Comparison of radiofrequency ablation or microwave ablation combined with TACE in unresectable liver cancer

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Introduction. Primary liver cancer has high incidence and mortality, and most of them do not meet the indications for surgery. Radiofrequency ablation, microwave ablation and transcatheter arterial chemoembolization (TACE) are commonly used in the treatment of patients with unresectable liver cancer. Combined therapy can improve clinical efficacy and prolong survival. However, how to choose the ablation method still needs to be further explored.

To compare the short-term and long-term efficacy of radiofrequency ablation or microwave ablation combined with TACE in patients with unresectable liver cancer.

Methods. A total of 112 patients with unresectable liver cancer admitted to our hospital from March 2017 to March 2019 were enrolled for the experiment and divided into 2 groups according to a random number table. Group A was treated with radiofrequency ablation combined with TACE, while group B was treated with microwave ablation combined with TACE. The treatment effect, serum tumor marker levels [including alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199)], liver function indicators [including alanine aminotransferase (ALT), aspartate aminotransferase (AST)] before and after treatment and complications were compared between the two groups. All were followed up by outpatient or telephone for 3 years. Progression-free survival (PFS) and overall survival (OS) were compared between the two groups. Kaplan-Meier method was used for the survival analysis on the two groups.

Results. The clinical benefit rate and total effective rate of group B were 62.50% and 76.79%, which were higher than those of 42.86% and 58.93% in group A (P<0.05). There were no significant differences in serum tumor marker levels and liver function indexes between the two groups before treatment (P>0.05). After treatment, serum tumor marker levels in the two groups were decreased (P<0.05), which in group B was lower than those in group A [AFP:(867.75±569.21)ng/mL vs (1817.35±311.75)ng/mL; CEA:(11.50±5.15)ng/mL vs (20.65±4.36)ng/mL; CA125:(68.53±37.70)U/mL vs (137.35±20.25)U/mL; CA199:(54.75±20.71)U/mL vs (84.85±11.65)U/mL](P<0.05). After treatment, liver function indexes in the two groups were increased (P<0.05), which in group B were higher than those in group A [AST:(37.53±11.48)U/L vs (27.15±4.95)U/L; ALT:(35.79±11.62)U/L vs (20.75±4.25)U/L] (P<0.05). The liver damage in group B was 19.64%, more than that of 3.57% in group A (P<0.05), PFS of group B was 12(8,16) months, longer than that of 8(5,11) months in group A (P<0.05), and the 1-year survival rate of group B was 94.64%, higher than that of 75.00% in group A (P<0.05). There were no significant differences in the other complications, OS, 2-year and 3-year survival rates between the two groups (P>0.05). Conclusions. Microwave ablation combined with TACE is better than radiofrequency ablation combined with TACE in unresectable liver cancer patients, which can prolong OS and improve short-term survival rate, but liver damage is aggravated, other complications, PFS and long-term survival rate are similar between the two.

Keywords: Radiofrequency ablation; Microwave ablation; Transcatheter arterial chemoembolization; Liver cancer

INTRODUCTION

Primary liver cancer refers to malignant tumors originating from liver epithelium or mesenchymal tissue. Currently, there are about 700,000 to 800,000 new cases in the world each year, and about 45% of new cases in China each year (1). According to statistics (2), liver cancer ranks third among cancer deaths, accounting for 8.3%. Other data show that the incidence of liver cancer in China ranks fifth among

malignant tumors, and the mortality rate ranks second, and both the morbidity and mortality have increased. Patients with early-stage liver cancer often lack typical clinical features, and patients with advanced-stage liver cancer often show symptoms such as liver pain, fever, and fatigue. According to the survey, about 70% to 80% of patients with primary liver cancer miss the opportunity of surgery when they are diagnosed, and the survival time of unresectable liver cancer patients who only receive symptomatic and supportive treatment is often shorter than 6 months(3~5). However, if patients are actively treated with anti-tumor therapy, their survival time can be significantly prolonged.

Both radiofrequency ablation and microwave ablation are commonly used treatment measures for unresectable patients with primary liver cancer, and are often used in conjunction with TACE. The principle of radiofrequency ablation is to use radiofrequency current to interfere with the electromagnetic field of the tumor tissue, so that the positive and negative ions in the tumor cells move rapidly and generate heat, thereby achieving the purpose of coagulation and necrosis of the tumor tissue (6). Microwave ablation is a physical therapy that uses the electromagnetic field formed by microwaves to make water molecules rotate at high speed in the magnetic field, thereby generating heat and rapidly heating the tumor tissue to cause coagulation necrosis. This therapy belongs to a "self-heating" process, and microwave ablation can select multiple probes for treatment according to the size of the tumor, and use the synergy between different probes to achieve the purpose of wide-ranging treatment (7). Both are unresectable thermal ablation techniques for liver cancer, and their effects have been affirmed in previous reports. Some studies have compared the short-term efficacy of radiofrequency ablation and microwave ablation for patients with advanced liver cancer and found that the former is better (8~10). However, the short-term and long-term effects of the two combined with TACE treatment and their effects on serum tumor markers and liver function need further comparative analysis. This study selected 112 patients with unresectable liver cancer to conduct a randomized controlled trial, aiming to provide a reference for the selection of

anti-tumor therapy for such patients.

MATERIALS AND METHODS

Patient selection

112 patients with unresectable liver cancer admitted to our hospital from March 2017 to March 2019 were enrolled for the experiment. Inclusion criteria: (1) Primary liver cancer confirmed by pathological examination; (2) Unresectable patients; (3) Voluntary cooperation in this study and signed informed consent. Exclusion criteria: (1) Patients with recurrence of liver cancer or other types of cancer metastasized to the liver; (2) Those with a history of anti-tumor therapy; (3) Those with other types of fatal diseases, such as severe trauma, acute cardiovascular and cerebrovascular diseases; (4) Those with severe organ insufficiency, such as renal failure; (5) Those with other types of diseases that may affect the results of this study, such as tuberculous peritonitis; (6) Those with mental disorders. Among these patients, there were 90 male and 22 female, range 30~76 years old, TNM stages: IIIa 38 cases and IIIb 74 cases, Child-pugh classification: A 44 cases and B 68 cases, maximum tumor size range 1.3~7.6 cm. Those were divided into two groups by a random digital table, namely A group and B group, with 56 cases in each.

Methods

Group A was treated with radiofrequency ablation combined with TACE. (1) The puncture position and depth under ultrasound guidance was determined, local anesthesia was implemented, and the number of electrodes according to the size of the tumor was selected, then electroacupuncture reasonably distributed. Percutaneous puncture was performed until the center of the tumor, and electrode needle ablation was gradually started after penetrating the tumor, and the ablation treatment time for each point was 12 minutes. If the scope of the lesion was large, layered and multi-point superimposed ablation was required, and the ablation scope was larger than 0.5-1.0 cm of the scope of the lesion. During operation, dynamic electrocardiogram, respiration and blood pressure monitoring should be performed at

the same time, and the patient's vital signs should be observed. The needle tract was ablated after treatment to prevent needle tract bleeding or tumor cell shedding and seeding. (2) Seldinger's method was used to percutaneously puncture the femoral artery to perform TACE. After the puncture, angiography of the celiac trunk, superior mesenteric artery and common hepatic artery was performed to evaluate the blood supplying artery and the course of the tumor. According to the arterial blood supply of the lesion site and the tumor, under the guidance of the guide wire, the tumor blood supply artery was selectively intubated. Liver-protecting symptomatic and supportive treatment was implemented postoperatively.

Group B was treated with microwave ablation combined with TACE. (1)Under the guidance of ultrasound, the optimal needle insertion site and route were selected to puncture the cold circulation microwave antenna to the predetermined site of the tumor, and the power was determined according to the size of the tumor. High-power microwave ablation was performed on tumor tissue, and the farthest point of radiation was 0.5 cm from the periphery of the tumor. Dynamic electrocardiogram, respiration and blood pressure monitoring were also performed during the operation, and the patient's vital signs were observed. (2) The TACE operation was exactly the same as that of Group A.

Follow-up

Patients were followed-up by review, phone etc. methods, lasted for 3 years.

Outcome Parameters

The treatment effect, serum tumor marker levels [including alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199)], liver function indicators [including alanine aminotransferase (ALT), aspartate aminotransferase (AST)] before and after treatment and complications were compared between the two groups. All were followed up by outpatient or telephone for 3 years. Progression-free survival (PFS) and overall survival (OS) were compared between the two groups. The treatment effect was evaluated according to the response evaluation criteria in solid tumor 1.1 after 1

month of treatment (11), in which the complete disappearance of the target lesions and lasting at least 1 month was recorded as complete remission (CR), the target lesions were reduced by at least 50% and lasted for at least 1 month as partial remission (PR), the target lesions had an increase of <20% or a shrinkage of less than 50% for at least 1 month was recorded as stable disease (SD), and the target lesions had an increase of at least 20% of the target lesion or the appearance of new lesions was recorded as progression disease (PD). The serum tumor marker levels and liver function indicators were detected by enzyme linked immunosorbent assay (ELISA), and 5 ml of cubital venous blood before and after treatment was drawn from both groups of patients on an empty stomach, and centrifuged at 3500 r/min for 10 min. Then, the supernatant was detected by an automatic biochemical analyzer (Beckman Coulter, AU7600) and a matching ELISA kit. Complications included liver damage, fever, abdominal pain, intestinal obstruction and arrhythmia, and liver damage was evaluated according to elevated liver enzymes and elevated bilirubin.

Statistical analyses

Data were analyzed with IBM SPSS statistical software, version 23.0. For enumeration data, percentages were calculated and data were compared using the Pearson chisquared test or Fisher's exact test. For continuous data, medians with range or means with standard deviations were calculated as appropriate. Depending on the data distribution, either the independent t-test and analysis of variance test or the Mann–Whitney U tests were used. Kaplan-Meier method was used for the survival analysis. *P* values less than 0.05 were considered statistically significant.

RESULTS

Patient general data

Table 1 shows there were no statistical differences in the gender, age, TNM stages, maximum tumor size, Child-pugh classification between the two groups (P>0.05).

Table 1 Comparison of general data between the two groups

General data	A group (n=56)	B group (n=56)	Chisquared/*U*	*P*
Gender			0.474	0.636
Male	46(82.14)	44(78.57)		
Female	10(17.86)	12(21.43)		
Age (years old)[M(Q1,Q3)]	55(50,68)	55(51,68)	0.475	0.635
TNM stages			0.397	0.691
IIIa	20(35.71)	18(32.14)		
IIIb	36(64.29)	38(67.86)		
Child-pugh classification			0.770	0.441
A	24(60.71)	20(35.71)		
B	32(57.14)	36(64.29)		
Maximum tumor size (cm)[M(Q1,Q3)]	3.2(2.8,4.5)	3.1(2.8,4.4)	0.079	0.937

Effectiveness

Table 2. shows the clinical benefit rate and total effective rate of group B were higher than those of group A ($P<0.05$).

Table 2 Comparison of effectiveness between the two groups [n(%)]

Effectiveness	A group (n=56)	B group (n=56)	Chisquared	*P*
CR	10(17.86)	19(33.93)		
PR	14(25.00)	16(28.57)		
SD	9(16.07)	8(14.29)		
PD	23(41.07)	13(23.21)		
Clinical benefit rate	24(42.86)	35(62.50)	2.072	0.038
Total effective rate	33(58.93)	43(76.79)	2.014	0.044

Tumor marker levels

Table 3. shows there were no significant differences in serum tumor marker levels between the two groups before treatment (P>0.05). After treatment, serum tumor marker levels in the two groups were decreased (P<0.05), which in group B was lower than those in group A (P<0.05).

Table 3 Comparison of tumor marker levels between the two groups ($\bar{x} \pm s$)

Tumor markers	Time	A group (n=56)	B group (n=56)	*t*	*P*
AFP(ng/mL)	Before treatment	1815.15±316.05	1817.35±311.75	0.037	0.971
	After treatment	1241.26±532.45	867.75±569.21	3.586	0.001
	t	7.354	10.967	_	_
	P	<0.001	<0.001	_	_
CEA(ng/mL)	Before treatment	20.35±4.55	20.65±4.36	0.356	0.722
	After treatment	15.23±4.82	11.50±5.15	3.965	<0.001
	t	5.169	10.685	_	_
	P	<0.001	<0.001	_	_
CA125(U/mL)	Before treatment	138.55±20.65	137.35±20.25	0.310	0.757
	After treatment	95.99±34.59	68.53±37.70	4.016	<0.001
	t	7.843	11.357	_	_
	P	<0.001	<0.001	_	_
CA199(U/mL)	Before treatment	85.55±11.25	84.85±11.65	0.323	0.747
	After treatment	69.29±14.37	54.75±20.71	4.317	<0.001
	t	6.481	8.686	_	_
	P	<0.001	<0.001	_	_

Liver function levels

Table 4. shows there were no significant differences in serum liver function indexes between the two groups before treatment (P>0.05). After treatment, liver function indexes in the two groups were increased (P<0.05), which in group B were higher

than those in group A (*P*<0.05).

Table 4 Comparison of liver function levels between the two groups ($\bar{x} \pm s$)

Tumor markers	Time	A group (n=56)	B group (n=56)	*t*	*P*
AST(U/L)	Before treatment	26.45±4.45	27.15±4.95	0.785	0.434
	After treatment	31.31±7.25	37.53±11.48	3.429	0.001
	t	4.155	5.696	_	_
	P	<0.001	<0.001	_	_
ALT(U/L)	Before treatment	21.35±4.35	20.75±4.25	0.736	0.463
	After treatment	26.28±6.48	35.79±11.62	5.347	<0.001
	t	4.615	8.911	_	_
	P	<0.001	<0.001	_	_

Complications

Table 5. shows liver damage in group B was more than group A (*P*<0.05), and there were no significant differences in other complications between the two groups (*P*>0.05).

Table 5 Comparison of complications between the two groups [n(%)]

Complications	A group (n=56)	B group (n=56)	Chisquared	*P*
Liver damage	2(3.57)	11(19.64)	2.643	0.008
Fever	4(7.14)	6(10.71)	0.660	0.509
Abdominal pain	5(8.93)	8(14.29)	0.881	0.378
Intestinal obstruction	4(7.14)	2(3.57)	0.836	0.403
Arrhythmia	1(1.79)	3(5.36)	1.014	0.311

PFS and OS

Table 6. shows there was no significant difference in the OS between the two groups (*P*>0.05), and the PFS of group B was longer than that of group A (*P*<0.05).

Table 6 Comparison of PFS and OS between the two groups [M(Q1,Q3)]

Survival time	A group (n=56)	B group (n=56)	*U*	*P*
PFS(months)	8(5,11)	12(8,16)	4.123	<0.001
OS(months)	20(11.5,30)	20(13.5,31.5)	0.577	0.564

Following-up outcomes

Table 7. and Figure 1 show the 1-year survival rate of group B was higher than that of group A ($P<0.05$), and there were no significant differences in 2-year and 3-year survival rates between group B and group A ($P>0.05$). Figure 1 shows there was no statistical difference in the survival rates between the two groups (Chisquared=0.049, $P=0.825>0.05$).

Table 7 Comparison of survival rates between the two groups [n(%)]

Survival rates	A group (n=56)	B group (n=56)	Chisquared	*P*
1-year survival rate	42(75.00)	53(94.64)	2.884	0.004
2-year survival rate	24(42.86)	21(37.50)	0.193	0.847
3-year survival rate	8(14.29)	7(12.50)	0.276	0.782

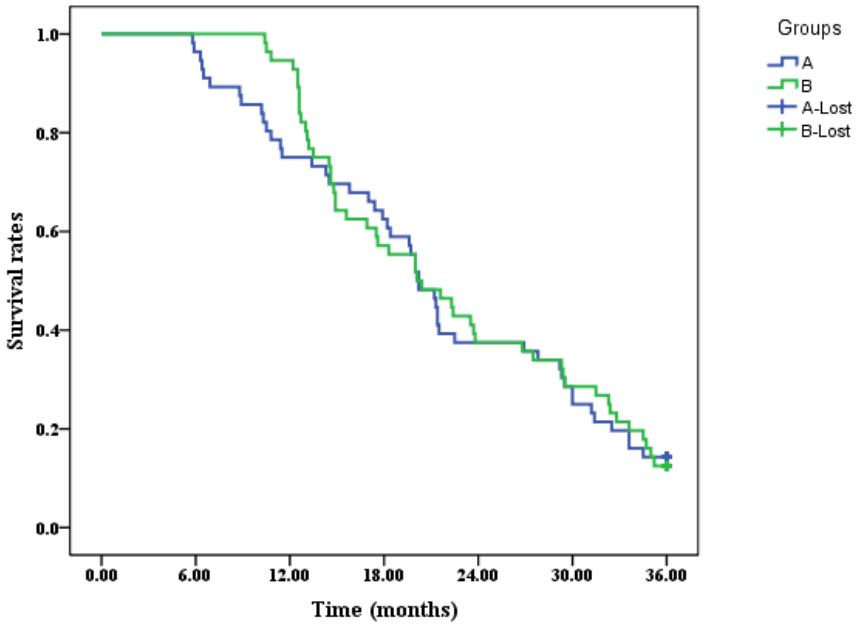

Figure 1 Kaplan-Meier analysis for survival rates between the two groups

DISCUSSION

The etiology and pathogenesis of primary liver cancer is still unclear. It is generally believed that the occurrence of the disease is related to liver cirrhosis, viral hepatitis, exposure to carcinogens and environmental factors. In my country, about 85% of liver cancer patients have liver cirrhosis characteristics or tendencies, and liver cirrhosis can increase the difficulty of surgery or even severely limit surgical resection, making clinical treatment very difficult (12). Therefore, it is necessary to pay attention to the protection of the liver in the process of anti-cancer treatment. In addition, the natural course of primary liver cancer is only 3 to 6 months (13), and most patients are diagnosed late, which is also an important reason for inoperability. In addition, some liver cancers have special sites and multiple characteristics, and it is difficult to perform surgical resection (14). Therefore, how to effectively implement anti-tumor therapy to prolong the survival period of patients with inoperable liver cancer is still a problem that needs to be paid attention to.

The results of this study showed that the clinical benefit rate and total effective rate of group B were 62.50% and 76.79%, respectively, which were higher than 42.86% and 58.93% of group A, respectively, indicating the short-term efficacy of microwave ablation combined with TACE in patients with unresectable liver cancer was better than radiofrequency ablation combined with TACE. In addition, in the results of this study, the PFS of group B was shorter than that of group A, and the 1-year survival rate was higher than that of group A, which was consistent with the above conclusions. In this study, the OS, 2-year survival rate and 3-year survival rate were comparable between the two groups, suggesting that the long-term effect and survival rates of radiofrequency ablation or microwave ablation combined with TACE in patients with unresectable liver cancer were comparable. Microwave ablation can achieve a "self-heating" process with multiple probes at the same time, resulting in a larger treatment range and better treatment effect. It has been reported that among thermal ablation techniques, microwave ablation has stronger blood vessel coagulation ability and faster tumor ablation speed than other methods, which is also

an important reason why microwave ablation is more effective than radiofrequency ablation (15). Yuan P et al (16) reported that 117 HCC patients were divided into TACE group and TACE+RFA group according to the treatment method, and the DCR of the later was 88%, higher than that of 69% of the former, it sugguests that TACE+RFA can achieve better effect. While the clinical benifit rate in group A was 62.50% only, lower than thise report, and it may be related to the patient's condition, treatment compliance, efficacy evaluation criteria, etc. In addition, in this study, serum tumor markers in group B after treatment were lower than those before treatment, and those were significantly lower than those in group A. The level of serum tumor markers are important indicators for evaluating the condition of liver cancer, and the decrease of their levels mean that the patient's condition has been relieved. This result also proves that microwave ablation combined with TACE has a better remission effect on patients with unresectable liver cancer than radiofrequency ablation combined with TACE.

This study also found that serum AST and ALT levels in group B increased after treatment, and they were much higher than those in group A. The incidence of liver damage in group B was 19.64%, higher than 3.57%, suggesting that microwave ablation combined with TACE caused liver damage. The risk is higher than that of radiofrequency ablation combined with TACE, which may be due to the larger treatment range of microwave ablation, which is likely to cause damage to surrounding normal tissues. Yang Y et al (17) reported based on systematic review and meta-analysis pointed out that radiofrequency ablation or microwave ablation combined with TACE can increase the curative effect of intermediate-stage hepatocellular carcinoma without more complications. The results of this study on liver damage are inconsistent with the report, and the results of other complications are consistent with this report, which may be related to the patient's condition and surgical trauma. At the same time, it is also suggested that clinicians should strictly control the treatment power and ablation range when implementing microwave ablation therapy to avoid liver damage.

CONCLUSION

This study found that microwave ablation combined with TACE is better than radiofrequency ablation combined with TACE in unresectable liver cancer patients, which can prolong OS and improve short-term survival rate, but liver damage is aggravated, other complications, PFS and long-term survival rate are similar between the two. It is recommended to choose microwave ablation combined with TACE treatment for patients with unresectable liver cancer. However, during microwave ablation treatment, attention should be paid to controlling the treatment power and range to avoid liver damage, and liver protection support should be actively given before and after treatment to reduce the incidence of liver damage.

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