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ORIGINAL ARTICLE

Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: A systematic review and meta-analysis

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Summary
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 tumours or younger patients with HCC.

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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 tumour 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 on 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 Fig. 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 Fig. 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.