Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular [hepatocellular] carcinoma: a meta-analysis

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CRD summary
This review of local ablation therapy for hepatocellular carcinoma concluded that radio-frequency ablation seemed to be superior to percutaneous ethanol injection, especially for tumours greater than 2cm in size; but that percutaneous acetic acid injection did not differ significantly from ethanol injection. Overall, this was a well-conducted and reported review, and the authors' conclusions are likely to be reliable.

Authors' objectives
To compare radio-frequency ablation, percutaneous ethanol injection and percutaneous acetic acid injection as local ablation therapy for hepatocellular carcinoma.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched up to December 2008 without language restrictions; search terms were reported.

Study selection
Randomised and quasi-randomised clinical trials that compared two or more of radiofrequency ablation, percutaneous ethanol injection and percutaneous acetic acid injection for the treatment of hepatocellular carcinoma were eligible for inclusion. Trials were required to report survival, recurrence (local and/or new hepatocellular carcinoma development), tumour response (complete necrosis), and adverse events.

The inclusion criteria of the trials varied in the number of nodules, but most included three or fewer nodules that were 3cm or less. The mean number of hepatocellular carcinoma per patient ranged from 1.18 to 1.68, with a mean size from 1.9 to 2.9 cm; 53 to 86% of patients had a single nodule; 27 to 74% of patients had a carcinoma of 2cm or less (where reported).

Studies were screened by two reviewers independently, with disagreements resolved by a third reviewer.

Assessment of study quality
Risk of bias was assessed covering the generation of the randomisation sequence, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias.

The assessment was performed by two reviewers independently, with disagreements resolved by consensus.

Data extraction
Hazard ratios (HR) and 95% confidence intervals (CI) were extracted for overall survival time and time to recurrence; if these were not reported in the trial, they were calculated using the Parmar method. Binary outcomes were extracted as odds ratios (OR) and continuous outcomes as mean differences (MD), both with 95% confidence intervals.

Data were extracted by two reviewers independently, with disagreements resolved by consensus.

Methods of synthesis
Data were pooled using both random-effects and fixed-effect models; if the results were similar, the results from the random-effects model were reported; if the results differed, both sets of results were reported. All analyses were on an intention-to-treat basis. The I² statistic was used to measure heterogeneity. An adjusted indirect comparison was used, using the Bucher method and the random-effects model results, to compare treatments if there was a lack of direct
comparison within trials.

Subgroup analyses were used to compare hepatocellular carcinomas less than or greater than 2cm in size. Sensitivity analyses excluding quasi-randomised trials were also performed.

A funnel plot and Egger’s regression test were used to explore publication bias.

**Results of the review**

Eight trials were included (n=1,035 patients). Six were randomised controlled trials and two were quasi-randomised trials. All trials were classed as high risk of bias. Six trials had adequate randomisation, two had adequate allocation concealment, and none reported blinding and four addressed incomplete outcome data. Mean follow-up was between 10 and 37 months.

**Radiofrequency ablation versus percutaneous ethanol injection** (five trials): Radio-frequency ablation reduced the number of deaths (OR 0.52, 95% CI 0.35 to 0.78; five trials) and local tumour recurrences (OR 0.27, 95% CI 0.16 to 0.45; four trials) compared with percutaneous ethanol injection; there was little or no heterogeneity ($I^2=0$ to 15%). Similar benefits were seen for radio-frequency ablation when these outcomes were measured as time to event outcomes. Radio-frequency ablation also resulted in more complete nodule necrosis (OR 0.29, 95% CI 0.16 to 0.53) and needed four sessions less than percutaneous ethanol injection on average to achieve complete necrosis (MD -4.16, 95% CI -4.69 to -3.64). No statistically significant differences were seen for de novo tumours, adverse events or major complications. For subgroup analyses by tumour size, radio-frequency ablation was significantly superior to percutaneous ethanol injection for number of deaths and local recurrence in patients with carcinomas greater than 2cm in size, but these analyses were based on small sample sizes (64 radiofrequency ablation patients and 61 percutaneous ethanol injection patients). No differences were seen for any other outcomes or for sensitivity analyses excluding the quasi-randomised trials. There was no evidence of publication bias.

**Percutaneous acetic acid injection versus percutaneous ethanol injection** (three trials): Percutaneous acetic acid injection needed less treatment sessions than percutaneous ethanol injection to achieve complete necrosis (MD -7.40, 95% CI -12.24 to -2.57). There were no statistically significant differences between percutaneous acetic acid injection and percutaneous ethanol injection for any other outcomes, subgroup analyses by tumour size or sensitivity analyses by study design.

**Radiofrequency ablation versus percutaneous acetic acid injection** (one trial): One trial compared radio-frequency ablation, percutaneous acetic acid injection and percutaneous ethanol injection. The combined direct and indirect estimates of radio-frequency ablation compared with percutaneous acetic acid injection showed less local recurrence for radio-frequency ablation (OR 0.29, 95% CI 0.15 to 0.55); on average, one session less of radio-frequency ablation treatment was needed (MD -1.20, 95% CI -1.43 to -0.97). No significant differences were found between radio-frequency ablation and percutaneous acetic acid injection for any other outcomes or subgroup analyses. There were also no discrepancies between the direct and indirect estimates.

**Authors' conclusions**

Radio-frequency ablation seemed to be a superior ablative therapy than percutaneous ethanol injection for hepatocellular carcinoma, especially for tumours greater than 2cm in size. Percutaneous acetic acid injection did not differ significantly from ethanol injection. Radio-frequency ablation and acetic acid injections had similar survival rates. For tumours of 2cm or less, outcomes from radio-frequency ablation and ethanol injection were similar, but acetic acid injection needs further research in comparison with these treatments.

**CRD commentary**

This review had a clearly stated research question and specified inclusion criteria for study designs, interventions, participants and outcomes. The search covered three main databases. There were no language restrictions, although there were no attempts to locate unpublished studies, increasing the risk of publication bias. Study selection, validity assessment and data extraction were performed by two reviewers independently, minimising the risk of error and bias.

The statistical analysis methods were appropriate and considered the use of both fixed-effect and random-effects
models. The subgroup analysis results should be treated cautiously given their smaller sample sizes. An indirect comparison was used in the lack of head-to-head trial evidence for one of the treatment comparisons using an appropriate method. The authors assessed the consistency between the indirect and direct treatment comparisons.

Overall, this was a well-conducted and reported review, and the authors’ conclusions are likely to be reliable.

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

**Practice**: The authors did not make any recommendations for practice.

**Research**: The authors stated that further trials with a low risk of bias are needed to compare different percutaneous treatments for hepatocellular carcinoma, especially for tumours less than 2cm in diameter. Trials comparing radiofrequency ablation with percutaneous ethanol injection and with percutaneous acetic acid injection are needed.

**Funding**

Not stated, except that no industry funding was received.

**Bibliographic details**


**PubMedID**

20149473

**DOI**

10.1016/j.jhep.2009.12.004

**Original Paper URL**

http://www.jhep-elsevier.com/article/S0168-8278(09)00805-8/abstract

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Acetic Acid /administration & dosage /therapeutic use; Administration, Cutaneous; Carcinoma, Hepatocellular /drug therapy /pathology /surgery; Catheter Ablation /methods; Ethanol /administration & dosage /therapeutic use; Humans; Injections; Liver Neoplasms /drug therapy /pathology /surgery; Necrosis /chemically induced; Neoplasm Recurrence, Local /prevention & control; Publication Bias; Regression Analysis; Survival Rate; Treatment Outcome

**AccessionNumber**

12010001747

**Date bibliographic record published**

23/06/2010

**Date abstract record published**

13/04/2011

**Record Status**

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.