

# Radiofrequency ablation, TACE and combined treatment for multiple recurrent HCC patients within the Milan criteria

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## Research

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# Abstract

**Aim** The aim of this study was to compare radiofrequency ablation ,TACE and their combined treatment in terms of safety and efficacy.

**Methods** Retrospective analysis was carried out on the medical records of patients who had previously undergone curative hepatic resection and suffered multiple recurrent HCCs within the Milan criteria. The cohort of patients receiving RFA was compared to the cohort of patients receiving TACE and combined treatment. Disease outcome was investigated in terms of survival after recurrence.

**Results** From January 2006 to April 2014, 964 patients with recurrent HCC were enrolled in the database of West China Hospital. A total of 360 patients (37.3%) were enrolled in this retrospective study based on the inclusion criteria. In these patients, 177 (49.2%) received TACE, 121 (33.6%) received RFA, and 62 (17.2%) underwent combined treatment (CT). There was a statistically significant difference between the survival rates among the 3 groups: in the TACE group, the median survival time (MST) was 25 months, with 1-, 2-, and 3-year survival rates of 93.1%, 50.0% and 26.4%, respectively; in the RFA group, the MST was 33 months, with 1-, 2-, and 3-year survival rates of 96.7%, 65.7% and 40.1%, respectively; and in the CT group, the MST was 36 months, with 1-, 2-, and 3-year survival rates of 96.8%, 78.1% and 48.6%, respectively.

**Conclusion** Compared with TACE, RFA and combined treatment demonstrated a survival benefit for managing patients who had HCC recurrence with a total of 2–3 tumours.

## Introduction

The optimal treatment for hepatocellular carcinoma (HCC) is hepatic resection. In some selected patients, the 5-year survival rate after hepatic resection exceeds 50%[1–3]. Although notable advances have been made, the high rate of postoperative HCC recurrence is disappointing in terms of long-term results of HCC resection. The high recurrence rate, which has been reported to be as high as 70% within 5 years, is the major problem after resection[4, 5].

The majority of patients develop intrahepatic recurrence, and a smaller proportion of patients develop both intrahepatic and extrahepatic recurrence. Aggressive and appropriate treatment is important for prolonging survival after recurrence. Strict follow-up plans and the development of imaging tools have contributed to the early detection of recurrent HCC, especially of single or multiple small intrahepatic nodules. Developing treatment for recurrent HCC with these characteristics is vital for improving the overall outcome of HCC. Repeat hepatectomy is still the optimal treatment for resectable recurrent HCC, especially for single tumours[6–8]. For multiple tumours, unfortunately, there are no uniform criteria, and many methods are available, including radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and local percutaneous ethanol injection (PEI). The purpose of this study was to evaluate the different non-surgical treatments for multiple recurrent HCC in the early stage.

# Materials And Methods

## Patients

Retrospective analysis was carried out on the medical records of patients who had previously undergone curative hepatic resection for the treatment of HCC and suffered tumour recurrence between January 2006 and April 2014 from the database of West China Hospital. During this study period, 964 recurrent HCC patients were enrolled in the database. According to the research purpose, the following inclusion criteria were established: an initial pathological diagnosis of HCC; 2 to 3 lesions no more than 3 cm in diameter; no radiologic evidence of invasion into the major portal/hepatic vein or extrahepatic metastasis; Child A-B liver function; and patients who had undergone RFA and/or TACE (Fig. 1).

In this series, the diagnosis of tumour recurrence was made in the presence of diagnostic features on contrast-enhanced computed tomography or magnetic resonance imaging with an elevated level of  $\alpha$ -fetoprotein (AFP). Recurrence occurring within 1 year of surgery is typically defined as the local tumor progression, while recurrence occurring later than 1 year after resection is defined as newly developed lesion.

## Treatment and Follow-up

All enrolled patients did not undergo repeat hepatectomy for various factors, including multifocality, tumour location, the degree of cirrhosis and the subjective refusal of aggressive treatment. RFA or TACE was performed according to the tumour number, size and location; liver function; and patient request. A small group of patients who underwent RFA also received TACE for a combined treatment. Based on the status of the patient, RFA and TACE could be performed repeatedly.

All patients received follow-up at West China Hospital. Serum AFP assays, chest radiography and abdominal ultrasonography were performed every 3 months during the first year and every 6 months in subsequent years. Contrast-enhanced computed tomography or magnetic resonance imaging was performed every 6 months.

## Statistical Analysis

All clinicopathological and demographic data had been prospectively collected in a computer database before this retrospective analysis. Continuous variables were compared by unpaired t tests and were presented as the mean  $\pm$  standard deviation. Categorical variables were compared by the chi-square test. Survival curves were generated using the Kaplan-Meier method and were compared with the log-rank test. A Cox proportional hazard model was used for multivariate analysis. A statistical significance threshold was set at  $P = 0.05$ .

# Results

## Clinical characteristics

From January 2006 to April 2014, 964 patients with recurrent HCC were enrolled in the database of West China Hospital. The number of patients undergoing TACE, repeat hepatectomy and RFA was 452 (46.8%), 143 (14.8%) and 217 (22.5%), respectively. A total of 360 patients (37.3%) were enrolled in this retrospective study based on the inclusion criteria. Of these patients, 177 (49.2%) received TACE, 121 (33.6%) received RFA, and 62 (17.2%) underwent combined treatment (CT). The characteristics of the patients in this study are summarized in Table 1. There were more patients with 2 tumours than with 3 tumours. The mean total tumour size in the TACE group was 3.5 cm; in the RFA group was 3.7 cm; and in the CT group was 3.9 cm. The mean time from primary resection to the first HCC recurrence in the TACE group was 19.8 months; in the RFA group was 21.3 months; and in the CT group was 26.6 months. There were no significant differences in age, sex, serum AFP level, liver function, cause of liver disease, recurrence time or postoperative complications compared with each group.

**Table 1 Characteristics of patients with HCC recurrence treated with TACE, RFA and combined treatment.**

	TACE (n=177)	RFA (n=121)	CT (n=62)	P (TACE vs. RFA)	P (TACE vs. CT)	P (RFA vs. CT)
Age, yr	53.2±11.9	52.6±12.5	50.9±14.4	0.103	0.999	0.250
Sex, M/F	145/32	101/20	50/12	0.729	0.823	0.634
Total tumour size	3.5±1.2	3.7±1.5	3.9±1.6	0.306	0.065	0.571
Tumour number, 2/3	127/50	99/22	49/13	0.046	0.263	0.650
Serum AFP, n (%), ng/ml	56	27	19	0.186	0.988	0.463
≥400	121	94	43			
<400						
Prothrombin time, s	12.2±1.0	12.2±1.1	12.1±1.9	0.635	0.520	0.200
Serum albumin, g/l	41.6±5	40.6±6	42.5±5.8	0.335	0.353	0.109
Total bilirubin, µmol/l	16.3±5.9	17.7±7.2	16.0±6.6	0.236	0.455	0.329
AST, IU/l	50.7±28.2	55.4±48.5	44.7±24.6	0.088	0.748	0.111
ALT, IU/l	41.1±23.6	46.1±32.2	39.9±29.1	0.300	0.068	0.343
Child-Pugh Class A/B	163/14	113/8	58/4	0.674	0.708	0.967
Cause of liver disease	149/15/13	93/16/12	54/6/2	0.273	0.506	0.186
Hepatis B/Hepatis C/non B-C						
Recurrence time, mo	19.8±21.3	21.3±19.7	26.6±21.7	0.249	0.256	0.052
Tumour differentiation	72	43	22	0.060	0.471	0.483
well	105	98	40			
moderate+poor						
Complication grade						
I/II	10	8	4	0.732	0.817	0.967
III~V	2	3	1	0.373	0.769	0.704

CT: combined treatment; AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

## Overall survival

The overall survival curves for the three groups are depicted in Fig. 2. The median survival time (MST) and survival rates of each group are shown in Table 2: in the TACE group, the median survival time (MST) was 25 months, with 1-, 2-, and 3-year survival rates of 93.1%, 50.0% and 26.4%, respectively; in the RFA group, the MST was 33 months, with 1-, 2-, and 3-year survival rates of 96.7%, 65.7% and 40.1%, respectively; and in the CT group, the MST was 36 months, with 1-, 2-, and 3-year survival rates of 96.8%, 78.1% and 48.6%, respectively. There was a statistically significant difference between the survival rates

among the three groups ( $P < 0.001$ ). In this study, CT was the most effective treatment, followed by RFA and TACE.

Table 2  
The median survival time (MST) and survival rates

	No.	Median survival time (mo)	Survival time			P (TACE vs. RFA)	P (TACE vs. CT)	P (RFA vs. CT)
			1 year (%)	2 year (%)	3 year (%)			
TACE	177	25 ± 0.9	93.1	50.0	26.4	< 0.001	< 0.001	0.037
RFA	121	33 ± 1.9	96.7	65.7	40.1			
CT	62	36 ± 2.1	96.8	78.1	48.6			
CT: combined treatment								

As shown in Table 3 and Table 4, the multivariate Cox proportional hazards model identified the following prognostic factors that predicted an increased risk of mortality in the total population: an age of 60 years or older, a tumour size of 5 cm or larger, a tumour number of three, a serum AFP level of 400 ng/mL or more and a recurrence time less than 12 months.

Table 3  
Multivariate analysis of clinicopathological factors predictive of poor survival

	Hazard Ratio	95% Confidence Interval	p
Age ≥ 60 yr	1.012	0.799–1.280	0.922
Total tumour size ≥ 5 cm	1.055	0.800–1.394	0.720
Tumour number = 3	1.834	1.394–2.409	0.000
Serum AFP ≥ 400 ng/mL	1.326	1.055–1.667	0.016
Recurrence time < 12 mo	2.141	1.692–2.710	0.000

Table 4  
Univariate analysis of clinicopathological prognostic factors for overall survival

		No.	Median survival time (mo)	Survival time			P (TACE vs. RFA)	P (TACE vs. CT)	P (RFA vs. CT)
				1 year (%)	2 year (%)	3 year (%)			
Total population	TACE	177	25 ± 0.9	93.1	50.0	26.4	< 0.001	< 0.001	0.037
	RFA	121	33 ± 1.9	96.7	65.7	40.1			
	CT	62	36 ± 2.1	96.8	78.1	48.6			
Subgroup analysis									
Tumour number	TACE	127	29 ± 1.2	97.6	59.7	30.2	< 0.001	< 0.001	0.012
	RFA	99	33 ± 2.0	98.0	68.4	39.6			
	CT	49	38 ± 1.8	98.0	81.2	55.5			
	TACE	50	19 ± 0.8	82.0	26.0	17.3			
	RFA	22	30 ± 6.5	90.9	63.3	43.3			
	CT	13	26 ± 3.8	92.3	64.6	18.5			
Total tumour size	TACE	29	25 ± 2.2	96.6	51.7	10.3	< 0.001	0.007	< 0.001
	RFA	27	29 ± 3.6	100	59.3	40.7			
	CT	23	36 ± 5.9	91.3	72.1	48.1			
	TACE	148	24 ± 1.3	92.5	49.7	29.8			
	RFA	94	33 ± 1.8	95.7	67.6	39.9			
	CT	39	36 ± 2.4	100	81.7	49.0			
Recurrence time	TACE	99	30 ± 0.6	100	76.0	32.1	0.042	< 0.001	0.015
	RFA	80	34 ± 2.4	100	78.3	46.2			
	CT	53	38 ± 2.0	98.1	86.3	51.4			
	TACE	78	18 ± 0.8	84.6	28.2	17.6			
	RFA	41	23 ± 1.0	91.2	41.4	29.2			
	CT	9	24 ± 2.0	88.9	33.3	11.1			
CT: combined treatment									

Subgroup analysis of the entire study population

To more precisely compare the efficacy of each treatment, subgroup analyses were performed on the basis of tumour size and number, as well as recurrence time.

### **Subgroup Analysis by tumour size**

Patients in each group were divided into subgroups of patients with a total tumour size of 5 cm and above or those with a total tumour size smaller than 5 cm. Among patients with a total tumour size of 5 cm and above, CT provided the best long-term survival compared with TACE and RFA. The median survival time in the CT group was 36 months, and CT showed a survival benefit at 2 years (72.1%) and 3 years (48.1%). Similar results were obtained for patients with tumour sizes smaller than 5 cm. The prognosis of patients with large ( $\geq 5$  cm) recurrent HCC was poorer than that of patients with smaller ( $< 5$  cm) recurrent HCC.

### **Subgroup Analysis by tumour number**

Patients receiving each kind of treatment were divided into subgroups of patients with 2 or 3 tumours. Among patients with 2 tumours, the median survival time in the CT group was up to 38 months, and survival rates were the highest in the CT subgroup at 2 years (81.2%) and 3 years (55.5%). Among patients with 3 tumours, RFA provided the best median survival time (30 months) and showed a survival benefit at 3 years (43.4%).

### **Subgroup Analysis by recurrence time**

Patients were stratified according to a recurrence time of 12 months and older or a recurrence time of less than 12 months. Among patients with a recurrence time of 12 months or more, the median survival time in the CT group was up to 38 months, and survival rates were the highest in the CT subgroup at 2 years (86.3%) and 3 years (51.4%). Patients with early recurrence ( $< 12$  months) had a poorer prognosis than patients with late recurrence.

## **Discussion**

Long-term prognosis after curative resection is unsatisfactory because of the high incidence of recurrence. Due to strict follow-up plans and the development of imaging tools, an increasing number of patients with recurrent HCC are detected in the early stage. As previous studies have reported, the mean size of recurrent HCC is 2–4 cm in diameter, and 32–43% of recurrent HCC cases contain 2–3 nodules not larger than 3 cm[9–11]. In this study, the pattern of recurrence was in accordance with previous reports that 62.7% of patients were detected in the early stage (according to the Barcelona Clinical Liver Cancer Staging system), and multiple tumours were detected in 62.6%. Therefore, the appropriate management of recurrent HCC in the early stage is central to improving the overall long-term efficacy of HCC. For this research purpose, the inclusion criteria mentioned previously were established at the beginning state of this study. Salvage liver transplantation might be the ideal treatment, but it plays a limited role in areas where there is the shortage of organs. Repeat hepatectomy has been performed as the most effective therapy, with a 5-year survival rate ranging from 37–70%. Unfortunately, the repeat hepatectomy rate is unsatisfactory for various reasons. One of the reasons is that many patients prefer



treatments with minimal damage. In our population, the repeat hepatectomy rate was 14.8%, which is similar to the rates observed in other studies which have repeat hepatectomy rates of approximately 10–30%[12]. Therefore, non-surgical treatment is critical for prolonging survival time after recurrence.

Although various therapeutic modalities have been used to treat recurrent HCC, the effects of different treatment methods have not been sufficiently compared. There is no standard strategy used to select the modality for multiple recurrent tumours. Due to the fact that the patients enrolled in this retrospective study had the criteria of “2–3 tumours, each < 3 cm in size at recurrence”, TACE and RFA were the most frequent treatments performed. It is generally accepted that RFA is a reliable, effective and safe therapy for intra-hepatic recurrent HCC, especially for the small single tumour, but a substantial number of patients undergo TACE as the first-line treatment for several reasons, including objective medical parameters, subjective concerns, or insurance coverage[13–17]. The prognosis of TACE therapy after recurrence compared to that of repeat resection or RFA is very poor, with a reported 5-year survival rate of 0–27%. According to our results, TACE therapy demonstrated a significantly worse prognosis than RFA. TACE is still considered a useful modality based on the fact that the 3-year survival rate of patients with recurrence but without treatment is 8%[18]. Only in patients with unfavourable tumour conditions or poor liver function, TACE may be the first-line treatment of choice.

The use of RFA for multiple tumours is limited because of the presence of undiscovered minute lesions and the increased probability of insufficient ablation. Due to the development of contrast-enhanced intraoperative ultrasound, minute tumours that are undetected during preoperative examinations have been confirmed in 9–23% of patients with HCC[19, 20]. On the other hand, the rates of local recurrence attributed to insufficient ablation at an ablated site after RFA vary from 3–26%[20, 21]. In theory, RFA combined with TACE has advantages as a supplemental treatment for uncompleted necrotic areas; however, to date, there have been few reports on combined treatment. Although no evidence was reported in the published work, our study suggested that combined treatment is superior to TACE and RFA, and RFA was better than TACE. To minimize the possibility of selection bias, patients were divided into subgroups on the basis of tumour size, tumour number and recurrence time. Subgroup analyses showed a survival benefit of CT over TACE and RFA, except for patients with 3 tumours. Considering the small number of patients, the results of patients with 3 tumours do not provide strong evidence for the survival benefit of CT.

Independent prognostic factors for post-recurrence survival include tumour status, liver reserve, and recurrence status[22, 23]. Recurrence time was identified as a prognostic factor in the multivariate analysis with a high hazard ratio (HR = 2.85). Early recurrence was defined as intrahepatic, regional, or systemic recurrence within 1 year after curative resection. Previous studies have demonstrated that differences in pathogenesis lead to better outcome for late recurrence (> one year after resection) than for early recurrence[24–26]. The results suggest that aggressive treatment should be adopted as frequently as possible for patients with late recurrence.

There are some limitations in this study: (1) it is a single-institutional and non-randomized study; (2) treatments for recurrence were more likely to be self-selected by patients; and (3) some bias could have been present due to the preferences of doctors. Nevertheless, a prospective, randomized trial will be needed to confirm these results.

In summary, although there was inevitable selection bias in terms of the patients and treatments, our study suggested several important points for multiple recurrent HCCs in the early stage: first, long-term survival was achievable when an aggressive regimen was used to improve survival in patients with HCC recurrence, especially in patients with late recurrence; second, RFA combined with TACE offered the best chance of survival for patients who did not undergo repeat hepatectomy; and finally, compared with TACE, RFA still demonstrated a survival benefit for managing patients who had HCC recurrence with a total of 2–3 tumours.

## Abbreviations

HCC = hepatocellular carcinoma, RFA = radiofrequency ablation, TACE = transarterial chemoembolization, PEI = percutaneous ethanol injection, AFP= a-fetoprotein, CT = combined treatment, MST = median survival time.

## Declarations

**Ethics approval and consent to participate:** The Ethics Committee of West China Hospital, Sichuan University approved this study.

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets generated and/or analysed during the current study are not publicly available due to internal data of West China Hospital but are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests

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**Authors' contributions:** Bo Zhang analyzed and interpreted the patient data regarding the multiple recurrent HCC patients within the Milan criteria, and was a major contributor in writing the manuscript. Bo Zhang was the first author for this paper. Juan Wan collected, analyzed and interpreted the patient data, and revised the manuscript. Juan Wan was a joint first author. Bo Zhang and Juan Wan contribute equally. Xi Xu, YongKun Li collected the patient data, too. Tao Lv gave guidance on data analysis. Jiayin Yang provided guidance on research ideas and funding for the research, and was a corresponding author. All authors read and approved the final manuscript.

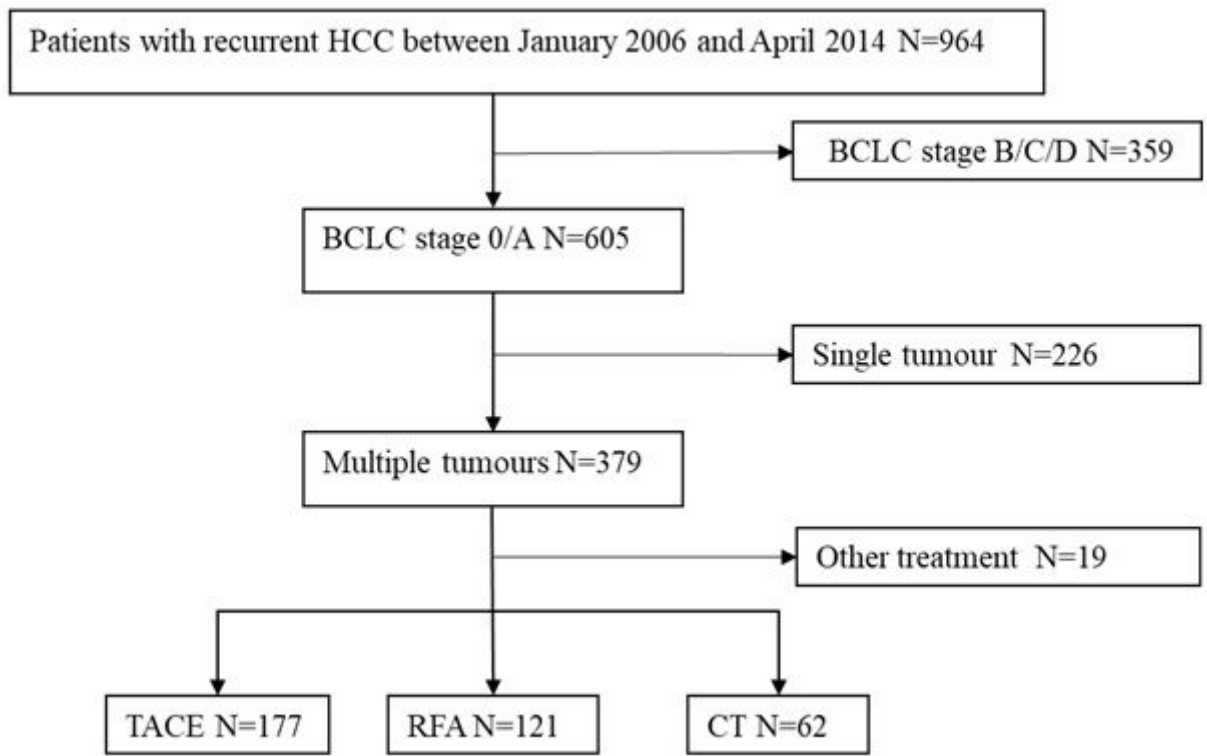
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## Figures



**Figure 1**

Study profile. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization CT, Combine treatment

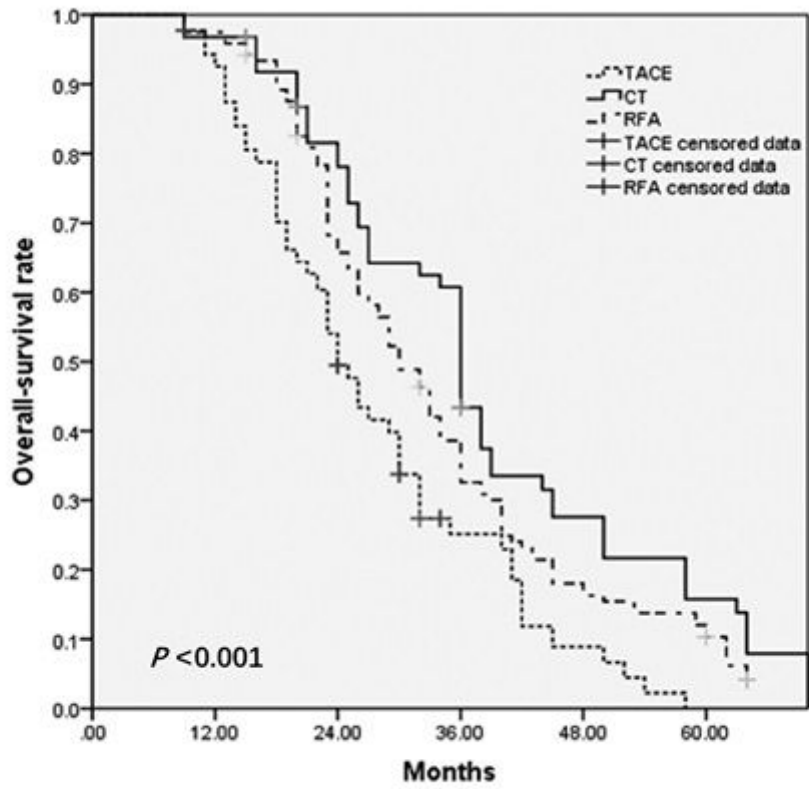


Figure 2

Overall survival of patients who were treated with RFA, TACE or combined treatment.