Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis

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CRD summary
This generally well-conducted review concluded that transcatheter arterial chemoembolization combined with percutaneous ablation therapy (especially percutaneous ethanol injection) improved the overall survival status of patients with unresectable hepatocellular carcinoma. Given a number of issues concerning the limited quality and clinical variation of the evidence, the authors' conclusion should be interpreted with caution.

Authors' objectives
To identify the survival benefits of transcatheter arterial chemoembolization combined with percutaneous ablation therapy (radio-frequency ablation or percutaneous ethanol injection) for patients with unresectable hepatocellular carcinoma.

Searching
PubMed, EMBASE and Web of Science were searched for relevant articles published between 1990 and July 2009. The Cochrane library was also searched. Search terms were reported. Reference lists from reviews and published clinical trials were handsearched for relevant studies.

Study selection
Eligible studies used a prospective randomised controlled design, and were of patients with unresectable hepatocellular carcinoma (aged over 18 years), who were scheduled to undergo transcatheter arterial chemoembolization and/or radio-frequency ablation or percutaneous ethanol injection. Trials that used a non-randomised design or where patients had liver metastases or recurrence of hepatocellular carcinoma after hepatectomy were excluded.

Eligible outcomes included overall survival rate (primary outcome), complete treatment response rate and tumour recurrence rate.

There were more male than female participants in included trials; the mean tumour size ranged from less than 30mm to over 60mm and many patients had multiple tumours (where reported). Included trials were conducted in Europe or Asia. Over half of the included trials compared transcatheter arterial chemoembolization plus percutaneous ethanol injection versus transcatheter arterial chemoembolization; some trials compared transcatheter arterial chemoembolization plus radio-frequency ablation versus transcatheter arterial chemoembolization alone; some studies compared combination therapy with percutaneous ethanol injection alone or radio-frequency ablation alone.

Two reviewers independently selected the included studies. The authors did not report how disagreements between reviewers were resolved.

Assessment of study quality
Two reviewers independently assessed review quality using the Jadad scale. Trials were assigned a quality score up to a maximum of 5 points according to adequacy and description of randomisation, blinding, and drop-outs and withdrawals. Scores of 3 points or more were considered high quality. Disagreements were resolved by consensus.

Data extraction
Data were extracted to calculate of survival rates, initial complete response rates and tumour recurrence rates.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Odds ratios (ORs), with 95% confidence intervals (CIs), were pooled using a random-effects model. The $Q$, $X^2$, $I^2$ and $\tau^2$ estimates were calculated to assess statistical heterogeneity. Subgroup analyses were undertaken by type of combination versus monotherapy comparison. Publication bias was assessed through visual inspection of funnel plots.

**Results of the review**

Overall, ten randomised controlled trials (RCTs) were included in the review (n=627 patients, range 44 to 102). Two RCTs received a Jadad score of 3 out of 5 points, one RCT scored 1 point, and the remaining seven RCTs scored 2 points.

Nine RCTs (n= 512 patients) reported one-year survival rates, producing a statistically significant pooled effect favouring combination therapy over monotherapy (OR 3.18, 95% CI 1.09 to 9.26; $I^2$=56%; different results were reported in the text).

Seven RCTs (n=437 patients) reported two-year survival rates, producing a statistically significant pooled effect favouring combination therapy over monotherapy (OR 4.53, 95% CI 2.62 to 7.82; $I^2$=0%).

Seven RCTs (n=425 patients) reported three-year survival rates, producing a statistically significant pooled effect favouring combination therapy over monotherapy (OR 3.50, 95% CI 1.75 to 7.02; $I^2$=43%).

A range of subgroup analyses were also conducted. Survival rates were not significant at one year for transcatheter arterial chemoembolization plus percutaneous ethanol injection versus transcatheter arterial chemoembolization. Transcatheter arterial chemoembolization plus radio-frequency ablation versus radio-frequency ablation alone was significant for survival at two years, but not for survival one or three years. Results for tumour response, recurrent and side effects were also reported.

**Authors’ conclusions**

Transcatheter arterial chemoembolization combined with percutaneous ablation therapy (in particular with percutaneous ethanol injection) improved the overall survival status for patients with large hepatocellular carcinoma.

**CRD commentary**

The study selection criteria were clearly described. Multiple databases were searched, although efforts were not reported to identify unpublished studies, which increased the risk of publication bias. The number of reviewers performing study selection and validity assessment was clearly reported, but the number of reviewers who performed data extraction was not.

A standard instrument was used to assess trial quality; most were of poor quality, which raised the risk of bias. Sufficient primary trial details were reported; these indicated that there was significant clinical heterogeneity between trials. A standard method of synthesis was reported. Sensitivity analyses were performed. Funnel plots were not reported, so it was unclear if there was any publication bias. There was some evidence of statistical heterogeneity and sample sizes were small.

Overall, the review was generally well conducted. However, due to the above issues, the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Research:** The authors stated that well-designed and powered double-blind randomised controlled trials comparing transcatheter arterial chemoembolization plus radio-frequency ablation with transcatheter arterial chemoembolization alone are required to provide solid clinical evidence about the effectiveness and side effects of combination therapy over monotherapy.

**Practice:** The authors did not state any implications for practice.

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