter randomized controlled trials.

Disclosure of conflict of interest

None.

Address correspondence to: Jing Ma, Emergency Department and Intensive Care Unit, Liyuan Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Donghuliyuan, Wuchang District, Wuhan City, 430077, Hubei Province, China. Tel: +86-027-86793043; Fax: +86-027-86793043; E-mail: majiang0809@163.com; Jie Li, Department of Digestive Disease, Liyuan Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Donghuliyuan, Wuchang District, Wuhan City, 430077, Hubei Province, China. Tel: +86-027-86785196; Fax: +86-027-86785196; E-mail: lijie0809@163.com

References

[1] Choi C, Koom WS, Kim TH, Yoon SM, Kim JH, Lee HS, Nam TK and Seong J. A prospective phase 2 multicenter study for the efficacy of radiation therapy following incomplete transarterial chemoembolization in unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2014; 90: 1051-1060.

[2] Cruz JE, Saksena R, Jabbour SK, Nosher JL, Hermes-DeSantis E and Moss RA. The power of genes: a case of unusually severe systemic toxicity after localized hepatic chemoembolization with irinotecan-eluted microspheres for metastatic colon cancer. Ann Pharmacother 2014; 48: 1646-1650.

[3] Tang YL, Qi XS and Guo XZ. Hepatic resection after initial transarterial chemoembolization versus transarterial chemoembolization alone for the treatment of hepatocellular carcinoma: a meta-analysis of observational studies. Asian Pac J Cancer Prev 2015; 16: 7871-7874.

[4] Hammond JS, Franko J, Holloway SE, Heckman JT, Orons PD and Gamblin TC. Gemcitabine transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma. Hepatogastroenterology 2014; 61: 1339-1343.

[5] Sato Y, Watanabe H, Sone M, Onaya H, Sakamoto N, Osuga K, Takahashi M and Arai Y. Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602. Ups J Med Sci 2013; 118: 16-22.

[6] Teratani T, Yoshida H, Shiina S, Obi S, Sato S, Tateishi R, Mine N, Kondo Y, Kawabe T and Omata M. RFA for hepatocellular carcinoma in so-called high-risk locations. Hepatology 2006; 43: 1101-1108.

[7] Yuan G, Zeng CL, Zhu DD and Shi XJ. Influences of RFA combined with TACE on the HIF-1alpha and EGR level of patients with primary hepatic carcinoma. Eur Rev Med Pharmacol Sci 2017; 21: 1738-1745.

[8] Wang Y, Deng T, Zeng L and Chen W. Efficacy and safety of RFA and transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: a meta-analysis. Hepatol Res 2016; 46: 58-71.

[9] Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G and Gandini G. Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). Eur Radiol 2006; 16: 661-669.

[10] Dutta R and Mahato RI. Recent advances in hepatocellular carcinoma therapy. Pharmacol Ther 2017; 173: 106-117.

[11] Araki T. 9. Transcatheter arterial chemoembolization for hepatocellular carcinoma. Nihon Hoshasen Gijutsu Gakkai Zasshi 2016; 72: 1039-1048.

[12] Liu C, Sun L, Xu J and Zhao Y. Clinical efficacy of postoperative adjuvant transcatheter arterial chemoembolization on hepatocellular carcinoma. World J Surg Oncol 2016; 14: 100.

[13] Li L, Tian J, Liu P, Wang X and Zhu Z. Transarterial chemoembolization combination therapy vs monotherapy in unresectable hepatocellular carcinoma: a meta-analysis. Tumori 2016; 2016: 301-310.

[14] Butros SR, Shenoy-Bhangle A, Mueller PR and Arellano RS. RFA of intrahepatic cholangiocarcinoma: feasability, local tumor control, and long-term outcome. Clin Imaging 2014; 38: 490-494.

[15] Eggert T and Greten TF. Current standard and future perspectives in non-surgical therapy for hepatocellular carcinoma. Digestion 2017; 96: 1-4.

[16] Casaccia M, Santori G, Bottino G, Diviacco P, Negri AD, Moraglia E and Adorno E. The procedure outcome of laparoscopic resection for 'small' hepatocellular carcinoma is comparable to vlaparoscopic RFA. J Minim Access Surg 2015; 11: 231-235.

[17] Yazici P, Akyuz M, Yigitbas H, Dural C, Okoh A, Aydin N and Berber E. A comparison of perioperative outcomes in elderly patients with malignant liver tumors undergoing laparoscopic liver resection versus RFA. Surg Endosc 2017; 31: 1269-1274.

[18] Kirikoshi H, Saito S, Yoneda M, Fujita K, Mawatari H, Uchiyama T, Higurashi T, Goto A, Takahashi H and Abe Y. Outcome of transarterial chemoembolization monotherapy, and in com-

bination with percutaneous ethanol injection, or RFA therapy for hepatocellular carcinoma. Hepatology Research 2009; 39: 553–562.

[19] Yang DJ, Luo KL, Liu H, Cai B, Tao GQ, Su XF, Hou XJ, Ye F, Li XY and Tian ZQ. Meta-analysis of transcatheter arterial chemoembolization plus RFA versus transcatheter arterial chemoembolization alone for hepatocellular carcinoma. Oncotarget 2017; 8: 2960-2970.

[20] Koh PS, Chan AC, Cheung TT, Chok KS, Dai WC, Poon RT and Lo CM. Efficacy of RFA compared with transarterial chemoembolization for the treatment of recurrent hepatocellular carcinoma: a comparative survival analysis. HPB (Oxford) 2016; 18: 72-78.

[21] Xu C, Lv PH, Huang XE, Wang SX, Sun L and Wang FA. Efficacy of transarterial chemoembolization combined with RFA in treatment of hepatocellular carcinoma. Asian Pac J Cancer Prev 2015; 16: 6159-6162.

[22] Honda Y, Kimura T, Aikata H, Nakahara T, Naeshiro N, Tanaka M, Miyaki D, Nagaoki Y, Kawaoka T, Takaki S, Hiramatsu A, Waki K, Ishikawa M, Kakizawa H, Kenjo M, Awai K, Nagata Y and Chayama K. Pilot study of stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma. Hepatogastroenterology 2014; 61: 31-36.