# Ablative and non-surgical therapies for early and very early hepatocellular carcinoma: a systematic review and network meta-analysis

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# Scientific summary

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# Scientific summary

## Background

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Around one-third of people with cirrhosis go on to develop HCC. The prognosis of symptomatic HCC is poor, so the National Institute for Health and Care Excellence recommends that patients with cirrhosis are monitored for early HCC with six-monthly ultrasound scans.

Patients with early HCC and good liver function can be offered surgical or non-surgical interventions with curative intent. However, liver resection is not always possible due to the location of the tumour, poor liver function or portal hypertension, and liver transplantation is limited by availability. Therefore, ablative or non-surgical therapies are frequently used for treating early HCC, including microwave ablation (MWA) and radiofrequency ablation (RFA). There has been no definitive assessment of these therapies.

## Objectives

The aim of this project was to evaluate and compare the effectiveness of ablative and non-surgical therapies for patients with small HCC.

The key objectives were to:

- systematically identify all randomised controlled trials (RCTs) of ablative and non-surgical therapies for HCC
- evaluate their quality and applicability to UK populations
- determine the comparative effectiveness of therapies using network meta-analysis (NMA)
- where the evidence base is insufficient, supplement the RCT evidence with high-quality, non-randomised, prospective comparative studies
- identify priority areas where additional high-quality evidence is required (in collaboration with patients and clinicians)
- assess whether future economic analysis would be feasible and worthwhile.

## Methods

### *Systematic review of randomised controlled trials*

Nine databases (including MEDLINE, Embase, CENTRAL, Science Citation Index) were searched for RCTs and systematic reviews published from 2000 to March 2021. Two trial registries were searched in April 2021 to identify ongoing and unpublished RCTs. The reference lists of relevant systematic reviews were checked and clinical advisors were consulted.

Randomised controlled trials of patients with HCC up to 3 cm in size (or data on a subgroup(s) of patients with tumours ≤ 3 cm) were eligible for inclusion. Any ablative or non-surgical therapy was eligible, including:

- RFA
- MWA
- laser ablation
- high-intensity focused ultrasound (HIFU)

- cryoablation
- percutaneous ethanol injection (PEI)
- percutaneous acetic acid injection (PAI)
- irreversible electroporation (IRE)
- transarterial chemoembolisation (TACE)
- transarterial embolisation
- selective internal radiation therapy
- electrochemotherapy (ECT)
- histotripsy
- stereotactic ablative radiotherapy [SABR; the term stereotactic body radiotherapy (SBRT) is also used for this technology]
- wider radiotherapy techniques.

Any comparator was eligible, except a different method of undertaking the same intervention. Outcomes of interest were overall survival (OS), progression-free survival (PFS), time to progression (TTP), serious adverse events (AEs), intervention-specific AEs and quality of life.

Titles and abstracts were screened by one reviewer, with 10% checked by another reviewer. Full texts were screened by two reviewers independently. Data extraction was checked by a second reviewer. Risk of bias (RoB) was assessed using the Cochrane RoB 2 tool. When studies did not report hazard ratios (HRs) and their variances, Kaplan–Meier data were extracted.

### *Network meta-analysis*

After mapping the identified RCTs, NMAs were conducted for four outcomes: OS, PFS, overall recurrence and local recurrence. They were conducted in a Bayesian framework using Markov chain Monte Carlo techniques. The NMAs were used to assess and rank interventions by comparative effectiveness.

### *Threshold analysis*

Threshold analysis was conducted at the contrast level to examine the impact of potential changes to the evidence on each treatment contrast. Results of the analysis were used to identify treatment comparisons which lacked robust RCT evidence and where non-randomised evidence should be sought for further review.

### *Systematic review of non-randomised evidence*

A second systematic review of non-randomised evidence was undertaken. This review included studies of comparisons where additional evidence could plausibly change the NMA conclusions, as identified by the threshold analysis. Four databases were searched in August 2021 for studies that compared the selected interventions (RFA, MWA and laser ablation), either with each other or with resection.

The databases were also searched in July 2021 for interventions that the advisory group identified as being of particular interest and where there was no RCT evidence: HIFU, cryoablation, IRE, ECT, histotripsy, SABR and wider radiotherapy techniques.

Prospective non-randomised comparative trials of patients with HCC up to 3 cm (or data on a subgroup(s) of such patients) were eligible. The outcomes of interest were OS, PFS, TTP and quality of life.

Methods of screening and data extraction were the same as outlined above. A validity assessment tool for non-randomised trials was developed.

### *Updated network meta-analysis and threshold analysis*

Where the non-randomised trials were of sufficient quality, the NMAs were repeated after pooling (without any adjustments) the non-randomised evidence with the RCT evidence, to assess whether estimates were improved. A threshold analysis was conducted on the updated NMA results to explore robustness and sensitivity to bias of the new results.

## Results

### *Systematic review of randomised controlled trial results*

Thirty-seven RCTs were included. Most were small, with sample sizes ranging from 30 to 308 patients. The majority of RCTs were conducted in China or Japan. The most frequently assessed therapy was RFA. The majority of RCTs assessed OS, PFS/disease-free survival and/or recurrence, along with response and AEs. One RCT assessed patient satisfaction. The RoB judgement was low for 9 RCTs, high for 12 RCTs and some concerns for 14 RCTs (two RCTs that reported no relevant outcomes were not assessed).

For many comparisons, data were limited. Based on a narrative synthesis, RFA appears to be better than both PEI and PAI in terms of OS, PFS and recurrence, although AEs were more frequent after RFA. PAI appears to have similar effectiveness to PEI. For RFA versus resection, results were inconsistent, with some RCTs favouring RFA and some resection; AEs were more frequent after resection. Data from RCTs comparing RFA with MWA, laser ablation or proton beam therapy were limited. RCTs assessing RFA in combination with other treatments were also limited by small sample sizes. AEs were reported inconsistently. There was no RCT evidence for HIFU, cryoablation, IRE, ECT, histotripsy, SABR or wider radiotherapy techniques.

### *Network meta-analysis and threshold analysis results*

The treatment rankings from the NMAs were very uncertain for all four outcomes (OS, PFS, overall and local recurrence). There was no meaningful difference in effectiveness for many of the treatment comparisons.

There was evidence that PEI is worse than RFA for OS [HR 1.45, 95% credible interval (CrI) 1.16 to 1.82], PFS (HR 1.36, 95% CrI 1.11 to 1.67), overall recurrence [relative risk (RR) 1.19, 95% CrI 1.02 to 1.39] and local recurrence (RR 1.80, 95% CrI 1.19 to 2.71). PAI was worse than RFA for PFS (HR 1.63, 95% CrI 1.05 to 2.51). Resection was better than PEI for OS (HR 0.60, 95% CrI 0.39 to 0.92). RFA combined with PEI decreased the risk of local recurrence compared with PEI alone (RR 0.33, 95% CrI 0.12 to 0.94).

Radiofrequency ablation + iodine-125 appears superior to RFA alone in terms of OS (HR 0.50, 95% CrI 0.31 to 0.80) and overall recurrence (RR 0.69, 95% CrI 0.48 to 0.99). There was also evidence to suggest that RFA + iodine-125 is better than PEI, PAI, TACE + PAI, RFA + TACE and laser ablation for OS, and better than PEI and TACE + PEI for overall recurrence. However, according to our clinical advisors RFA + iodine-125 is only used in selected centres in China.

There was evidence to suggest an increased risk of overall recurrence with MWA + sorafenib, compared with both resection (RR 2.09, 95% CrI 1.12 to 3.89) and RFA + iodine-125 (RR 2.93, 95% CrI 1.31 to 6.56). Also, RFA + systemic chemotherapy decreased the risk of overall recurrence compared with MWA + sorafenib (RR 0.26, 95% CrI 0.08 to 0.92).

The threshold analysis suggested that additional evidence could plausibly change the NMA result for comparisons including RFA, MWA, laser ablation, RFA + TACE, RFA + systemic chemotherapy or RFA + iodine-125. RFA, MWA and laser ablation were agreed to be interventions of interest by the advisory group.

### *Systematic review of non-randomised evidence results*

Fourteen non-randomised studies were identified. The majority were conducted in China or Japan, with sample sizes ranging from 21 to 740 patients. No comparative studies were identified on ECT, histotripsy, SABR or wider radiotherapy techniques.

The quality and reporting of the non-randomised studies were poor; 12 had a high RoB. Several studies allocated patients to treatments based on tumour characteristics, so there were potentially prognostic differences between groups at baseline. There was one study with a low RoB. It compared RFA with MWA and included 42 patients. Local tumour progression was similar between groups but new intrahepatic tumours were more frequent in the RFA group. One study of RFA compared with resection had an unclear RoB and included 346 patients. It reported significantly better health-related quality of life (HRQoL), fewer AEs and a shorter hospital stay in the RFA group.

### *Updated network meta-analyses and threshold analysis results*

Due to the significant limitations of the non-randomised studies identified, only the two studies that were not at a high RoB were included in the updated NMAs. Additional non-randomised comparative data (RFA vs. MWA vs. IRE) made available prior to publication by a clinical advisor were also included. Updated NMAs using RCT and non-RCT evidence were undertaken for OS, PFS and local recurrence.

Most results of the updated NMAs were consistent with the original results. There remained a high level of uncertainty in treatment rankings. However, the updated NMAs suggested that MWA improves OS and PFS compared with PEI (OS: HR 0.60, 95% CrI 0.40 to 0.90; PFS: HR 0.66, 95% CrI 0.46 to 0.95) and PAI (OS: HR 0.48, 95% CrI 0.24 to 0.99; PFS: HR 0.55, 95% CrI 0.33 to 0.94). Resection also improves PFS compared with PEI (HR 0.72, 95% CrI 0.54 to 0.96) and PAI (HR 0.61, 95% CrI 0.38 to 0.98). The NMA showed IRE to be worse than RFA (RR 2.97, 95% CrI 1.45 to 6.09) and RFA + PEI (RR 4.96, 95% CrI 1.50 to 16.36) for local recurrence, although the CrIs were very wide for both comparisons. There was also evidence that RFA + iodine-125 is better than resection in terms of OS (HR 0.53, 95% CrI 0.30 to 0.94).

The threshold analysis suggested that additional evidence could plausibly change the NMA result for comparisons including MWA, RFA, IRE, RFA + TACE and laser.

### *Feasibility of economic modelling*

Limitations in available clinical data may impact the feasibility of undertaking robust economic analysis. However, a value of information (VOI) analysis may be helpful as there are currently several treatments with limited evidence on effectiveness. VOI analysis quantifies the value of reducing decision uncertainty in monetary terms. This can then be compared with the costs of conducting further studies. This could help prioritise which treatments should (or should not) be assessed in future trials. This may be of particular relevance in considering treatments that are currently rarely used in NHS practice but may be effective.

### *Patient and public involvement*

The project team included a patient collaborator, who was involved throughout the project. Four additional patients were recruited to the project advisory group, attending meetings at key stages of the project. Patients provided helpful information about the outcomes most important to them, which informed the development of the data extraction tool. Patients were surprised by the lack of data on patient preference and quality-of-life outcomes. Patient and public involvement added context to the review findings and informed the conclusions of the report and recommendations for further research.

### *Workshop*

Two workshops were held with clinicians and patients to discuss the project findings and identify key priorities for future research. It was agreed that MWA would be the most appropriate comparator in future trials as it is widely used as the standard of care in the UK, and therapies that are more complex

to deliver were considered unlikely to replace it. MWA is preferred over RFA due to technological advances and ease of use, rather than data on improved clinical effectiveness. However, future research may be most useful if focused on the subgroup of patients with tumours in challenging locations, less fit patients and those with incomplete response to primary therapy. SABR and proton beam therapy were considered to be of particular interest. They are not suitable for patients with advanced or moderately advanced liver disease and, unlike ablation, can usually only be delivered once, but may be appropriate for a subgroup of patients. Histotripsy is at an early stage of regulatory approval, so should not be assessed until efficacy has been demonstrated.

It may be most feasible to undertake an international multicentre RCT as the marginal benefit of novel treatments compared with the existing standard of care is likely to be small, so future studies would need to be large to demonstrate a significant difference in outcomes, and the number of early HCC patients in the UK eligible for all treatments is limited. Outcomes that should be assessed in future trials include local recurrence, overall recurrence, OS, PFS, HRQoL and patient acceptability.

## Conclusions

### *Implications for health care*

There are considerable limitations to the evidence on ablative and non-surgical therapies for early and very early HCC. There is insufficient evidence to draw any conclusions on quality-of-life outcomes. The only firm conclusions that can be drawn from the available data are that PEI and PAI are inferior to RFA, and also appear to be inferior to MWA and resection for certain survival outcomes. MWA and resection are the first-line standard of care for single HCC ≤ 3 cm in the UK. The uptake of specific ablative therapies in the UK appears to be based more on technological advancements and ease or speed of use than on high-quality evidence demonstrating superior clinical effectiveness.

### *Recommendations for research*

It is difficult to make firm recommendations for research based on our findings. There are currently no comparative data on several ablative and non-surgical therapies, particularly those treatments reserved for the subgroup of patients with more challenging tumours. However, owing to the small number of such patients who would be eligible for both treatment arms within a trial, along with the marginal benefit of novel treatments compared with the existing standard of care, it is likely to be difficult to recruit sufficient numbers of patients.

Future studies should assess local recurrence, overall recurrence, OS, PFS, HRQoL and patient acceptability, using clear and consistent definitions, in order to allow results to be compared across studies.

Further research on SABR, and possibly other technologies, such as IRE, is required to identify where they should sit in the treatment pathway.

Feasibility studies could address potential issues and complexities in undertaking research in this area prior to undertaking a trial. This would enable: investigation of the acceptability of the intervention (and comparator) to both clinicians and patients, and their willingness to participate in a trial; the practicality of delivering the intervention; and the ability to measure relevant outcomes.

## Study registration

This study is registered as PROSPERO CRD42020221357.

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