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Original Article

Combination therapy of hepatic arterial chemoembolization and radiofrequency ablation for primary liver cancer

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Abstract: Objective: To explore the therapeutic effect of the combination therapy of hepatic arterial chemoembolization and radiofrequency ablation (RFA) in the treatment of primary liver cancer (PLC). Methods: From January 2014 to May 2016, 80 patients with PLC undergoing interventional therapy in our hospital were recruited in the current study. They were subdivided into the experiment group (n=40) and the control group (n=40). The experiment group underwent the combination therapy of hepatic arterial chemoembolization and RFA, whereas the control group received hepatic arterial chemoembolization alone. The two groups were compared regarding the changes in the tumor recurrence-related markers (serum alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA)) and tumor activity-related markers (E-calcium protein and vascular endothelial growth factor (VEGF)) at 1 month after surgery, the total response rate at month 3 after surgery as well as the rates of recurrence and survival at month 6. Results: The levels of serum AFP, CEA, E-calcium protein, and VEGF of the patients in the experiment group were all markedly lower at 1 month after surgery when compared with those in the control group, (All $P<0.05$); the total response rate was strikingly higher in the experiment group at month 3 (82.5% vs 60%; $P=0.026$); at month 6, the recurrence rate lowered substantially but the survival rate increased significantly in the experiment group (45% vs 20%; 75% vs 92.5%, respectively; both $P<0.05$). Conclusion: Compared with hepatic arterial chemoembolization alone, the combination therapy of radiofrequency ablation and hepatic arterial chemoembolization for treating PLC strikingly is associated with reduced tumor recurrence and activity-related markers, improved survival rate and lower recurrence rate, which is worthy of clinically extensive use.

Keywords: Hepatic arterial chemoembolization, radiofrequency ablation, primary liver cancer, tumor markers

Introduction

Primary liver cancer (PLC) is a malignant tumor which occurs most frequently in the digestive system. It poses a serious threat to the life and health of the patients due to its high malignancy and mortality [1, 2]. Surgical treatment is the major treating method for PLC, but it gives rise to great trauma and high postoperative recurrence rate [3]. Additionally, 80% of patients with advanced PLC are not candidates for surgery because of tumor metastasis, special lesion sites and other reasons [4, 5]. Interventional therapy, such as hepatic arterial chemoembolization, is considered to be a preferred technique for PLC patients, but it cannot enter into the tumor as it may cause damage to the normal liver parenchyma. Besides, incomplete filling of embolic agents, incomplete necrosis of the tumor cells and relapse predisposition lead to poor curative effect of hepatic arterial chemoembolization [6, 7]. Radiofrequency ablation (RFA) is a novel technique for treatment of PLC. It is effective in killing local tumor cells completely [8]. Clinical practice over years has proven its favorable effect [9]. It is reported that hepatic arterial chemoembolization in combination with RFA has some synergistic effect in the treatment of PLC [10]. Nevertheless, another study revealed no substantial difference in the survival rate between the combination therapy and hepatic arterial chemoembolization alone [11]. Therefore, whether the combination therapy of RFA and hepatic arterial chemoembolization can improve the therapeutic effect of PLC remains controversial, and needs further comprehensive evaluation. In this context, this study was mainly designed to investigate the therapeutic effect of RFA in combination with hepatic arterial chemoembolization for the treatment of PLC, in hope of laying experimental basis for the treatment of the disease in the future.

Materials and methods

Clinical data

Each patient and their families provided written informed consent, and approval was obtained from the Hospital Ethics Committee. From January 2014 to May 2016, a total of 80 PLC patients undergoing interventional therapy in our hospital were enrolled as subjects in this study. Diagnosis of all the patients was confirmed by CT, MRI, B ultrasound and other imaging examinations, laboratory diagnosis including serum alpha fetoprotein (AFP), and pathology of cytopuncture. Among the eligible patients, 55 were male and 25 were female, with a mean age of (57.2±6.4) years. Patients were included if they met the indications for hepatic arterial chemoembolization or RFA, but they could not undergo surgical resections due to high risk for anesthesia and other reasons or they clearly refused surgical treatment; no previous systemic chemotherapy or radiotherapy; the Karnofsky Performance Status (KPS) score ≥70; the liver function Child-Pugh of Grade A or B; the number of tumor <3. Patients were not eligible for enrollment if they had contraindications to hepatic arterial chemoembolization or RFA; tumor located in the sites near major blood vessels, the portal hepatis or the bowels; the presence of extrahepatic metastases of tumor, or with cachexia, jaundice and ascites; severe cardiovascular and cerebrovascular disease; massive or diffuse hepatocellular carcinoma; abnormal blood coagulation, with platelet counts of less than $50*10^9$/L; incomplete clinical data or reluctance to cooperate in follow-ups. The eligible 80 patients were assigned to the experiment group (n=40) and the control group (n=40) according to a random number table.

Methods

Hepatic arterial chemoembolization: The patients in the control group underwent hepatic artery chemoembolization alone. They were required to be anesthetized with an intramuscular injection of diazepam (10 mg) half an hour before chemoembolization after fasting for 4 h. With conventional disinfection draping and under local anesthesia, the patients had the femoral artery punctured by the Seldinger method and hepatic artery angiography performed. After the blood-supply artery for hepatic tumor was confirmed, an artery catheter was inserted selectively, into which 5 ml of nonionic contrast agent lipiodol, 2 g of 5-fluorouracil, and 200 mg of oxaliplatin were injected. Some gelatin sponge and polyvinyl alcohol particles were also injected under angiography guidance. The catheter was removed, followed by pressurized bandaging at the punctured site. The patients had their lower limbs kept 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 were also under close observation.

Radiofrequency ablation: The patients in the experiment group received RFA within 15 days after completion of hepatic artery chemoembolization. The procedure of RFA was follows: The patients were anesthetized with a conventional intramuscular injection of diazepam (10 mg) half an hour before RFA after fasting for 4 h. The puncture point and the direction of the needle insertion were determined based on comprehensive analysis of the site, number and size of the lesions as demonstrated by CT scans. With conventional disinfection draping and under local anesthesia, the radiofrequency (RF) electrode was inserted into the distal end of the tumor lesion under CT guidance, and then a RF ablation device was started and lasted for 10-15 min, with the ablation power set at 80-100 W and the center temperature at 90-100°C. The RFA was extended to the range 1 cm inside the normal tissues to ensure complete necrosis of the tumor tissues. The catheter was removed at the end of the needle ablation, followed by pressurized bandaging at the punctured site to prevent catheter implantation and bleeding in the ablation puncture pathway (**Figure 1**).

Outcome measures

The levels of serum alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA) were compared between the two groups before surgery

Figure 1. RFA of primary liver cancer. A: Before ablation; B: During ablation; C: One week after ablation.

and at month 1 after surgery, respectively. A sample of 5 mL of fasting venous blood was drawn from each patient before surgery and at month 1 after surgery, respectively. Serum was isolated from the sample after anticoagulation, and the AFP and CEA levels were measured with the use of the enzyme-linked immunosorbent assay (ELISA). All the ELISA kits for serum AFP and CEA measurements were purchased from R&D Systems, USA.

The total response rates of the patients were compared between the two groups. At 3-month follow-up, abdominal enhanced CT imaging was used to assess the treatment outcomes [12]. Complete response was defined as the invisibility or disappearance of all target lesions; partial response was defined as the product of length and width of a target lesion after treatment was lower than 1/2 of that of the target lesion before operation. The total effective rate was calculated by complete and partial response. The formula states as follows: Total effective rate=(Cases of complete response + Cases of partial response)/total number of patients *100%.

The tumor activity-related markers were compared between the two groups before therapy and at month 1 after therapy. The levels of E-calcium protein and vascular endothelial growth factor (VEGF) were measured by the ELISA method. All the ELISA kits for serum E-calcium protein and VEGF measurements were purchased from R&D Systems, USA.

The rates of survival and recurrence at month 6 of follow up were compared between the two groups. Tumor recurrence was defined as the appearance of new lesions or increased primary lesions.

All the patients were given follow-up visits, either in the clinic or by telephone, once monthly for 6 months for observation of their clinical outcomes.

Statistical analysis

The data analyses were performed with the use of SPSS software, version 19.0. Quantitative data were represented as $\bar{x}\pm s$, with the independent-samples t-test for inter-group comparisons and the paired-t test for intragroup comparisons. Count data were represented as percentage, with the chi square test for inter-group comparisons. $P<0.05$ showed that there were significant differences.

Results

Basic data of patients

No remarkable differences between the two groups were observed in age, sex, body mass index (BMI), liver function classification and liver cancer stages ($P>0.05$), so they were comparable (**Table 1**).

AFP and CEA levels of the patients

No striking disparities were showed in the levels of preoperative AFP and CEA between the experiment group and the control group ($P=0.415$); the AFP and CEA levels of both groups after surgery were significantly decreased as compared with those before surgery (Both $P<0.001$); at month 1 after surgery, the AFP and CEA levels in the experiment group were substantially different from those in the control group ($P<0.001$; **Figure 2**).

Total response rate of the two groups

At month 3 after surgery, complete response occurred in 18 patients (45%), and partial response in 15 patients (37.5%) in the experiment group, with a total response rate of approximately 82.5%; complete response occurred in 8 patients (20%), and partial response in 16 patients (40%) in the control group, with a total response rate of approximately 60%. The total response rate of the experiment group increased markedly compared with that in the control group,, and the difference was statistically significant ($\chi^2=4.943$, $P=0.026$), as shown in **Figure 3**.

Table 1. Basic data of patients

Variable	Group		t/χ²	P
	Experiment	Control		
Case	40	40		
Male/Female (n)	26/14	29/11	χ^2=0.524	0.469
Age (year)	58.5±6.7	55.9±6.1	t=0.497	0.645
BMI (kg/m²)	24.5±1.2	23.9±1.0	t=0.665	0.542
Child-Pugh class of hepatic function (n, %)			χ^2=1.455	0.228
A	25 (62.5)	30 (75)		
B	15 (37.5)	10 (25)		
Hepatic cancer stage (n, %)			χ^2=1.386	0.500
I	11 (27.5)	14 (35)		
II	19 (47. 5)	20 (50)		
III	10 (25)	6 (15)		

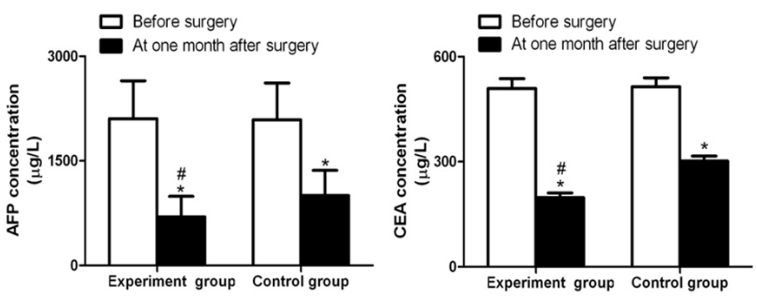

Figure 2. Comparison of serum AFP and CEA levels between the two groups. *P<0.001 for the comparison between before and after surgery within the same group; compared the control group, #P<0.001.

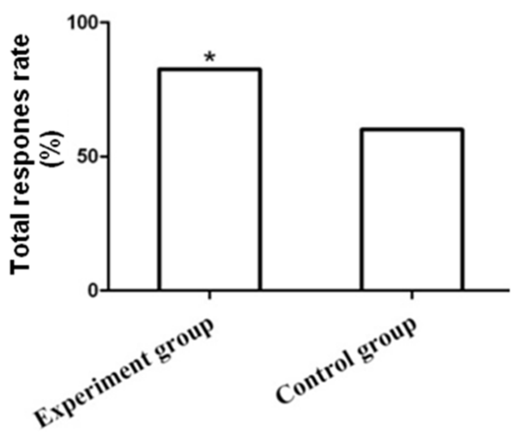

Figure 3. Comparison of the total response rate between the experiment group and the control group. Comparison with the control group, *P=0.026.

Tumor activity-related markers

Before surgery, there were no differences in the serum E-calcium protein and VEGF levels between the two groups. The serum E-calcium protein and VEGF levels after surgery were markedly lower than those before surgery in both groups (Both P<0.001). Moreover, at month 1 after surgery, the serum E-calcium protein and VEGF levels in the experiment group dropped considerably as compared with those in the control group (Both P<0.05; **Table 2**).

Tumor recurrence and survival of patients

At 6-month follow-up, when compared with the control group, the experiment group had a significantly lower rate of tumor recurrence (45% vs 20%, χ^2=5.698, P=0.017) but a significantly higher rate of survival (75% vs 92.5%, χ^2=4.501, P=0.034), as sh-own in **Figure 4**.

Discussion

Currently, the treatment modality of PLC evolves from surgery alone to the multidisciplinary comprehensive treatment based on surgical resection. Clinically, most patients tend to miss the best chance for surgical resection as they are confirmed as having intermediate or advanced liver cancer when they are diagnosed. Hepatic arterial chemoembolization is a technique of interventional therapy supplying blood to liver tumor by blocking the vessel with iodinated oil and then injecting chemotherapy drugs into the specific blood vessel; in this way, the goal of

Table 2. Tumor activity-related markers of the two groups

Variable	Case	E-calcium protein (ng/mL)		VEGF (pg/mL)	
		Before surgery	After surgery	Before surgery	After surgery
Experiment group	40	2537.4±190.8	1645.3±123.4	413.1±76.8	225.6±32.3
Control group	40	2558.1±202.3	2024.9±145.6	419.2±80.1	346.2±50.9
t		0.129	3.277	0.095	3.465
P		0.904	0.031	0.929	0.026

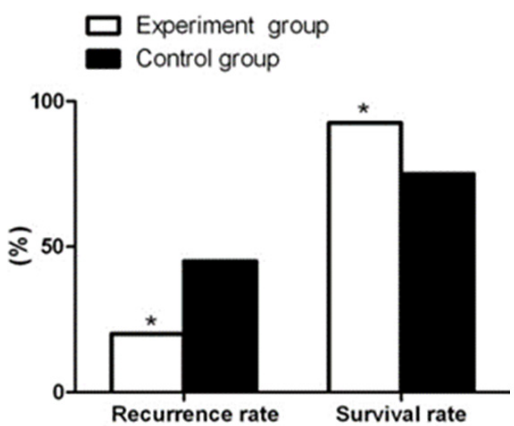

Figure 4. Comparison of the rates of recurrence and survival between the two groups. Compared with the control group, *P<0.05.

treatment thus achieves [13]. With the advance of clinical research, hepatic arterial chemoembolization alone has definite indications for PLC, and its curative effect is limited [14]. On the other hand, with RFA, an ablation needle is percutaneously punctured into the tumor site under the guidance of CT and other imaging tools; local tumor cells are degenerated by the heat from the high-frequency current, resulting in faster tumor necrosis [15]. Studies have shown that compared with hepatic arterial chemoembolization alone, the combination therapy of arterial chemoembolization and RFA significantly improves the survival rate of patients [16]. Koh and colleagues have reported that hepatic arterial chemoembolization in combination with RFA is effective in the treatment of patients who cannot receive re-embolization or have residual tumor after repetitive embolization [17]. The results of this study indicated that the total response rate of RFA in combination with hepatic arterial chemoembolization was significantly higher than that of hepatic arterial chemoembolization alone (P<0.05). This may be due to the fact that the electromagnetic waves reflected by iodine ions in hepatic artery chemoembolization enhanced the high-temperature effect of RFA, which in turn significantly weakened tumor cells but improved the anti-cytotoxicity of the drugs used in hepatic artery chemoembolization [18]. Thus, complementation of the two techniques improved the efficacy of the treatment. However, Veltri et al. reported no significant differences in the survival rate between the patients with the combination therapy and those with hepatic artery chemoembolization alone, which might be related to the small sample size, short follow-up and tumor diameter of greater than 5 cm in their studies [11].

AFP and CEA are key tumor markers. The changes in the blood AFP and CEA concentrations have shown to be closely related to the onset and development of PLC [19]. In the present study, the AFP and CEA levels at month 1 after surgery were markedly lower than those before surgery in both groups. Additionally, the AFP and CEA levels after surgery in the experimental group were obviously lower than those in the control group (Both P<0.05), which suggests that the patients were improved considerably and the short-term efficacy was ideal. What's more, the combination therapy of RFA and hepatic arterial chemoembolization was more effective than hepatic arterial chemoembolization alone in increasing coagulative necrosis of the tumor tissues and reducing release of AFP and CEA into the blood, which is consistent with the results reported in previous studies [20, 21].

Tumor activity-related markers E-calcium protein and VEGF play a crucial role in invasion and metastasis of tumor cells, and are also considered as bio-markers of malignant behavior of tumor cells. E-calcium protein belongs to calcium-dependent cell adhesion glycoprotein. Its main function is to maintain intercellular connection and polarity of epithelial cells, and a reduction in its expression is helpful to reduce cell-cell adhesiveness, leading to increased activity of cells. This is beneficial for tumor cells to penetrate into the surrounding tissues via basilar membrane, which is the key factor for invasion and metastasis of tumor cells [22]. VEGF can regulate the functions of vascular endothelial cells, promote their proliferation and increase the permeability of blood vessels. VEGF has also been proven to promote growth and metastasis of liver tumor cells [23]. The result of the current study demonstrates that E-calcium protein and VEGF levels after the combination therapy were markedly lower those after hepatic arterial chemoembolization alone ($P<0.05$), suggesting that RFA in combination with hepatic arterial chemoembolization can effectively reduce the activity of tumor cells, suppress their invasion and metastasis. This was consistent with the finding reported by Wu [24]. At 6-month follow-up, the experiment group had a strikingly lower recurrence rate but a significantly higher survival rate than the control group (20% vs 45%, 92.5% vs 75%, respectively; $P<0.05$). This shows that RFA in combination with hepatic arterial chemoembolization is associated with remarkable short-term efficacy, significantly lower rate of tumor recurrence, improved survival rate, and is conducive to the prognosis of patients. These are basically consistent with previous reports [25, 26].

In conclusion, the combination therapy of RFA and hepatic artery chemoembolization in treatment of PLC patients remarkably reduced the tumor recurrence and activity-related markers, improved the survival rate and reduced the recurrence rate, which is worthy of wide application. Nevertheless, this study has some limitations, such as the small sample size and single center study. Multicenter and randomized controlled trials with large sample size are required for further validation.

Disclosure of conflict of interest

None.

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