CLINICAL EFFICACY OF RADIOFREQUENCY ABLATION FOR PRIMARY LIVER CANCER AND ITS EFFECTS ON T LYMPHOCYTE SUBSETS, SIL-2R, TSGF LEVELS AND PROGNOSIS

Weidi Ming[1], Jin Liu[2], Xiaochun Chen[2], Jialin Liu[3], Lei Sun[1], Zhengming Wang[1*]
[1]Department of radiotherapy, General Hospital of PLA Rocket Force, Beijing 100088, China - [2]Department of radiology. Beijing Jingmei Group General Hospital, Beijing 102399, China - [3]Department of radiology.Beijing Friendship Hospital Pinggu Campus, Beijing 101299, China

ABSTRACT

Objective: *To determine the clinical efficacy of radiofrequency ablation (RFA) for primary hepatocellular carcinoma and analyze the effects of RFA treatment on T lymphocyte subsets, soluble interleukin-2 receptor (sIL-2R), tumor specific growth factor (TSGF) levels, and prognosis.*

Methods: *A total of 48 patients with liver cancer admitted to the cardiovascular department of our hospital from May 2017 to April 2018 were randomized into observation and control groups of 24 patients each. The control group received conventional embolization chemotherapy intervention, and the observation group received RFA in conjunction with conventional embolization chemotherapy. After treatment, the clinical outcomes and complications of the two groups were observed. The changes in T lymphocyte subsets [CD_3^+, CD_4^+, CD_8^+ and CD_4^+/CD_8^+], sIL-2R, and TSGF in the two groups were compared.*

Results: *The total effective rate of treatment in the observation group was 87.50%, significantly higher than that of the control group, 70.83%, (P<.05); The total incidence of complications in the observation group was 29.17%, significantly lower than that in the control group, 58.33% (P<.05). After treatment, the levels of CD_3^+, CD_4^+, and CD_4^+/CD_8^+ T cells in the observation group were significantly increased compared with the control group, and the levels of CD8+ cells were significantly decreased from before-treatment levels (P<.05). After treatment, the sIL-2R and TSFG levels in the observation group were significantly lower than those in the control group (P<.05).*

Conclusion: *Radiofrequency ablation has a significant clinical effect in the treatment of primary liver cancer that can significantly improve outcomes, effectively regulate the balance of T lymphocyte subsets, reduce sIL-2R and TSGF, and improve the quality of life of patients.*

Keywords: *Clinical efficacy, primary liver cancer, prognosis, radiofrequency ablation, RFA, sIL-2R, T lymphocyte subsets, TSGF.*

DOI: 10.19193/0393-6384_2021_6_531

Received *March 15, 2020;* ***Accepted*** *October 20, 2020*

Introduction

Primary liver cancer (PLC) is a malignant tumor arising from hepatocytes or intrahepatic bile duct cells. Worldwide, it is a very common tumor of the digestive system[(1)]. The clinical pathological changes of PLC include ascites, hematemesis, collateral circulation, and edema of the limbs, along with symptoms caused by the tumor itself, such as hepatomegaly, pain in the liver area, and weight loss. In China, PLC ranks second in malignant tumor mortality, behind lung cancer in urban areas and gastric cancer in rural areas, causing 20.37 million deaths annually. Cholangiocarcinoma and hepatocellular biliary cell mixed carcinoma account for only 10% to 20% of patients with primary liver cancer in China, with hepatocellular carcinoma accounting for most of the remainder.

It has been shown in Asian countries that the principal cause of liver cancer is the development

of viral hepatitis and subsequent cirrhosis, whereas in European and American countries, the occurrence of liver cancer most often follows cirrhosis due to chronic excessive ethanol intake. At present, surgery is still the preferred treatment, but because patients with primary liver cancer often present with vague, nonspecific symptoms, especially early in the course of the disease, most patients are diagnosed late in the disease process[2]. When the patient's remaining liver tissue cannot compensate, liver functions and general condition decline, making the patient unsuitable for surgery and in need of an alternative treatment for PLC. Radiofrequency ablation (RFA), a nonsurgical treatment, has many advantages and has become a common treatment for liver cancer in recent years[1]. Soluble interleukin-2 receptor (sIL-2R) was found to be a pluripotent cytokine in patients with primary liver cancer; it plays an important role in inflammatory responses and anti-tumor immunity. Tumor-specific growth factor (TSGF) is related to the growth of various malignant tumors, and its measurement can assist in the clinical diagnosis of malignant tumors. This study explored the effects of treating primary liver cancer with RFA, including clinical outcomes and changes in T lymphocyte subsets, sIL-2R, and TSGF.

Materials and methods

General information

This study was approved by the hospital ethics committee. Patient selection continued from May 2017 to April 2018, accruing 48 patients with liver cancer, 27 male, 21 female, aged 41 to 75, randomly assigned to either the observation group or control group, with 24 patients in each group. All patients had a clear diagnosis of PLC and were imaged with a chest X-ray, chest CT, ultrasound and magnetic resonance imaging.

Inclusion criteria included:

• No relevant treatment before admission;

• Generally good health with no obvious dysfunction or lesion of the heart, lungs, or kidneys;

• A tumor diameter ≤7cm, and fewer than 4 tumors in the liver;

• No extrahepatic metastasis;

• Liver function is adequate, with a Child's grade of A or B[4];

• Platelet count greater than 50×109/L, prothrombin time less than 18 s;

• All patients and their family members gave and signed informed consent.

Exclusion criteria included:

• Inability to cooperate with treatment;

• Incomplete medical records;

• Intolerance of the treatment.

There were no statistically significant differences in gender distribution or average age between the two groups (P<.05) (Table 1).

Group	Gender	Age	Stage (%)			
	(M/F, n)	($\bar{x}$±SD, years)	I	II	III	IV
Control group (n=24)	(14/10)	65.3±16.3	3(12.5)	9(33.33)	8(37.5)	4(16.7)
Observation group (n=24)	(11/13)	67.6±15.4	4(16.7)	11(20.83)	5(45.83)	4(16.7)
χ^2/t	0.751	0.502	0.167	0.343	0.950	0.057
P	0.386	0.618	0.683	0.558	0.330	0.665

Table 1: Comparison of the treatment groups.

Methods

Patients in the control group were treated with conventional embolism chemotherapy[5], including hepatic artery perfusion of adriamycin (Hisun-Pfizer Pharmaceuticals Co., Ltd., production batch number: 33021980, specifications: 10 mg, 5 bottles), 50 mg 5-fluorouracil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., production batch number: 31020593, specifications: 10 ml: 0.25 g /5 pieces) 500 mg, mitomycin 10 mg (Hisun-Pfizer Pharmaceutical Co., Ltd., production batch number: 20179025), and iodine oil 10 to 20 mg mixed for tumor blood supply artery embolism chemotherapy.

Patients in the observation group were treated with RFA in conjunction with conventional embolization chemotherapy. Patients were placed in a supine position and the location, size, and number of tumors were determined by ultrasound examination. The puncture point and the insertion direction were then selected. With the patient under general anesthesia, a radio frequency biopsy needle was advanced with ultrasound guidance, then opened to 2 cm. Ablation continued until the tumor mass was completely ablated. The impedance was maintained at its maximum about 1 min to complete a single point of treatment. The needle was withdrawn, anesthesia discontinued, and the patient returned to the ward after recovering from anesthesia. Both groups of patients were followed for 2 months.

Observation

Before and after treatment, 4 ml fasting blood was collected in the morning from patients in both groups. Serum and cells were separated

by centrifugation. The supernatant was stored in a cryogenic freezer at -80 °C.

The tumor volume change was used as a measure of curative effect, defined as follows:

• Cure (complete remission): visible tumor

• Disappearance lasting more than one month;

• Excellent (partial remission): the product of the largest perpendicular diameters of the two largest tumors decreased by more than 50% for more than one month;

• Effective (stable): the product of the two largest perpendicular diameters of the two largest tumors decreased by less than 50% or increased by less than 25% in one month of observation;

• Invalid: The product of the two perpendicular diameters of the two largest tumors increased by 25% or more.

The total effective rate = (significant efficiency + effective rate) ×100%. Enzyme linked immunosorbent assay (ELISA) was used to assay sIL-2R content[6]. The detection of CD_3^+, CD_4^+ and CD_8^+ cells was performed by the APAAP bridging enzyme labeling method[7]. An automatic biochemical analyzer was used to measure TSGF. All the above measurements were carried out in accordance with the manufacturers' instructions. In both groups, the patient's level of post-procedure discomfort was recorded following the treatment.

Statistical methods

SPSS 19.0 statistical software was used for data statistics, and the measurement data expressed by standard deviation ($\bar{x}\pm SD$), and t-test applied to determine the significance of differences.

Counting data were expressed as [n (%)] and the χ^2 test was used to compare groups. Statistical significance was at P<.05.

Results

Comparison of clinical efficacy

After treatment, the total effective rate was 87.50% in the observation group, significantly higher than the total effective rate of 70.83% in the control group, (P<0.05) (Table 2).

Changes in T Lymphocyte Subsets

Before treatment, the levels of CD_3^+, CD_4^+, CD_8^+, and CD_4^+/CD_8^+ were similar between the two groups, and the difference was not statistically significant (P>.05). After treatment, the number of CD_3^+ CD_4^+, and CD_4^+/CD_8^+ cells in both groups increased significantly, and the number of CD_8^+ cells decreased significantly. Moreover, the changes in the observation group were significantly greater than those in the control group (P<0.05) (Table 3).

Group	Excellent n (%)	Effective n (%)	Invalid n (%)	Total effective rate n (%)
Observation group (n = 24)	12 (50.00)	9 (37.50)	3 (12.5)	21 (87.50)
Control group (n = 24)	9 (37.50)	8 (33.33)	7 (29.17)	17 (70.83)
χ^2				4.000
P				0.046

Table 2: Comparative analysis of clinical efficacy.

Group	n	Time	T lymphocyte subsets (%, $\bar{x}\pm SD$)			
			CD_3^+	CD_4^+	CD_8^+	CD_4^+/CD_8^+ (μg L)
Observation group	24	Before	63.91±15.86	36.45±6.12	28.51±7.20	0.70±0.92
		After	74.33±5.31*#	43.19±15.03*#	21.05±14.64*#	1.91±0.37*#
Control group	24	Before	62.52±15.14	36.22±5.93	28.84±7.03	0.75±0.84
		After	69.23±9.01*	39.34±10.58*	26.95±9.11*	1.26±0.6*

Table 3: Comparison of T lymphocyte subsets between the two groups.

*Note: *denotes significant differences (P<.05) from measurements before treatment in the same group; #indicates a significant difference from the control group four weeks after treatment.*

Comparison of sIL-2R levels: control vs. observation and before vs. after treatment

Before treatment, the levels of sIL-2R in the two groups were similar and the difference was not statistically significant (P>.05).

After treatment, sIL-2R was significantly reduced in both groups (P<.05), and the reduction in the observation group was significantly greater than that of the control group (Table 4).

Group	n	SIL-2R ($\bar{x}\pm SD$)	
		Before	After
Observation group	24	296.32±29.45	96.21±103.65*
Control group	24	285.31±26.54	168.27±96.36*
χ^2		1.361	2.495
P		0.180	0.016

Table 4: Comparison of sIL-2R between control and observation groups.

*Note: *denotes a significant difference from the same group before treatment (P<.05).*

Comparison of TSGF levels

Before treatment, TSGF levels in the two groups were not significantly different (P>.05). After treatment, TSGF in both groups decreased significantly (P<.05), and the change in the observation group was significantly greater than that of the control group (P<.05) (Table 5).

Group	n	TSGF ($\bar{x}$±SD)	
		Before	After
Observation group	24	93.59±9.75	61.13±8.92*
Control group	24	94.35±9.62	75.34±9.03*
χ^2		0.272	5.485
P		0.787	0.000

Table 5: Comparison of TSGF levels.
*Note: *denotes a significant difference from the before-treatment level in the same group, P<.05.*

Postoperative complications of the two groups of patients

During and after treatment, the total incidence of complications in the observation group was 29.17%, and in the control group, 58.33%, a statistically significant difference (P<.05) (Table 6).

Group	n	Internal hemorrhage n (%)	Pneumothorax n (%)	Stomachache n (%)	Fever n (%)	Total n (%)
Observation group	24	2 (8.33)	1 (4.17)	1 (4.17)	3 (12.50)	7 (29.17)
Control group	24	3 (12.50)	3 (8.33)	4 (16.67)	5 (20.83)	14* (58.33)
t						4.148
P						0.042

Table 6: Frequency of complications.

Discussion

PLC is a malignant tumor that poses a serious threat to human health. In China, it occurs mainly in middle-aged men. The symptoms of early PLC are not obvious and mostly affect the whole body and the digestive system. A study found that 60% to 80% of patients with PLC had loss of body weight with symptoms such as anorexia and local tumor effects, followed by fatigue, abdominal distention, fever, and diarrhea. Later, patients had anemia, jaundice, ascites, lower extremity edema, subcutaneous bleeding, and cachexia. Liver cancer poses a serious threat to patient's quality of life.

Clinical diagnosis tools [of ICM methods] include imaging, serological examination, and liver biopsy[8]. Treatment by surgical resection is preferred and provides a significant curative effect, but because initial symptoms are often vague and nonspecific, most patients are not diagnosed until the optimal treatment period has passed. Although liver transplantation can achieve a better curative effect, liver transplantation resources are scarce. The operation and immunosuppressive drugs are expensive, so most patients cannot afford it. In addition, some patients will experience rejection and related complications. As a result, liver transplantation cannot be widely used as treatment. With the emergence and improvement of new medical technologies, minimally invasive treatment methods such as transarterial chemoembolization (TACE) and RFA have been applied in clinical practice. These new treatments have been accepted by an increasing number of patients.

RFA can be considered for other aspects of tumor therapy. In its cardiac use, a high frequency electromagnetic wave is sent through the catheter into the heart to specific parts of the myocardium to desiccate diseased tissue and cause coagulation necrosis of a particular area to eliminate lesions or to block cardiac conduction re-entry loops. In tumor treatment, RFA has advantages including easy operation, few complications and high repeatability[9]. The results of this study show that RFA treatment of primary liver cancer can have a significant clinical benefit, effectively reduce patients' pain, and improve their quality of life.

T lymphocyte subsets are an important part of the body's immune system and reflect the immune regulatory function of the body[10]. Measurement of T lymphocyte subsets in blood is an important method for observing cellular immunity status, and it plays an important role in the diagnosis, treatment, and prognosis of malignant tumors, autoimmune diseases, immunodeficiency diseases, and hematological diseases. Circulating sIL-2R, a complex mucin, is an important immunosuppressant[11, 12]. It can neutralize the interleukin-2 (IL-2) around activated T cells, weaken the endocrine effects of IL-2 on the body, inhibit activated T cells, and play an important role in monitoring tumor immunity.

TSGF plays an important role in the vascular formation of malignant tumors[13, 14]. Studies have found that the level of TSGF in the blood of patients with early malignant tumors is significantly increased. Because TSGF has a broad spectrum and good sensitivity and specificity for screening early malignant tumors, its measurement can support the early diagnosis of malignant tumors[15].

The results of this study showed that RFA can improve the immune function of patients with primary liver cancer, which may help them better resist and kill tumor cells and improve their overall condition. In summary, RFA has a significant clinical effect on primary liver cancer, and can effectively regulate the levels of CD_3^+, CD_4^+, CD_8^+, CD_4^+/CD_8^+, sIL-2R, and TSGF in patients.

RFA effectively and safely improves the remission rate and alleviates patients' pain. With a low incidence of complications, RFA is worthy of clinical use for primary liver cancer.

References

1) Jonard F, De Cannière S, Brüggemann N, Gentine P, Short Gianotti DJ, et al. Value of sun-induced chlorophyll fluorescence for quantifying hydrological states and fluxes: Current status and challenges. Agric For Meteorol 2020; 291: 108088.
2) Yuan HJ, Liu FY, Li X, Guan Y, Wang MQ. Transcatheter arterial chemoembolization combined with simultaneous DynaCT-guided radiofrequency ablation in the treatment of solitary large hepatocellular carcinoma. La Radiologia Med 2019; 124: 7.
3) Zhu P, Wang DS, Tian DF. Clinical observation of 124 cases of primary liver cancer treated by hepatic arterial chemoembolization combined with radiofrequency ablation. J Hepatobiliary Pancreat Surg 2018; 30: 7-10.
4) Song JL, Li ZW, Chen PY, Zhou NN, Zhang Y, et al. The correlation between molecular pathological profiles and metabolic parameters of 18F-FDG PET/CT in patients with gastroesophageal junction cancer. Abdom Radiol 2019; 45: 312-321.
5) He X, Zhan MX, Lu LC. Current situation and prospect of hepatic arterial chemoembolization for hepatocellular carcinoma. Chin J Interventional Radiol 2018; 6: 124-126.
6) Hajissa K, Zakaria R, Suppian R, Mohamed Z. An evaluation of a recombinant multiepitope based antigen for detection of Toxoplasma gondii specific antibodies. BMC Infect Dis 2017; 17: 807.
7) Yoshinami T, Kagara N, Motooka D, Nakamura S, Miyake T, et al. Detection of ctDNA with Personalized Molecular Barcode NGS and Its Clinical Significance in Patients with Early Breast Cancer. Transl Oncol 2020; 13: 100787.
8) Yan TM. Comparative Study of CT and MRI in diagnosis of liver cancer. Mod Med Imaging 2018; 27: 160-161.
9) Mariappan P, Weir P, Flanagan R, Voglreiter P, Alhonnoro T, et al. GPU-based RFA simulation for minimally invasive cancer treatment of liver tumours. Int J Comput Assist Radiol Surg 2017; 12: 59-68.
10) Ottonello S, Genova C, Cossu I, Fontana V, Rijavec E, et al. Association Between Response to Nivolumab Treatment and Peripheral Blood Lymphocyte Subsets in Patients with Non-small Cell Lung Cancer. Front Immunol 2020; 11: 125.
11) Wang FB, Liu MZ, Huo XT, Chen L, Chen JX. Using femtosecond laser processing quartz glass microchannel sample cell. Microw Opt Technol Lett 2019; 61: 2225-2233.
12) Yu SH, Ma Q, Dang YL. Efficacy of tacrolimus combined with cyclophospham in the treatment of systemic lupus erythematosus and its effect on serum monocyte chemotaxis protein 4 and soluble interleukin-2 receptor. J Clin Mili Med 2019; 47: 258-260.
13) Fei LX, Gao JC. Study on the value of combined detection of serum AFP-L3, GPC3, DCP and TSGF in the early diagnosis of primary liver cancer. Labeled Immunoassay Clin Pract 2018; 3: 407-409,420.
14) Chang JJ, Xu L. The value of combined detection of TSGF AFP CEA CA199 CA50 for early diagnosis of malignant tumors of digestive system. J Clin Psychosomatic Dis 2018; 24: 116-119.
15) Gu WJ, Du XL. TSGF combined with tumor markers CEA and CA724 in the diagnosis of gastric cancer. J Lab Med Clin Pract 2019; 16: 1709-1711.

Corresponding Author:
Zhengming Wang
Email: pr71rv@163.com
(China)