Meta-analysis: evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma

CRD summary
This review assessed adjuvant chemotherapy following curative liver resection for hepatocellular carcinoma. The authors concluded that although post-operative transarterial chemotherapy may improve survival, the limitations of the included studies prevented a firm conclusion. The tentative conclusions are appropriate.

Authors’ objectives
To evaluate adjuvant modalities after curative liver resection for hepatocellular carcinoma (HCC).

Searching
MEDLINE, EMBASE and Cancerlit were searched (the dates and search terms were not specified). The authors also stated that manual searches were carried out, although further details were not provided. General reviews and references from published RCTs and non-RCTs were used. Only full papers were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and non-randomised controlled trials (non-RCTs) were eligible.

Specific interventions included in the review
Studies that compared adjuvant therapy with the absence of treatment, or with another therapeutic modality, were eligible. The included studies were of pre- and post-operative transarterial chemotherapy, systemic chemotherapy, and systemic chemotherapy combined with transarterial chemotherapy. In the majority of studies the control group received curative liver resection alone.

Participants included in the review
Patients who had undergone curative liver resection for HCC were eligible. The following patients were excluded: those with unresectable HCC; those who had undergone non-curative resection; and those who had cholangiocellular carcinomas or liver metastases.

Outcomes assessed in the review
Studies assessing overall survival or cumulative probability of no recurrence at a minimum of 1 and 2 years were eligible.

How were decisions on the relevance of primary studies made?
Three reviewers independently assessed studies for inclusion.

Assessment of study quality
The authors stated that a validated questionnaire was used to assess quality. Two reviewers independently assessed each study.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The extracted data included the treatment regimen used, multiple tumours (%), mean tumour size, cirrhosis, and overall survival (%) and cumulative probability of no recurrence (%) at 1, 2 and 3 years. Data were extracted
according to intention-to-treat. When necessary, actuarial survival curves were used to estimate the number of deaths or recurrences. Mean differences (MDs) between the treatment and control groups were estimated, along with 95% confidence intervals (CIs).

**Methods of synthesis**

How were the studies combined?

The studies were combined where two or more studies of a therapeutic modality were available (7 studies were excluded because only one study evaluated a particular treatment modality). The methods of Peto, and DerSimonian and Laird were used; only the results for the latter were reported. The studies were weighted, based on the inverse of the variance.

How were differences between studies investigated?

The chi-squared test was used to investigate statistical heterogeneity. RCTs where the comparison was with no adjuvant treatment were analysed separately (core analyses). A pre-specified sensitivity analysis was conducted on the basis of study design and control group treatment.

**Results of the review**

Twenty-one studies were included: 10 RCTs (n=634) and 11 non-RCTs (n=944).

Pre-operative transarterial chemotherapy (2 RCTs; 7 non-RCTs).

Core analysis (2 RCTs): there was no significant difference in survival between pre-operative transarterial chemotherapy and no adjuvant treatment at 1 year (MD 0.5%, 95% CI: -11, 11.8), 2 years (MD -6%, 95% CI: -32.4, 20.1) or 3 years (MD -0.2%, 95% CI: -14.1, 13.7). There was also no significant difference in the cumulative probability of no recurrence at 1, 2 or 3 years (data reported in the paper). There was statistically significant heterogeneity between the control groups for survival at 3 years only (P=0.003). When non-RCTs comparing treatment with no adjuvant treatment were added to the analysis the effect of pre-operative transarterial chemotherapy on survival remained non significant at each follow-up period, although there was a statistically significant beneficial effect on the cumulative probability of no recurrence at 2 years, but not 1 or 3 years. This remained significant when studies in which the control group received treatment in some cases were included. There was statistically significant heterogeneity for some of these analyses.

Post-operative transarterial chemotherapy (4 RCTs; 3 non-RCTs).

Core analysis (4 RCTs): there was a statistically significant benefit in survival for post-operative transarterial chemotherapy compared with no adjuvant treatment at 2 years (MD 22.8%, 95% CI: 8.6, 36.9, P=0.002) and 3 years (MD 27.6%, 95% CI: 8.2, 47.1, P=0.005), but not 1 year (MD 13.2%, 95% CI: -1.8, 28.2, P=0.08). There was a significant improvement in the cumulative probability of no recurrence at 1 year (MD 28.8%, 95% CI: 16.7, 40.8, P<0.001), 2 years (MD 27.6%, 95% CI: 8.2, 47.1, P=0.005) and 3 years (MD 28%, 95% CI: 8.2, 47.9, P=0.006). There was significant heterogeneity for cumulative probability of no recurrence at 3 years only (P=0.03). When non-RCTs were added to the analysis there was also a beneficial effect of treatment compared with no treatment for survival at 1 year. The inclusion of non-RCTs increased heterogeneity.

Systemic chemotherapy (1 RCT; 1 non-RCT).

There was no significant difference in survival between systemic chemotherapy (5-fluorouracil) and no adjuvant treatment at 1 year (MD 3%, 95% CI: -7.2, 13), 2 years (MD 1.2%, 95% CI: -9.6, 12) or 3 years (MD 2.5%, 95% CI: -8.6, 13.6). There was also no significant difference in the cumulative probability of no recurrence at 1 or 3 years (data reported in the paper). There was statistically significant heterogeneity for survival at 1, 2 and 3 years and in the probability of no recurrence at 1 year.

Post-operative systemic chemotherapy combined with transarterial chemotherapy (3 RCTs).

Core analysis (2 RCTs): there was no significant difference in survival between the combination treatment and no
adjuvant treatment at 1 year (MD -9.2%, 95% CI: -23.2, 5) or 3 years (MD -3.4%, 95% CI: -19.3, 12.4). Treatment had a detrimental effect on the cumulative probability of no recurrence at 1 year (MD -19.7%, 95% CI: -35.2, -4.3, P=0.01) and 3 years (MD -21.3%, 95% CI: -41.6, -1, P=0.04). There was no statistically significant heterogeneity. When a study with an active control group was added to the analysis there was still no beneficial effect of treatment on either outcome.

Authors’ conclusions
After curative resection, post-operative transarterial chemotherapy may improve survival and the cumulative probability of no recurrence. However, a firm conclusion regarding this therapy was hampered by the limitations of the included studies. Although data were not provided, the authors stated that most of the studies were performed in Asian patients and the data could not be extrapolated to non-Asian populations.

CRD commentary
The review question was clear in terms of the intervention, outcome, participants and study design. Some relevant electronic databases were searched, although details of the search strategy were not provided. No attempt to identify unpublished data appears to have been made and only full reports were eligible for inclusion; studies may therefore have been missed. The study selection and quality assessment were carried out in duplicate, but since there was no information on the data extraction process used there is a possibility of some error or bias. Although some appropriate details on the individual studies were provided, it would have been helpful to have had more information on the study participants.

It was appropriate to group the RCTs separately and on the basis of whether or not the control group received no adjuvant treatment. There was evidence of statistical heterogeneity in some of the analyses, therefore some of the pooling may have been inappropriate. The authors reported that they carried out a quality assessment, but did not report the findings. They did, however, discuss some general limitations of the included studies. On the basis of such limitations, it was appropriate that they made tentative conclusions and drew attention to the issue of generalisability to other racial groups.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice

Research: The authors recommended that studies evaluating post-operative transarterial chemotherapy be conducted.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.