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ORIGINAL ARTICLE

Clinical efficacy analysis of transcatheter arterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) in primary liver cancer and recurrent liver cancer

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Summary

Purpose: *To compare the efficacy of transcatheter arterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) in primary hepatocellular carcinoma and recurrence of hepatocellular carcinoma after hepatectomy, and analysis the prognostic factors affecting therapeutic outcomes.*

Methods: *A total of 132 hepatocellular carcinoma patients treated with TACE combined with RFA were divided into primary group (n=89) and recurrent group (n=43). Their clinical date were reviewed. The overall survival (OS), tumor-free survival (TFS) and safety between 2 groups were compared. Prognostic factors were analyzed with univariate and multivariate analyses.*

Results: *OS rates at 1 and 3 years were 94.4% (84/89) and 70.8% (63/89) in the primary group, and TFS were 76.4% (68/89) and 37.1% (33/89), respectively. The OS rates in the recurrent group were 93.0% (40/43) and 65.1% (28/43), and TFS rates were 41.9% (18/43) and 13.9% (6/43), respectively. The OS rates had no significant difference between 2 groups (x^2=0.0068, 0.4353, p=0.9342, 0.5094), but the TFS rates in primary group were significantly higher than in the recurrent group (x^2=15.2378, 7.4483, p=0.0001, 0.0063). Multivariate analysis identified presence of portosystemic collaterals, AFP level, total bilirubin and Child-Pugh grading as factors affecting OS, and the presence of portosystemic collaterals and AFP level were two unfavorable prognostic factors influencing TFS.*

Conclusions: *TACE combined with RFA is helpful in improving the survival rate of patients with primary and recurrent hepatocellular carcinoma. Presence of portosystemic collaterals, AFP level,ptotal bilirubin and Child-Pugh grading were the factors affecting OS.*

Key words: *hepatocellular carcinoma, transcatheter arterial chemoembolization, radiofrequency ablation, prognosis*

Introduction

Primary liver cancer is one of the high-incidence malignant tumors in China. Due to its hidden onset, the vast majority of patients have already been in the advanced stage at the time of treatment, and only 15-20% of patients may have undergone the surgical resection [1]. Even among the patients who have undergone surgical treatment, there are still a large number of patients with recurrence, while the re-operation may result in higher mortality due to insufficient residual liver capacity, liver dysfunction, surgical adhesions and other factors.

Radiofrequency ablation (RFA) is an effective means for the treatment of malignant tumors. RFA, liver transplantation and surgical resection have

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been jointly listed as the radical treatment methods of liver cancer at in China and abroad [2]. They can significantly improve the therapeutic effect when combined with TACE [3,4]. However, there are currently fewer reports about their clinical efficacy on the recurrent liver cancer, and there is also a lack of effective references for comprehensive assessment of prognosis.

In view of this situation, this study retrospectively analyzed the primary/recurrent liver cancer patients who have undergone the combined therapy of TACE and RFA, evaluate and compare its therapeutic effect and safety, as well as analyze the relevant factors which influence prognosis.

Methods

Clinical data collection

From August 2010 to March 2013, 132 patients with liver cancer underwent TACE combined with RFA in our hospital. Ninety eight patients were male and 34 female. Age: 26-78 years old (mean 58.6±4.4); the largest foci diameter: 1.2-6.8 cm (mean 3.6±1.4); single lesion 59 cases, multiple lesions 73 cases, among whom, 89 cases from the primary group were diagnosed as primary liver cancer for the first time and preferred therapy with TACE combined with RFA; 43 cases from the recurrent group had postoperative recurrence and preferred therapy with TACE combined with RFA at the time of re-treatment. General data comparing the two groups of patients are shown Table 1. This study was approved by the ethics committee of China-Japan Union Hospital of Jilin University. Signed informed consents were obtained from all participants before the study entry.

Inclusion and exclusion criteria

Inclusion criteria: (1) Diagnosed as primary liver cancer by combining clinical symptoms and signs, radiology, laboratory and/or pathology; (2) Primary or recurrent liver cancer patients preferred therapy with TACE combined with RFA; (3) Number of foci ≤3; (4) The largest diameter of tumors ≤5 cm, the largest diameter of single tumor ≤7 cm; (5) Child-Pugh grading A or B; (6) Complete clinical and follow-up information.

Table 1. Comparison of general data of two groups of patients

	Group		x^2	*p*
	Primary group	*Recurrent group*		
Age (y)			0.0668	0.7961
≤60	62	29		
>60	27	14		
Tumor size (cm)			0.6392	0.4240
≤3	41	23		
>3	48	20		
Number of lesions			1.6717	0.1960
Single	50	19		
Multiple	39	24		
Hepatitis B surface antigen			0.0000	0.9953
Positive	58	28		
Negative	31	15		
Portal vein collateral circulation			0.0000	0.9977
Yes	45	22		
No	43	21		
AFP(ng/ml)			0.0023	0.9617
≤50	41	20		
>50	48	23		
Child-Pugh grading			0.3206	0.5713
A	44	19		
B	45	24		
Total bilirubin (mg/dl)			1.4403	0.2301
≤1.5	65	27		
>1.5	24	16		
Albumin (g/dl)			0.1473	0.7011
≤35	32	14		
>35	57	29		

Exclusion criteria: (1) Extrahepatic metastasis or extravascular invasion; (2) Past history of gastrointestinal bleeding; (3) Refractory ascites or hepatic encephalopathy; (4) Blood coagulation dysfunction.

Procedure for TACE

Common hepatic artery, celiac artery or mesentery were selected, on which angiography was performed to determine the tumor blood supply and staining situation. Then the catheter was inserted into the tumor blood supply vessel with injection of 40-60 mg lobaplatin (Hainan Changan International Pharmaceutical Co., Ltd, State Yaozhun Zi: H20050308, Haikou, China), 20-40 mg pirarubicin (Zhejiang Haizheng Pharmaceutical Co., Ltd. State Yaozhun Zi: H20045983, Taizhou, China). For larger liver cancer, gelatin sponge was re-used to give a blood vessel embolization. Embolism should be repeated once per 4-6 weeks.

Procedure for RFA

RFA was performed one week after TACE surgery. The patients underwent treatment under local anesthesia + intravenous anesthesia. CT positioning scan used TS-G4106A type RF Generator (Tektronix Technology Limited, Beaverton, OR, USA) and 14G Friendship Medical Electrode needle (Xi'an Fu Tak Medical Electronics Co., Ltd. Xi'an, China). The suitable puncture path was selected to prevent damaging of surrounding structures. The second CT scan could ensure the pinpoint position. During surgery, the superimposed ablation should be performed several times according to the tumor morphology and size. It is appropriate for the ablation range to cover the tumor for more than 1 cm, to effectively kill the tumor's possible infiltration area. After surgery, needle passage ablation should be performed to avoid tumor metastasis and hemorrhage. After surgery, we immediately performed CT scan to exclude complications such as pneumothorax, bleeding, perforation and so on. The patients should be observed for two weeks, with routine blood tests twice per week, as well as liver and kidney function once per week. IL-11 therapy was to be given to patients with platelet count $<25\times10^9$ and granulocyte-stimulating factor therapy should be given to patients with leukocyte count$<2.5\times10^9$/L or neutrophils count $<1.0\times10^9$/L.

Efficacy evaluation and follow-up

AFP and MRI examinations were performed 4 weeks after surgery. The therapeutic effect was evaluated according to specific videography performance [5]. Outpatient visits were performed once every three months. Telephone or outpatient follow-up can record each patient's survival time.

Statistics

SPSS 19.0 statistical software (IBM, Armonk, NY, USA) was employed to perform t-test on the measurement data and x^2-test on the counting data. For univariate analysis on all possible factors, we used Kaplan-Meier method and Log-rank test, as well as Cox proportional risk model to perform multivariate analysis. P<0.05 indicates statistical significance.

Results

General results

There were 118 cases (89.4%) of complete ablation through one-time therapy, 9 cases (6.8%) of complete ablation through the second RFA, 5 cases (3.8%) of incomplete ablation through the second RFA and transfer to other therapies. All of the 132 patients had complete follow-up of 37-56 months duration (mean 41.6±4.7). Until the end of follow-up 41 patients had died (31.1%), among whom, 26 cases (29.2%) from the primary group and 15 cases (34.9%) from the recurrent group. Deaths were mainly due to liver failure and upper gastrointestinal bleeding.

Overall survival rate and influential factors

One-year and 3-year OS was 94.4% (84/89) and 70.8% (63/89) in the primary group and 93.0%

Table 2. Univariate and multivariate analyses of factors that affect the overall survival rate

Factors	*Univariate analysis*		*Multivariate analysis*	
	HR	*p*	*95%CI*	*p*
Age (≤60/>60 y)	-	0.6320	-	-
Tumor size (≤3/>3 cm)	1.4264	0.0247	1.1352-3.7961	0.7294
Number of lesions (Single/Multiple)	-	0.5729	-	-
Hepatitis B surface antigen (positive/negative)	-	0.4386	-	-
Portal vein collateral circulation (Yes/No)	1.0164	0.0014	1.2062-2.9785	0.0058
AFP (≤50/>50 ng/mL)	2.2128	0.0000	1.1266-2.8342	0.0031
Child-Pugh grading (A/B)	1.352	0.0017	1.2973-3.3148	0.0376
Total bilirubin (≤1.5/>1.5 mg/dl)	1.359	0.0052	1.1842-2.9047	0.0246
Albumin (≤35/>35 g/dl)	-	0.3672	-	-

Table 3. Univariate and multivariate analyses of factors that affect the tumor-free survival

Factors	*Univariate analysis*		*Multivariate analysis*	
	HR	*p*	*95%CI*	*p*
Age (≤60/>60 y)	-	0.9241	-	-
Tumor size (≤3/>3 cm)	-	0.9136	-	-
Number of lesions (Single/Multiple)	-	0.2237	-	-
Hepatitis B surface antigen (positive/negative)	-	0.4942	-	-
Portal vein collateral circulation (Yes/No)	1.2436	0.0057	1.2168-5.8977	0.0238
AFP (≤50/>50 ng/mL)	2.5964	0.0061	1.1268-2.8037	0.0069
Child-Pugh grading (A/B)	-	0.9428	-	-
Total bilirubin (≤1.5/>1.5 mg/dl)	-	0.0674	-	-
Albumin (≤35/>35 g/dl)	-	0.6416	-	-

(40/43) and 65.1% (28/43) in the recurrent group. There was no significant difference between the two patient groups (x^2=0.0068, 0.4353, p=0.9342, 0.5094). Tumor size, combined portal vein collateral circulation, AFP, total bilirubin and Child-Pugh grading were significantly related to the patient's OS (p<0.05), among whom, the combined portal vein collateral circulation, AFP, total bilirubin and Child-Pugh grading were independent risk factors that affected the overall coexistence rate (p<0.05) (Table 2).

Tumor-free survival rate and its influential factors

The primary group's 1-year and 3-year TFS rate was 76.4% (68/89) and 37.1% (33/89) respectively and 41.9% (18/43) and 13.9% (6/43) in the recurrent group. The primary group's TFS rate was higher than that of the recurrent group and the difference had statistical significance (x^2=15.2378, 7.4483, p=0.0001, 0.0063). Portal vein collateral circulation and AFP were independent risk factors that affected the TFS rate (p<0.05) (Table 3).

Complications

After surgery, there were 3 cases with pneumothorax (2.3%) which were later improved via closed pleural drainage, 2 transient liver function impairment cases (1.5%), 1 pleural effusion (0.8%) case which was self-absorbed, 2 biloma cases (1.5%) caused by biliary tract injury which was untreated due to lack of symptoms, and 1 liver abscess formation case (0.8%) which was improved via drainage. No complication was found on the remaining patients. In total there were 5 cases (5.6%) in the primary group and 4 cases (9.3%) in the recurrent group. Comparison of the complication incidence of the two patient groups showed no statistical significance (x^2=0.1753, p=0.6755).

Discussion

For patients with mid-stage and advanced-stage liver cancer, TACE is currently recognized as the preferred therapy [6]. However, due to the gradual establishment of collateral circulation of mid-stage and advanced-stage blood supply, as well as factors such as the multi-source of liver blood supply, it is difficult for pure TACE therapy to completely kill tumor cells. However, performing TACE therapy for several times can cause severe damage of liver function and accelerate the patient deterioration.

In terms of liver cancer treatment, RFA is as effective as surgical operation, but the tumor size can significantly affect its efficacy [7]. Research has proven that RFA was less effective in tumors with diameter larger than 3 cm. The main reason is that the lesion's rich blood supply can absorb part of the heat, so it is difficult for the local portion to reach the expected valid temperature. Furthermore, the larger lesion has three-dimensional space limitation, which can result in incomplete ablation therapy. Therefore, the Foreign Diagnosis and Treatment Guide indicates that RFA is the best choice for the treatment of liver cancer with diameter less than 2cm [8]. For mid-stage and advanced-stage liver cancer patients, lesions with diameter larger than 3cm are very common. Therefore, it is clear that purely relying on RFA therapy clinical needs cannot be met.

In view of the above reasons, the solution of TACE combined with RFA has been clinically applied and considered as an effective and safe method for current liver cancer treatment [9,10], with effect superior to single treatment [11]. In the joint application solution, TACE can determine the tumor position and number based on the Transcatheter Arterial Chemoembolization or via angiography, in order to provide reliable evidence for RFA positioning, while RFA will be performed one week after the TACE therapy. At this time, because the lesion's blood supply of the target vessel has already been embolized, the "Heat sink effect" was accordingly lowered and RFA inactivation effect was enhanced. In addition, TACE can shrink the tumor volume, which helps improve the RFA therapeutic effect. In this research, 1-year and 3-year survival rate after surgery in the primary group are 94.4% and 70.8% respectively, while the corresponding figures of the recurrent group are 93.0% and 65.1%, in Chinese and foreign reports [12,13].

Analysis of relevant factors which may affect the postoperative patient survival shows that the combined portal vein collateral circulation, AFP, total bilirubin and Child-Pugh grading are independent risk factors that affect the overall coexistence rate, and the above result is consistent with the report of Lee et al [14]. Portal hypertension can result in the formation of collateral circulation. Multivariate analysis shows that the formation of portal vein collateral circulation is one of the risk factors that affect the patient's postoperative survival. Previous researches consider that the presence of portal hypertension can significantly reduce the postoperative survival of patients who have undergone hepatectomy, regardless of Child-Pugh grading [15]. Combined with current research, the authors believe that the combined portal hypertension can be used to predict the survival of an individual liver cancer patient who has undergone TACE combined with RFA.

AFP is one of the major indicators for detecting and evaluating the recurrence and/or metastasis of liver cancer. The level of AFP can be used to predict the patient's recurrence and survival rate [16]. Liver cancer and liver cirrhosis can affect the patient's prognosis and most of our current liver cancers have developed from liver cirrhosis.

Child-Pugh grading is an important indicator which reflects liver function. Liver failure is still the most common cause for patient death [17]. The postoperative intensive supportive treatment can be used to improve the patient's liver function reserve, which may help improve the prognosis.

The research on tumor-free survival period has proven that the primary group's tumor-free survival rate is significantly higher than that of the recurrent group, and portal vein collateral circulation and AFP are independent risk factors that affect the tumor-free survival rate. The influential role of AFP level is described above. Repeat hepatectomy can reduce the patient's tumor-free survival rate [18], while portal hypertension reduces the patient's OS. Meanwhile, the postoperative liver cancer patient's poorer liver reserve function will result in easier tumor recurrence. Of course, we can't rule out the impact of surgery on the body's normal functions, which will thus facilitate the tumor recurrence. The above effect on older patients is more apparent.

The complications of the perioperative period were mainly pneumothorax, transient liver function damage, pleural effusion, biliary tract injury and liver abscess formation, with an overall incidence of 6.8% (9/132). Furthermore, the complication incidence of the two patient groups had no statistical difference. Because some patients had symptoms such as nausea, vomiting and fever before surgery, the research excluded them from the surgery complication list.

Conclusions

In summary, TACE and RFA combined therapy has good clinical efficacy and safety in the treatment of primary and recurrent liver cancer. Portal vein collateral circulation, AFP, total bilirubin and Child-Pugh grading are independent risk factors which affect the overall coexistence rate, while portal collateral circulation and AFP are independent risk factors which affect the tumor-free survival rate. For the patients with the above risk factors, follow-up should be enhanced to find timely abnormal signs and indicators. Early clinical intervention may help improve their survival.

Conflict of interests

The authors declare no conflict of interests.

References

1. Kim YS, Lim HK, Rhim H, Lee MW. Ablation of hepatocellular carcinoma. Best Pract Res Clin Gastroenterol 2014;28:897-908.
2. Chen L, Ma X, Liu X, Cui X. Sorafenib combined with radiofrequency ablation as treatment for patients with hepatocellular carcinoma: A systematic review and meta-analysis. JBUON 2017;22:1525-32.
3. Peng ZW, Zhang YJ, Liang HH, Lin XJ, Guo RP, Chen MS. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization

and RF ablation versus RF ablation alone: a prospective randomized trial. Radiology 2012;262:689-700.

4. Chen J, Zhang Y, Cai H, Yang Y, Fei DY. Comparison of the effects of postoperative prophylactic transcatheter arterial chemoembolization (TACE) and transhepatic arterial infusion (TAI) after hepatectomy for primary liver cancer. JBUON 2018;23:629-34.
5. Zhang S, Yue M, Shu R, Cheng H, Hu P. Recent advances in the management of hepatocellular carcinoma. JBUON 2016;21:307-11.
6. Goldberg SN, Ahmed M. Minimally invasive image-guided therapies for hepatocellular carcinoma. J Clin Gastroenterol 2002;35:S115-S29.
7. Li X, Liang P. Immunotherapy for hepatocellular carcinoma following thermal ablation. JBUON 2014;19:867-71.
8. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245-55.
9. Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer 2010;116:5452-60.
10. Kim JH, Won HJ, Shin YM et al. Medium-sized (3.1-5.0 cm) hepatocellular carcinoma: transarterial chemoembolization plus radiofrequency ablation versus radiofrequency ablation alone. Ann Surg Oncol 2011;18:1624-9.
11. Xu C, Lv PH, Huang XE, Wang SX, Sun L, Wang FA. Efficacy of Transarterial Chemoembolization Combined with Radiofrequency Ablation in Treatment of Hepatocellular Carcinoma. Asian Pac J Cancer Prev 2015;16:6159-62.
12. Peng ZW, Zhang YJ, Chen MS et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 2013;31:426-32.
13. Rossi S, Ravetta V, Rosa L et al. Repeated radiofrequency ablation for management of patients with cirrhosis with small hepatocellular carcinomas: a long-term cohort study. Hepatology 2011;53:136-47.
14. Lee DH, Lee JM, Lee JY et al. Radiofrequency ablation of hepatocellular carcinoma as first-line treatment: long-term results and prognostic factors in 162 patients with cirrhosis. Radiology 2014;270:900-9.
15. Roayaie S, Jibara G, Tabrizian P et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015;62:440-51.
16. Shiina S, Tateishi R, Arano T et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol 2012;107:569-78.
17. Gines P, Quintero E, Arroyo V et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987;7:122-8.
18. Yamashita Y, Shirabe K, Tsuijita E et al. Third or more repeat hepatectomy for recurrent hepatocellular carcinoma. Surgery 2013;154:1038-45.