Effects of interferon alpha treatment on recurrence and survival after complete resection or ablation of hepatocellular carcinoma: a meta-analysis of randomized controlled trials

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CRD summary
This review concluded that interferon alpha treatment as adjuvant postsurgical or ablative treatment could decrease early recurrence and increase one year survival in patients with primary liver cancer. Due to limitations in the review methods and available evidence, these conclusions should be interpreted with caution.

Authors' objectives
To evaluate the effect of interferon-alpha treatment on recurrence and survival after resection or ablation for primary liver cancer (hepatocellular carcinoma).

Searching
MEDLINE, EMBASE and the Cochrane Library were searched up to November 2008, search terms were reported. Reference lists were also searched. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) or clinical trials that assessed the effect of adjuvant interferon-alpha therapy on recurrence and survival after complete resection or ablation, in patients with primary hepatocellular carcinoma of any stage, were eligible for inclusion. Studies had to have placebo or no treatment control groups.

Included trials were conducted in China, Italy, Japan and Taiwan. Most studies were of treatment after resection; others were of treatment after ablation. Interferon-alpha regimes were 3 Million International Units (MIU) twice or three times a week, 6 MIU daily or three times a week, or 10 MIU/m² three times a week for between 16 weeks and 48 months. The mean patient age ranged from 49 to 67 years, between 68 and 100% were male. Two trials reported cancer grades: one had more grades I and II in the treatment group compared with control (70% treatment versus 40% control); the other had more grade I and II patients (77% treatment versus 65% control).

The authors did not report how many reviewers performed the study selection.

Assessment of study quality
The authors did not assess study validity.

Data extraction
Odds ratios (OR) with 95% confidence intervals (CI) were calculated for recurrence and survival. Numbers were estimated form percentages where necessary. Early recurrence was classed as events occurring within one or 1.5 years after surgery. Overall survival was calculated from the numbers of deaths reported at one, three or five years after surgery. For cross-over trials, data from the first period only were used. Authors were contacted for further information where necessary.

Data were extracted by two reviewers independently with discrepancies resolved by discussion.

Methods of synthesis
Results were pooled in meta-analyses using fixed-effect models (Peto or Mantel-Haenszel method). Statistical heterogeneity was assessed using a $\chi^2$ test ($p<0.10$). Subgroup analyses assessed the effect of resection alone and resection without pre-resection ablation. Sensitivity analyses repeated subgroup analyses using random-effects models. Publication bias was assessed with the fail safe N method.

Results of the review
Six RCTs (n=600 patients) were included in the review. The mean length of follow-up ranged from 27 to 85 months.

**Early recurrence:** Early recurrence was lower after interferon-alpha treatment (OR 0.62, 95% CI 0.42 to 0.93; five RCTs); there was no evidence of statistical heterogeneity (p=0.77). Early recurrence was also lower with interferon-alpha treatment after resection only (OR 0.58, 95% CI 0.37 to 0.91; three RCTs), after resection without pre-resection ablation therapy (results not reported), and from repeating analyses using random-effects models.

**Survival:** Survival at one year was improved with interferon-alpha treatment (OR 3.14 95% CI 1.79 to 5.52; five RCTs), there was no evidence of statistical heterogeneity (p=0.59). Similar results were seen after resection only (OR 3.19, 95% CI 1.80 to 5.67; four RCTs), after resection without pre-resection ablation therapy (OR 3.83, 95% CI 2.01 to 7.27; three RCTs) and from repeating analyses using random-effects models.

There was no evidence of any publication bias for either outcome.

**Authors' conclusions**
Interferon-alpha as adjuvant postsurgical or ablative treatment could decrease early recurrence and increase one year survival in patients with hepatocellular carcinoma.

**CRD commentary**
This review specified study inclusion criteria. A number of relevant databases were searched and, although there were no language restrictions, the authors acknowledged that some studies may have been missed; no specific attempts were made to locate unpublished studies. Data extraction was performed in duplicate, but it was not reported if the same approach was used to select the studies.

No assessment of trial quality was made, so it was not possible to assess the reliability of the evidence presented. The methods of meta-analysis were appropriate; statistical heterogeneity was assessed and sensitivity analyses were performed.

As the authors acknowledged, given some limitations in the review methods and available evidence, their conclusions should be interpreted with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that interferon-alpha treatment alone or in combination with other agents might offer a good therapeutic after complete resection or ablation in hepatocellular carcinoma patients.

**Research:** The authors stated that further research is needed exploring the efficacy of interferon-alpha on early recurrence in different hepatocellular carcinoma aetiologies, and on recurrence, survival and safety of this treatment in hepatocellular carcinoma overall.

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