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Original Article

Contrast-enhanced ultrasound guidance improves the therapeutic efficacy of radiofrequency ablation in liver cancer patients

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Abstract: Objective: To investigate the efficacy of contrast-enhanced ultrasound (CEUS)-guided radiofrequency ablation (RFA) in the treatment of liver cancer and its effect on patients' immune function. Methods: Clinical data of 84 liver cancer patients admitted to the Shandong Qishan Hospital from March 2018 to March 2020 were retrospectively analyzed. According to differences in treatment methods, patients were divided into a research group (42 cases treated by CEUS-guided RFA) and a control group (42 cases treated by RFA under conventional ultrasound). Clinical efficacy of two groups was observed two months after surgery. Liver function as well as IgA, IgG and IgM levels were evaluated. The incidence of complications, quality of life and survival were compared between the two groups. Results: The complete inactivation rate of large lesions in the research group was 23.81%, which was significantly higher than that of the control group (4.76%). Before treatment, the two groups showed similar levels of IgA, IgG and IgM. After treatment, significantly increased levels were observed in both groups, but the research group had higher IgA, IgG and IgM levels as compared to the control group ($P < 0.05$). The quality of life scores increased in both groups after the intervention, and the score in the research group was significantly higher than that in the control group ($P < 0.05$). The progression-free survival of patients in the research group (12.28±5.42) was longer than that of patients in the control group (8.50±4.47; $P < 0.05$). Conclusions: Comparing to RFA guided by conventional ultrasound, RFA guided by CEUS can reduce liver damage, lower the incidence of complications, enhance the body's immune system, and improve local control rate and progression-free survival time in patients with liver cancer.

Keywords: Contrast-enhanced ultrasound, liver cancer, radiofrequency ablation, curative effect, T-cell subsets

Introduction

Liver cancer is a malignancy that originates from hepatocytes and cholangiocytes. According to the epidemiological investigations, liver cancer ranks the fourth in incidence and the second in mortality among malignant tumors in China, severely affecting the health and life of patients [1]. The pathogenesis of liver cancer is closely related to immune function. The affected patients usually have low immunity due to immune function impairment [2]. Currently, liver cancer treatment is mainly based on radiotherapy, chemotherapy and surgery. Although these modalities can effectively relieve or reduce the tumor load, they are unable to completely eliminate the lesions, resulting in unsatisfactory clinical efficacy [3]. In recent years, with advances in research and clinical treatment techniques for liver cancer, radiofrequency ablation (RFA) has emerged as an effective treatment modality for liver cancer. In the treatment of hepatocellular carcinoma (HCC) with tumor diameter ≤ 5.00 cm, RFA has been shown to be capable of achieving complete inactivation of tumor lesions in a single treatment session, while also enhancing and activating the body's immune function [4, 5]. However, RFA also has some limitations, especially the challenge in locating lesions in blood vessels and diaphragm, resulting in incomplete coagulative necrosis [6].

At present, the main clinical treatments for liver cancer include removal of lesions, liver transplantation, and liver resection [7]. RFA as a new minimally invasive technique for tumor treatment [8] works by applying local thermal ablation to coagulate and kill HCC cells. It is simple to operate, with high efficacy, high safety, and few postoperative complications. However, some scholars found that conventional ultrasound (US)-guided RFA is prone to incomplete ablation of the lesions due to influence factors such as site, size, shape and lesion boundary [9], while contrast-enhanced ultrasound (CEUS)-guided RFA has been indicated by multiple studies to exhibit a better effect, because it allows for the timely and effective detection of the lesions, thereby providing better guidance for RFA [10]. RFA is considered to be one of the most feasible methods for liver cancer treatment for it has also been shown to delay tumor growth [11]. However, the limitations of RFA make it difficult to locate some lesions in the blood vessels and diaphragm, which affects the therapeutic effect [12]. Liver cancer cells can evade immune recognition and attack by modifying their surface antigens and altering the microenvironment around the HCC tissue, thus inducing tumor immune escape [13]. In recent years, many scholars believe that RFA can not only kill tumor cells and destroy tumor tissues, but also enhance the anti-tumor immune function of the host [14]. According to relevant studies, CEUS was able to help understand the circulatory perfusion state of local lesions, which was conducive to the diagnosis and treatment of liver cancer [15]. But it remains to be defined whether RFA guided by CEUS can help enhance the anti-tumor immunity while improving the treatment efficacy.

Therefore, the purpose of this study is to investigate the anti-tumor immunity of liver cancer patients treated with RFA guided by CEUS by analyzing the clinical data of 84 affected patients.

Information and methodology

General information

The clinical data of 84 patients with primary liver cancer treated at the Shandong Qishan Hospital from March 2018 to March 2020 were retrospectively analyzed. Inclusion criteria: (1) Patients who met the diagnostic criteria for “Standard of Diagnosis and Treatment of Primary Liver Cancer” and confirmed with primary liver cancer by pathology and imaging [16]; (2) Patients with preoperative liver function Child-Pugh grade A or B; (3) Patients without contraindications for RFA or transcatheter arterial chemoembolization; (4) Patients with complete clinical data. Exclusion criteria: (1) Patients with kidney, heart, brain or other major organ failure; (2) Patients with serious coagulation dysfunction or obvious peritoneal effusion; (3) Patients with other malignancies or combined liver cancers; (4) Patients with incomplete clinical data. This study was approved by the Ethics Committee of Shandong Qishan Hospital.

Methods

Both groups of patients were routinely examined for coagulation function, renal function, liver function and blood routine preoperatively. The tumor location was determined by liver computed tomography (CT) and magnetic resonance imaging (MRI). Before surgery, 5-8 mL of 2% lidocaine hydrochloride (No. H20023777, Shanghai Hefeng Pharmaceutical Co., Ltd., China) was injected at the puncture site. Patients requiring general anesthesia were subjected to water deprivation and fasting, and then 50-70 mg pethidine (No. H42022074, Yichang Renfu Pharmaceutical Co., Ltd., China) was injected intramuscularly 10 min before surgery.

All patients underwent US-guided RFA (Power Cool-tip Cold Circulating Radiofrequency Ablation System, USA). Preoperative color US was performed to observe the location and number of lesions and to identify the direction, location and path of the puncture. The relationship between lesions and peripheral tissues was analyzed. The control group underwent a conventional US, while the observation group underwent CEUS using a color doppler US diagnostic instrument (Sonix01, Shanghai Jumu Medical Devices Co., Ltd., China) with the frequency set at 3.0-5.0 MHz. The scan was initiated after 2.5 mL of the contrast medium sulfur hexafluoride microbubbles (SonoVue, Bracco, Italy) was injected intravenously into the patient’s elbow.

RFA procedure: The control group was probed with conventional US examination, and the research group was observed with CEUS. The surgery position was selected based on the lesion location of each patient. A negative electrode plate was attached to the side of the patient's thigh after the RFA system was connected. The ablation procedure was lasted for 12 min, during which the ablation electrode needle was punctured under the guidance of a US. The automatic ablation mode was selected, with an initial power of 25 W, and the power was controlled by the computer system. US was used to monitor the ablation process, and the ablation was considered complete if a hyperechoic mass ≥ 0.5 mm tumor edge was present or the lesion was completely covered. After the ablation, the cold ring circulation pump was turned off, and the tip temperature was maintained for 10 s at 85°C. Another ablation was performed in the presence of residuals. The two groups of patients underwent a re-examination two months after the treatment, and the curative efficacy was analyzed based on the results.

Outcome measures and evaluation of curative efficacy

(1) The curative efficacy was evaluated by re-examination (two months after treatment). The treatment response was categorized as complete inactivation and local residual. Complete inactivation referred to the absence of blood flow signal in the lesion site as shown by conventional US or time-phase change in the lesion site by CEUS, as well as the absence of enhanced echo nodules. Local residual was defined as the presence of linear blood flow signals at the lesion site as shown by conventional US, or the presence of irregular focal or ring-shaped echogenic nodules detected by CEUS.

(2) The liver function was compared between the two groups. Before and two months after surgery, 5 mL of venous blood was collected to determine changes in liver function indexes using an automatic biochemical analyzer (Ningbo Meikang Shengde Biotechnology Co. Ltd. Model: MS-480). The indexes included alanine aminotransferase (ALT), aspartate transaminase (AST), direct bilirubin (D-BIL), and serum total bilirubin (T-BIL).

(3) The incidence of complications was compared. The complications recorded included fever, diarrhea, nausea and vomiting, and bleeding.

(4) The serum immunoglobulin (Ig) levels, including IgA, IgG, and IgM were measured using a fully automated immunoassay analyzer (cobas 8000 e 801, Roche Diagnostics Ltd.).

(5) The quality of life was evaluated using the Generic Quality of Life Inventory-74 (GQOLI-74) score scale [17] in both groups before and 2 month after treatment. The questionnaire includes 4 dimensions, physical, social, somatic, and psychological functioning, and the score of each dimension was converted to a percentage scale.

(6) To analyze the survival, patients were followed up for 1 year, and their prognoses were evaluated according to the National Comprehensive Cancer Network guidelines [18]. Local control was defined as the absence of tumor enlargement or shrinkage, with the lesion size remaining stable at ≤ 6 cm, as indicated by MRI and CT examinations. Progression-free survival refers to the time from the beginning of treatment to the re-appearance of the tumor.

Statistical methods

The statistical analysis was carried out using SPSS 15.0 software. Measurement data were presented as mean ± standard deviation, and the Student's t test was used to compare the differences between the groups. Counting data were presented as percentages, and the chi-square test was used for inter-group comparisons. A significant difference is indicated by $P < 0.05$.

Results

Comparison of general information

The inter-group comparison of general information (sex, age, tumor diameter, and Child-pugh Grade) showed no significant difference ($P > 0.05$), indicating that the two groups were comparable, as shown in **Table 1**.

Comparison of curative efficacy

There was no marked difference in complete inactivation rate of small and medium lesions between the two groups ($P > 0.05$). As for large lesions, the research group exhibited a markedly higher complete inactivation rate and a

Table 1. Comparison of general information between the two groups

	Research (n=42)	Control (n=42)	χ^2/t	*P*
Sex			0.202	0.653
Male	27	25		
Female	15	17		
Age (years)	56.57±8.97	56.60±8.95	0.015	0.988
Tumor diameter (cm)	4.42±1.31	4.40±1.34	0.069	0.945
Child-pugh Grade			0.048	0.826
A	19	18		
B	23	24		

lower residual rate than the control group (P < 0.05). Also, an obviously higher total inactivation rate was determined in the research group, as compared with that in the control group (P < 0.05), as shown in **Table 2**.

Comparison of liver function before and after treatment

No statistical difference was determined in ALT, AST, D-BIL and T-BIL levels between the two groups before treatment (P > 0.05). After treatment, the ALT, AST, D-BIL and T-BIL levels decreased greatly in both groups, with lower levels in the research group, as compared with those in the control group (P < 0.05), as shown in **Table 3**.

Comparison of incidence of complications

The incidence of complications in the research group was statistically lower than that in the control group (P < 0.05), as shown in **Table 4**.

Comparison of changes in T-cell subsets before and after surgery

The preoperative IgA, IgG and IgM levels were not statistically different between the two groups (P > 0.05). Postoperatively, the IgA, IgG and IgM levels increased in both groups (P < 0.05), and the increases were more significant in the research group, as compared with those in the control group (P < 0.05), as shown in **Table 5**.

Comparison of quality of life

Before treatment, there was no statistically significant difference in the physical, social, somatic and psychological function scores between the two groups (P > 0.05). Two months after treatment, the physical, social, somatic and psychological function scores were increased in both groups as compared to those before treatment, and the research group exhibited higher scores than the control group, with statistically significant difference (P < 0.05), as shown in **Figure 1**.

Comparison of survival

The one-year follow-up revealed a higher local control rate and longer progression-free survival in the research group as compared with those in the control group (P < 0.05), as shown in **Table 6**.

Discussion

During RFA, CEUS can monitor the changes in the condition of patients with liver disease, allowing for early treatment of residual lesions. This can help complete removal of the tumor [19]. This study found that CEUS-guided RFA could effectively improve the ablation rate. Also, no notable difference was observed in the complete inactivation rate of small and medium lesions between the two groups, suggesting favorable efficacy of RFA on small and medium lesions.

In terms of large lesions, a higher complete inactivation rate was determined in the research group as compared with that in the control group (23.81% vs. 4.76%). In addition, the residual rate of large lesions in the research group was 9.52%, significantly lower than that in the control group (28.57%). It is suggested that with the guidance of CEUS, RFA can effectively improve the inactivation rate of large lesions, thus completely removing tumors and improving patient prognosis. Furthermore, markedly reduced ALT, AST, D-BIL, and T-BIL levels were observed in both groups after treatment, with more significant reductions in the research group. It is indicated that CEUS-guided RFA can effectively alleviate liver injury. Moreover, patients received CEUS-guided RFA exhibited fewer adverse reactions, with fever, pain, general discomfort, and leukocytosis as the common ones. Of them, fever is mainly attributed to ablation-induced apoptosis and inflammation. In this study, the incidence of

Table 2. Comparison of clinical efficacy between two groups

Group	Complete inactivation (%)			Local residual (%)		
	Small lesions	Medium lesions	Large lesions	Small lesions	Medium lesions	Large lesions
Research (n=42)	20 (47.26)	17 (40.48)	10 (23.81)	2 (4.76)	4 (9.52)	4 (9.52)
Control (n=42)	16 (38.10)	16 (38.10)	2 (4.76)	3 (7.14)	5 (11.90)	12 (28.57)
χ^2	0.778	0.050	6.222	0.265	0.124	4.941
P	0.378	0.823	0.013	0.607	0.724	0.026

Table 3. Comparison of liver function before and after operation

Group	ALT (U/L)		AST (U/L)		D-BIL (μmol/L)		T-BIL (μmol/L)	
	Before	After	Before	After	Before	After	Before	After
Research (n=42)	65.16±14.56	26.44±7.05[a]	76.55±14.87	35.34±7.38[a]	35.37±7.03	12.35±3.03[a]	45.16±9.31	31.15±4.26[a]
Control (n=42)	64.60±14.58	39.56±8.79[a]	76.43±14.76	44.28±8.68[a]	35.40±7.10	20.11±4.16[a]	45.22±9.29	38.44±4.83[a]
t	0.164	7.546	0.037	5.085	0.019	9.772	0.030	7.411
P	0.870	< 0.001	0.970	< 0.001	0.985	< 0.001	0.975	< 0.001

Note: By comparison with before operation, [a]*P* < 0.05. ALT: alanine aminotransferase, AST: aspartate transaminase, D-BIL: direct bilirubin, T-BIL: total bilirubin.

Table 4. Comparison of complications

Group	Fever	Diarrhea	Nausea and vomiting	Bleeding	Total incidence
Research (n=42)	5 (11.90)	8 (19.05)	3 (7.14)	1 (2.38)	19 (45.24)
Control (n=42)	10 (23.81)	14 (33.33)	5 (11.90)	3 (7.14)	32 (76.19)
t					5.332
P					0.021

Table 5. Comparison of changes in serum immunoglobulin levels

Group	IgA (g/L)		IgG (g/L)		IgM (g/L)	
	Before	After	Before	After	Before	After
Research (n=42)	2.21±0.23	5.04±0.37[b]	7.88±1.29	14.22±1.66[b]	1.38±0.13	2.84±0.27[b]
Control (n=42)	2.27±0.28	3.94±0.25[b]	8.03±1.25	10.16±1.12[b]	1.42±0.18	1.82±0.16[b]
t	1.1076	15.9645	0.5412	13.1395	1.1675	21.0623
P	0.3118	< 0.0001	0.5898	< 0.0001	0.2464	< 0.0001

Note: By comparison with before treatment, [b]*P* < 0.05. Ig: immunoglobulin.

complications in the research group was 45.24%, which was significantly lower than that in the control group, indicating that CEUS-guided RFA demonstrated the ability to reduce complications.

In this study, the serum IgA, IgG and IgM levels of patients in the research group increased more significantly after treatment, which suggested that CEUS-guided RFA can improve the immune resistance of patients. RFA, as a form of thermal therapy, can alter tumor antigens or expose cell surface antigenic clusters, thereby enhancing the antigenicity of the tumor [20, 21]. RFA can stimulate the production of heat shock proteins, such as HSP70, within the body. These proteins can have a positive effect on cellular immunity [22]. The results of this study suggest that CEUS-guided RFA can effectively enhance patients' anti-tumor immunity, possibly due to the following reasons. First, as confirmed by previous studies, RFA can strongly modulate the immune system and anti-tumor immune responses in metastatic liver patients [23, 24]. Second, due to various complex factors such as fatty liver, isoecho of HCC, small size, and liver hardening background, HCC may lack distinct sonographic differences from the surrounding liver tissue, resulting in the formation of "invisible liver cancer" that cannot be clearly visualized by conventional US. In such case, conventional US might not accurately

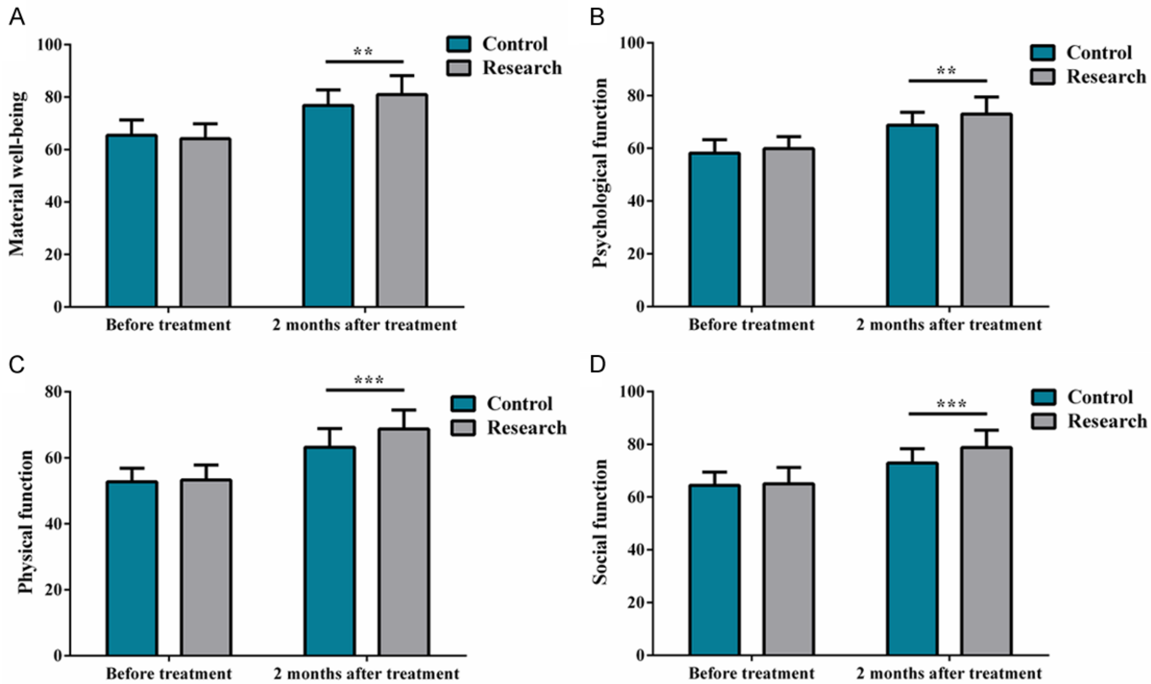

Figure 1. The quality of life of the patients. A: Material well-being score; B: Psychological function score; C: Physical function score; D: Social function score; **P < 0.01, ***P < 0.001.

Table 6. Comparison of survival

Group	Local control rate	Progression-free survival (month)
Research (n=42)	32 (76.19)	12.28±5.42
Control (n=42)	23 (54.76)	8.50±4.47
χ^2/t	5.185	3.449
P	0.023	< 0.001

locate HCC, affecting the effective implementation of RFA [25]. Third, CEUS can dynamically reflect the microcirculation perfusion status in the tumor in real time and the hemodynamic changes in the tumor before and after RFA treatment, so as to determine tumor inactivation [26]. Following the destruction of tumor cells, the tissue undergoes coagulative necrosis, leading to a reduction in tumor cell load. This reduction significantly decreases the production of immunosuppressive factors. Alleviating the immunosuppressive effect of the tumor on the body and thus improving immune function [27]. Therefore, RFA guided by CEUS can more effectively kill cancer cells and improve the therapeutic efficacy and immune function of patients. Through the one-year follow-up, we found that patients receiving CEUS-guided RFA had a higher local control rate and longer progression-free survival than those receiving conventional US-guided RFA. It is suggested that CEUS-guided RFA can improve the local control rate and patient survival. The reasons may be that the local tissue temperature of the lesion was increased under the action of RFA electrodes, and the tumor lesions were completely removed due to the accurate positioning under CEUS. It was also reported that US-guided RFA was effective in enhancing the therapeutic effect in patients with different lesions and recurrent liver cancer [28]. Furthermore, this study found that the GQOLI-74 scores were higher in the research group than those in the control group after the treatment, suggesting that CEUS-guided RFA helped to improve the quality of life of the patients.

However, this study still has the following limitations. First, retrospective data analysis carries the risk of information bias. Second, the sample size was small, which may limit the identification of possible adverse effects. Last, the follow-up was relatively short, making it difficult to evaluate long-term survival. Therefore, well-designed, randomized, and controlled trials with prospective data collection and sample size calculation are needed to confirm the findings in our study and to analyze the association of long-term survival with clinical outcomes.

Conclusion

To sum up, CEUS-guided RFA can improve the efficacy in the treatment of liver cancer, reduce liver damage and complications, enhance the immunity, ameliorate local control rate, and increase progression-free survival in tumor patients. Therefore, it is worthy of clinical application and promotion.

Disclosure of conflict of interest

None.

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