Systematic review of randomized trials for unresectable hepatocellular carcinoma:

chemoembolization improves survival

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CRD summary
This meta-analysis of 14 studies concluded that, compared with conservative management, chemoembolisation improves survival in people with unresectable hepatocellular carcinoma but tamoxifen has no survival benefits. There is insufficient evidence available about the other treatments. Though the search strategy was narrow, the evidence upon which the conclusions are based appears sound.

Authors' objectives
To assess the impact on survival of primary medical treatments for people with unresectable hepatocellular cancer.

Searching
MEDLINE, the Cochrane Library and Cancerlit were searched for studies published in peer-reviewed journals from 1978 to May 2002; the search terms were reported. Full papers published in the English language were eligible for inclusion. The authors handsearched journals and reference lists for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of any primary medical treatment for hepatocellular carcinoma (HCC) were eligible for inclusion. The two interventions included in the review were chemoembolisation/embolisation and tamoxifen. Only studies comparing treatment versus conservative management were included, or in the case of percutaneous treatments or embolisation, treatment versus suboptimal therapies without proven antitumour or survival impacts. The authors did not fully define 'suboptimal' therapies.

Participants included in the review
Studies of people with unresectable HCC were eligible. Studies including people with liver metastases were excluded. The authors tabulated details of cancer stage, cirrhosis and segmental portal thrombosis in individual studies.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported 1- or 2-year death rates. The primary end point of the review was survival. The secondary end point was response to treatment (complete and partial responses).

How were decisions on the relevance of primary studies made?
Study selection was conducted unblinded to the authors, institutions, journal, or interventions assessed. Both authors appear to have been involved in selecting the studies.

Assessment of study quality
Two authors used a modified version of the Jadad quality scale to assess allocation sequence generation, allocation concealment, blinding, and description of protocol deviations, withdrawals and drop-outs. The authors were not blind to publication or treatment details during the assessment. Any disagreements were resolved by consensus.

Data extraction
Two authors appear to have extracted the data for the review. They were not blinded to the authors, institutions, journal, or interventions assessed.

**Methods of synthesis**

**How were the studies combined?**
The studies were combined using a random-effects model (DerSimonian and Laird). The results were reported as pooled odds ratios (ORs) and 95% confidence intervals (CIs).

**How were differences between studies investigated?**
Between-study heterogeneity in the OR was assessed using Q statistics and was defined as a p-value of less than 0.1. The authors also described differences between the studies in the narrative. Exploratory sensitivity analyses (not specified a priori) were performed to assess the effects of overall study quality, treatment and comparator type, and follow-up duration. A cumulative meta-analysis was used to account for the effects of publication year.

**Results of the review**

Fourteen studies with 1,484 participants were included in the meta-analysis. A further 12 studies were identified, but these were excluded because they did not meet the estimated sample size requirement for meta-analysis. These studies, along with those excluded because they compared two active treatments, were tabulated in the paper.

A meta-analysis of 6 trials with 503 people assessed 2-year survival rates following embolisation/chemoemobilisation. Arterial embolisation improved 2-year survival in comparison with controls (OR 0.53, 95% CI: 0.32, 0.89, p=0.017). There was an objective response in 35% (range: 16 to 61) of the participants.

The sensitivity analysis suggested a significant benefit from chemoembolisation with doxorubicin or cisplatin (OR 0.42, 95% CI: 0.20, 0.88; 4 studies, 323 participants), but not with embolisation alone (OR 0.59, 95% CI: 0.29, 1.20; 3 studies, 215 participants). In addition, the survival advantage was maintained when looking only at randomised trials with a control arm of conservative management (4 RCTs, 367 participants) and when assessing only 'high quality' studies (5 RCTs, 440 participants). There was no statistically significant heterogeneity for the analysis or any of the sensitivity analyses.

A meta-analysis of 7 trials with 689 people found that tamoxifen had no impact on 1-year survival (OR 0.64, 95% CI: 0.36, 1.13, p=0.13). Sensitivity analyses found no impact in high-quality trials (4 studies, 512 participants), but benefits favouring tamoxifen when assessing the 3 low-quality trials (177 participants). A sensitivity analysis of 3 double-blind, placebo-controlled trials (259 participants) found no survival benefit. An analysis of all studies with tamoxifen as adjuvant therapy found similar negative results (7 trials, 898 participants). There was no statistically significant heterogeneity in the core analysis or in the sensitivity analyses.

**Authors' conclusions**
Chemoembolisation improves survival in people with unresectable HCC; tamoxifen offers no survival benefits for people with advanced disease.

**CRD commentary**
This review included a defined research question and inclusion criteria. The search strategy seemed suitable and two reviewers were involved in the study selection process to minimise bias. However, some biases might have been introduced because studies reported in languages other than English, those available only in abstract or unpublished form, and those published in non peer-reviewed journals were not eligible for inclusion.

The authors only included studies comparing treatment with conservative or suboptimal therapies. Suboptimal treatment appears to have been viewed as a 'surrogate' for conservative treatment in some instances. It may have been helpful for the authors to define the treatment options that they considered suboptimal. As the search timeframe was broad, the definition of 'unproven' or suboptimal therapies may have changed over time, so the authors could have accounted for
this by defining 'suboptimal' and perhaps including a comparative analysis of changes over time.

The authors identified, but did not include, studies of a wide range of other treatments for people with HCC. The inclusion of active comparators might have better addressed the issue of effectiveness as per the original review question. In some cases, the rationale for exclusion was that the number of participants in these studies was insufficient to justify meta-analysis. However, the exclusion of these studies means that only a narrow range of two treatments were examined in the review findings. A narrative summary of other studies might have been useful. Apart from this, the methods of analysis appeared appropriate and were described in some detail.

The authors' conclusions reflect the evidence presented and are likely to be reliable, allowing for caveats about the exclusion of non-English language, unpublished or non peer-reviewed studies.

Implications of the review for practice and research
Practice: The authors stated that chemoembolisation may become the standard treatment for people with unresectable HCC.

Research: The authors stated that further research into other forms of treatment, such as internal radiation and arterial chemotherapy, is needed.

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