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Running Title: RFA+TACE vs RFA

Title: Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: a meta-analysis

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Abstract

Background To determine whether the use of radiofrequency ablation (RFA) plus transcatheter arterial chemoembolization (TACE) is more effective than the use of RFA alone for patients with hepatocellular carcinoma (HCC).

Methods A computer-based search was performed. Randomised trials comparing RFA plus TACE and RFA alone for treatment of HCC were included in this meta-analysis. The outcome of interest for our analysis was survival (recurrence-free survival and overall survival).

Results Eight trials with 648 patients were eligible for this meta-analysis. Our pooled results suggest that RFA plus TACE is associated with a significant advantage in recurrence-free survival (RFS) (HR = 0.58; 95% CI = 0.42–0.80, $p=0.001$), and overall survival (OS) (HR=0.60; 95% CI=0.47-0.76, $p<0.001$).

Conclusion TACE combined with RFA was more effective than RFA alone, especially for treatment for intermediate and large-size hepatic tumors or younger patients with HCC.

Key words: Chemoembolization; Hepatocellular carcinoma; Meta-analysis; Radiofrequency Catheter Ablation; Survival

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world. HCC is a serious fatal disease worldwide and causes serious damage to human health[1]. The therapeutic options are mainly surgical for HCC. Surgery offers the chance of potential cure, either by curative hepatic resection or transplantation. It is known that only a proportion of patients may benefit from these therapeutic options. Radiofrequency ablation(RFA) has been shown to be successful for local tumor control in patients with HCC[2,3]. Single therapeutic regimen has its merits and shortcomings. The combination of transcatheter arterial chemoembolization (TACE) and RFA may have advantages over RFA alone. Many randomised trials[4-7], performed at several institutions, have examined whether TACE plus RFA is more effective than RFA alone in the treatment of patients with HCC over the past decade, but whether the real influence of combination of TACE and RFA on outcome of HCC patients is still controversial and not fully established.

Which is the optimal treatment to use in HCC, RFA plus TACE or RFA alone? There have been many studies aimed at establishing an ideal therapy for HCC, but some of them have failed to demonstrate the true superiority. When used to compare results from different studies, a meta-analysis can test hypotheses about sources of differences and can assess the magnitudes of biases [8]. To obtain comprehensive estimates of the clinical benefit from all of the available data, we performed a meta-analysis of all of the relevant randomised trials. This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

Methods

Search strategy

A computer-based search was performed of MEDLINE, EMBASE, the Cochrane-controlled trials registry, the Cochrane Library, the Science Citation Index, and Chinese databases (CBMdisc and Wanfang data) through March 2014. The search strategy included the medical subject headings of “hepatocellular carcinoma”, “radiofrequency ablation” and “transcatheter arterial chemoembolization”. The reference lists were screened of all of the identified trials and of the comprehensive reviews in the field.

Inclusion and exclusion criteria

For inclusion, the trials had to be prospective and randomised, with RFA plus TACE in one arm compared with RFA alone in the other arm as the therapy for patients with HCC. If the same author reported results that were obtained from the same patient population in more than one publication, then only the most recent or most complete report was included in our analysis. Only studies published as a journal article were eligible for this analysis. Studies without comparable data between the two comparative groups were excluded.

Statistical analysis

To estimate the treatment effects, the outcomes were calculated as hazard ratios (HRs), with their respective 95% confidence intervals (CIs). The survival outcome data were synthesised using the time-to-event HR as the effect measurement. When HRs were not given in a paper, the data were extracted from the appropriate Kaplan-Meier curves, or the survival rates of each group were used to calculate the HRs [10,11]. Heterogeneity assumptions were checked using the chi-square-based Q-test [12]. Heterogeneity was considered statistically significant if $P < 0.10$, and it was quantified using the I^2 metric, which is independent of the number of studies in the meta-analysis ($I^2 < 25\%$, no heterogeneity; $I^2 = 25-50\%$, moderate heterogeneity;

and $I^2 > 50\%$, large or extreme heterogeneity). Taking into account the inherited heterogeneity between these studies, we assumed the presence of statistical heterogeneity and decided to use a random effects model before pooling the data. In meta-analyses with at least four trials, Begg's test [13] and Egger's test [14] were performed to determine whether there was a publication bias ($P < 0.05$ indicated a statistically significant publication bias). Moreover, contour-enhanced funnel plotting was performed to aid in interpreting the funnel plot [15]. STATA, version 10.0, was used for the statistical analysis. The statistical tests for heterogeneity were one-sided, and the statistical tests for effect estimates and for publication bias were two-sided.

Results

Description of trials

The process for the identification and selection of the relevant randomised, controlled trials (RCT), according to the PRISMA statement, is depicted in [Figure 1](#). Since the 2000s, a total of 11 randomised trials have been described comparing RFA plus TACE and RFA alone in HCC patients[4-7,16-22]. Two trials were excluded because HRs were not given and the data could not be used to calculate the HRs[4,17]. One Chinese study was retracted by the journal due to the integrity of the data and the veracity of the report [16]. The eight trials [5-7,18-22] that fulfilled the inclusion criteria were published between 2002 and 2013, and included 648 patients (324 patients randomised to treat with combination of TACE and RFA and 324 control patients). All of the included trials were available as fully published papers. The characteristics of the trials included are shown in Table 1. Survival data could be extracted from all of studies for OS, and from seven studies for RFS[5-7,18-21].

Meta-analysis

Table 2 and [Figure 2](#) showed the results of our analysis. The recurrence-free

survival (RFS) was significantly improved with RFA plus TACE compared to RFA alone (HR = 0.58; 95% CI = 0.42–0.80, $p=0.001$; $p=0.094$ for heterogeneity). The difference in the overall survival (OS) was statistically significant (HR=0.60; 95% CI=0.47-0.76, $p<0.001$; $p=0.414$ for heterogeneity), indicating a 40.0% decrease in hazard events in RFA plus TACE arms compared with RFA arms. There was moderate heterogeneity ($I^2 = 44.6\%$, $p = 0.094$) for RFS. To eliminate heterogeneity, we divided the studies into different subgroups according to patients' characteristics. The difference in the RFS and OS were still statistically significant among younger or intermediate and large- tumor size tumors subjects. Subsequently, heterogeneity disappeared ($I^2 = 0\%$), which revealed that most of the studies could not be grouped based on different patients' characteristics.

Publication bias

Potential publication bias was estimated with the Begg-Mazumdar test and the Egger test. All of the studies investigating RFS yielded a Begg's test score of $p = 0.453$ and an Egger's test score of $p = 0.305$. Similar results were found for OS ($p = 0.216$ and 0.702 , respectively). Contour-enhanced funnel plots (Figure 3, A and B) indicated that all studies were within the nonsignificant area, and no studies were in significant areas (i.e., from $P < 0.01$ to $P < 0.05$) for both HRs. It suggested that there was no publication bias for RFS and OS.

Discussion

A prospective, randomised clinical trial is the accepted standard to compare different treatments for patients with HCC. The reported results of prospective, randomised, clinical trials were conflicting over the past decade. According to our data analysis, we found that RFA plus TACE is associated with a significant advantage in RFS (HR = 0.58; 95% CI = 0.42–0.80), and OS (HR =0.60; 95%

CI=0.47-0.76) compared with RFA alone. Additionally, the subgroups analysis indicated that there were no significant differences between TACE plus RFA and RFA alone in the treatment of small-size hepatic tumors or elder patients with HCC. Thus, our analysis suggested that TACE combined with RFA was more effective than RFA monotherapy, especially for treatment for intermediate and large-size hepatic tumors or younger patients with HCC. Both liver functional reserve and tumor factors (tumor size, and number) were crucial in determining post-RFA prognosis in HCC patients[23]. The limited volume of coagulative necrosis obtained with the RFA prevented the widespread use of RFA for the treatment of intermediate-size to large-size hepatic tumors [24]. The necrotic area induced by RFA may be increased by a combination of TACE, which might improve the chance of clearance of micrometastasis, reduce the chance of recurrence, and improve the survival rates for patients with intermediate-size to large-size hepatic tumors. Moreover, younger HCC patients have better overall survival and lower recurrence rate compared with elder patients[23].

Several meta-analyses have reported that RFA combined with TACE is more effective than RFA monotherapy for treatment of HCC[25-30]. However, the previous meta-analyses had several methodological mistakes. First, the combined HRs, which are the preferred summary statistics for reporting time-to-event data [11], were not used in the previously published meta-analyses. The most widely recommended approach for summarizing the effect of treatment from time-to-event data in clinical trials is to use a HR. The best statistic to use is the HR in Meta-analyses of published time-to-event outcomes. HRs given in trial reports can be used directly, or if sufficient summary statistical information or Kaplan-Meier curves are presented, then HRs can be estimated indirectly [11]. Second, Cheng *et al* study[16] which was retracted by

JAMA due to the integrity of the data and the veracity of the report, should not be included in the finally analysis. Third, some published studies were not included in their analyses. The major difference between this report and other meta-analyses is that time-to-event HR was pooled, instead of 1-, 2-, 3- year ORs being reported.

Several limitations should be considered when interpreting the results of our analysis. First, a more precise analysis could have been conducted if the individual data were available, which would have allowed for adjustment according to other co-variables. Second, although we divided the studies into different subgroups according to patients' characteristics to eliminate heterogeneity, the heterogeneity among the trials might be a limitation of this analysis. Third, we concluded that the concomitant therapy is more effective in “intermediate and large-size tumors or younger patients”, which was merely based on the subgroup analyses that the HR was significant in the subgroup of studies with median age > 60 years, and in the subgroup of studies with median size > 3cm. It is known that if the subgroup analyses were based on the study level, the results do not necessarily apply to the patient level (ie, studies with median age >60 do not equal to patients with age > 60). For patient and intervention characteristics, differences in subgroups that are observed within studies are more reliable than analyses of subsets of studies (Cochrane handbook Chapter 9.6.). **The results presented in our analysis should be taken with caution.** Finally, almost trials are made in China, whether TACE combined with RFA was more effective than RFA alone in Caucasian group is still unknown.

In conclusion, our analysis indicates that the combination of RFA with TACE provides better prognosis for patients with HCC. Further study is needed to determine whether specific subgroups of young HCC patients will benefit from RFA with TACE.

Conflict of Interest

None.

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Table 1 Study characteristics

Study	Country	Recurrent	Study Arm	Number of Patients	Age	Tumor size	Child-Pugh class A/B/C
Lin et al, 2013	China	No	TACE + RFA	32	64.9±8.8	4.09±0.55	NA
			RFA	30	60.1±10.2	3.94±0.54	NA
Morimoto et al,2010	Japan	No	TACE + RFA	19	70(57-78)	3.7±0.6	18/1/0
			RFA	18	73(48-84)	3.6±0.7	16/2/0
Peng et al, 2012	China	Yes	TACE + RFA	69	57.5±10	≤5.0	60/9/0
			RFA	70	55.1±9.5	≤5.0	59/11/0
Peng et al, 2013	China	No	TACE + RFA	94	53.3±11.0	3.47±1.44	90/4/0
			RFA	95	55.3±13.3	3.39±1.35	90/5/0
Shen et al, 2005	China	No	TACE + RFA	18	52.7(20-72)	5.6(2.2-15.8)	4/14/0
			RFA	16	56.1(36-75)	5.0(2.3-12.3)	6/10/0
Shibata et al, 2009	Japan	No	TACE + RFA	46	67.2±8.9	1.7±0.6	32/14/0
			RFA	43	69.8±8.0	1.6±0.5	33/10/0
Yang et al, 2009	China	Yes	TACE + RFA	31	57.8(43-78)	3.5(1.7-7.3)	20/10/1
			RFA	37	58.3(38-80)	3.8(2-6.4)	23/13/1
Zhang et al, 2002	China	No	TACE + RFA	15	57.8(39-72)	4.6(2.3-7.1)	NA
			RFA	15	61.8(38-78)	4.1(2.4-6.0)	NA

NA: not applicable

Table 2. Subgroup analysis according to the characteristics

Criteria		NO. of Studies	NO. of Patients	RFS			OS		
				HR (95% CI)	I ² (%)	P value Q test	HR (95% CI)	I ² (%)	P value Q test
All		8	648	0.58(0.42-0.80)	44.6	0.094	0.60(0.47-0.76)	2.1	0.414
Recurrent	+	2	207	0.48(0.31-0.73)	0	0.528	0.57(0.37-0.89)	0	0.943
	-	6	441	0.62(0.41-0.96)	53.8	0.071	0.61(0.43-0.87)	29.6	0.213
Median age >60 years old	+	4	218	0.56(0.25-1.24)	74.5	0.020	0.82(0.53-1.27)	11.7	0.322
	-	4	430	0.55(0.41-0.73)	0	0.625	0.51(0.38-0.68)	0	0.821
Tumor median size>3.0	+	6	420	0.53(0.40-0.71)	0	0.607	0.54(0.40-0.71)	0	0.804
	-	1	89	1.06(0.67-1.67)	NA	NA	1.27(0.62-2.60)	NA	NA

NA: not applicable

Figure Legend

Fig. 1. Process of identifying and selecting the relevant randomised controlled trials according to the PRISMA statement.

Fig. 2. Forest plot of the HR. The size of the squares reflects each study's relative weight, and the diamond ($\diamond$) represents the aggregate HR and 95% CI. (A)

Recurrence-free survival; (B) Overall survival.

Fig. 3. Contour-enhanced funnel plot for publication bias test. (A) Recurrence-free survival; (B) Overall survival.