Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis
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CRD summary
The authors concluded that transcatheter arterial chemoembolisation (TACE) in combination with radiotherapy was more therapeutically beneficial than TACE alone in patients with unresectable hepatocellular carcinoma, although further trials were needed before this treatment could be recommended routinely. There were some review limitations to the review, but data from the pooled randomised controlled trials supported the authors' cautious conclusions.

Authors' objectives
To evaluate the efficacy and safety of transcatheter arterial chemoembolisation in combination with radiotherapy in participants with unresectable hepatocellular carcinoma.

Searching
PubMed, EMBASE, CBM, CNKI and The Cochrane Library were searched from inception to May 2008; search terms were reported. References from reviews and relevant trials were searched. The authors excluded trials published in Japanese.

Study selection
Randomised controlled trials (RCTs) or non-randomised controlled trials that evaluated transcatheter arterial chemoembolisation (TACE) in combination with radiotherapy compared to TACE alone in participants with unresectable hepatocellular carcinoma were eligible for inclusion. Diagnosis had to be confirmed cytologically, pathologically or using computed tomography. Included studies had to report both survival and tumour response. Adverse events were evaluated. The authors excluded trials with small sample sizes (no details provided).

Participants in the included studies had tumours that ranged from stage I to IV. All included trials evaluated various anticancer drugs; these commonly included cisplatin, 5-fluorouracil, mitomycin-C and Adriamycin. The number of transcatheter arterial chemoembolisations ranged from one to six. Intervals between sessions ranged from four to eight weeks. Radiotherapy techniques included whole-liver irradiation and three-dimensional conformal radiotherapy. The interval between transcatheter arterial chemoembolisation and radiotherapy ranged from two to eight weeks.

Two reviewers independently selected the trials for inclusion. Any discrepancies were resolved by discussion.

Assessment of study quality
The authors used a format based on the Cochrane Handbook to assess the quality of studies in terms of randomisation, allocation concealment, blinding, withdrawal (and reasons for withdrawal), protection against contamination, sample size calculation and intention-to-treat analysis. The first four of these criteria were used in each study to determine whether a study had low, moderate, or high risk of bias.

Two reviewers independently assessed trial quality. Any discrepancies were resolved by discussion.

Data extraction
Survival data were extracted from the text or derived from survival curves. Missing data were sought through contact with the study authors. Survival was assessed at one, two, three and five years.

Two reviewers independently extracted data from the studies. Any discrepancies were resolved by discussion.

Methods of synthesis
Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were conducted using DerSimonian and Laird random-effects models. Subgroup analysis was conducted by study type. Heterogeneity was assessed with the Q statistic and by visual examination of L’Abbe plots. Publication bias was assessed with funnel plots, Begg and Mazumdar correlation test and Egger's regression method.

Results of the review
Seventeen trials (n=1,476) were included in the review: five RCTs and 12 non-randomised controlled trials. All five RCTs were all considered to have a moderate risk of bias. All non-randomised controlled trials were considered to have a high risk of bias.

Survival (at one, two, three and five years) and response (complete response and complete plus partial response) were significantly improved in the combination therapy group compared to the transcatheter arterial chemoembolisation treatment group. Serious adverse events (nausea/vomiting, leucocyte count and alanine transferase) were similar between treatment groups except that total bilirubin was significantly increased in the combined treatment group (OR 2.76, 95% CI 1.58 to 4.84; four studies). These findings were consistently observed when all studies were pooled and when RCTs and non-randomised controlled trials were analysed separately. There was no evidence of heterogeneity between studies except for one-year survival.

Compared to the transcatheter arterial chemoembolisation alone, combined therapy improved survival at one year (OR 2.23, 95% CI 1.76 to 2.83; 15 studies), two years (OR 2.39, 95% CI 1.85 to 3.09; 13 studies), three years (OR 2.75, 95% CI 2.08 to 3.64; 13 studies) and five years (OR 4.47, 95% CI 2.08 to 9.61; three studies).

Combined therapy improved complete response (OR 2.58, 95% CI 1.64 to 4.06; 11 studies), and complete plus partial response (OR 3.14, 95% CI 2.42 to 4.07; 12 studies).

Funnel plots revealed some potential for publication bias; other statistical techniques demonstrated no evidence of publication bias.

Authors’ conclusions
TACE in combination with radiotherapy was more therapeutically beneficial then TACE alone, although further trials were needed before this treatment could be recommended routinely.

CRD commentary
The review addressed a clear question in terms of participants, intervention, outcomes and study design. The authors attempted to obtain all relevant studies by searching a number of databases and appropriately assessed publication bias using different techniques. It was unclear whether the authors searched for unpublished studies, so it was possible that some relevant studies were missed. The authors took a number of steps to reduce potential for reviewer bias. Study quality was assessed using a published checklist; additional criteria used for controlled clinical trials were not reported. The authors expressed reservations about the quality of the studies. The results presented by study type were the most appropriate, rather than those from pooling of different study types.

The review had some review limitations, but data from the pooled RCTs supported the authors' cautious conclusions.

Implications of the review for practice and research
Practice: The authors stated that transcatheter arterial chemoembolisation in combination with radiotherapy was a promising treatment in patients with unresectable hepatocellular carcinoma.

Research: The authors stated more high-quality multicentre RCTs were needed to evaluate additional outcomes such as disease-free survival and symptoms improved. Future studies should continue to include data on adverse events. Studies were also needed to clarify the optimal radiation dose and optimal interval between transcatheter arterial chemoembolisation and radiotherapy.

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