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

*Ros Wade, Emily South, Sumayya Anwer, Sahar Sharif-Hurst, Melissa Harden,
Helen Fulbright, Robert Hodgson, Sofia Dias, Mark Simmonds, Ian Rowe, Patricia Thornton
and Alison Eastwood*



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

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Abstract

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

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Background: A wide range of ablative and non-surgical therapies are available for treating small hepatocellular carcinoma in patients with very early or early-stage disease and preserved liver function.

Objective: To review and compare the effectiveness of all current ablative and non-surgical therapies for patients with small hepatocellular carcinoma (≤ 3 cm).

Design: Systematic review and network meta-analysis.

Data sources: Nine databases (March 2021), two trial registries (April 2021) and reference lists of relevant systematic reviews.

Review methods: Eligible studies were randomised controlled trials of ablative and non-surgical therapies, versus any comparator, for small hepatocellular carcinoma. Randomised controlled trials were quality assessed using the Cochrane Risk of Bias 2 tool and mapped. The comparative effectiveness of therapies was assessed using network meta-analysis. A threshold analysis was used to identify which comparisons were sensitive to potential changes in the evidence. Where comparisons based on randomised controlled trial evidence were not robust or no randomised controlled trials were identified, a targeted systematic review of non-randomised, prospective comparative studies provided additional data for repeat network meta-analysis and threshold analysis. The feasibility of undertaking economic modelling was explored. A workshop with patients and clinicians was held to discuss the findings and identify key priorities for future research.

Results: Thirty-seven randomised controlled trials (with over 3700 relevant patients) were included in the review. The majority were conducted in China or Japan and most had a high risk of bias or some risk of bias concerns. The results of the network meta-analysis were uncertain for most comparisons. There was evidence that percutaneous ethanol injection is inferior to radiofrequency ablation for overall survival (hazard ratio 1.45, 95% credible interval 1.16 to 1.82), progression-free survival (hazard ratio 1.36, 95% credible interval 1.11 to 1.67), overall recurrence (relative risk 1.19, 95% credible interval

1.02 to 1.39) and local recurrence (relative risk 1.80, 95% credible interval 1.19 to 2.71). Percutaneous acid injection was also inferior to radiofrequency ablation for progression-free survival (hazard ratio 1.63, 95% credible interval 1.05 to 2.51). Threshold analysis showed that further evidence could plausibly change the result for some comparisons. Fourteen eligible non-randomised studies were identified ($n \geq 2316$); twelve had a high risk of bias so were not included in updated network meta-analyses. Additional non-randomised data, made available by a clinical advisor, were also included ($n = 303$). There remained a high level of uncertainty in treatment rankings after the network meta-analyses were updated. However, the updated analyses suggested that microwave ablation and resection are superior to percutaneous ethanol injection and percutaneous acid injection for some outcomes. Further research on stereotactic ablative radiotherapy was recommended at the workshop, although it is only appropriate for certain patient subgroups, limiting opportunities for adequately powered trials.

Limitations: Many studies were small and of poor quality. No comparative studies were found for some therapies.

Conclusions: The existing evidence base has limitations; the uptake of specific ablative therapies in the United Kingdom appears to be based more on technological advancements and ease of use than strong evidence of clinical effectiveness. However, there is evidence that percutaneous ethanol injection and percutaneous acid injection are inferior to radiofrequency ablation, microwave ablation and resection.

Study registration: PROSPERO CRD42020221357.

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List of abbreviations

BCLC	Barcelona Clinic Liver Cancer	PEI	percutaneous ethanol injection
CI	confidence interval	PFS	progression-free survival
CRD	Centre for Reviews and Dissemination	PSM	partition survival model
CrI	credible interval	RCT	randomised controlled trial
CT	computerised tomography	RE	random-effects
DIC	deviance information criteria	RFA	radiofrequency ablation
ECT	electrochemotherapy	ROB	risk of bias
FE	fixed-effect	RR	relative risk
HBV	hepatitis B virus	SABR	stereotactic ablative radiotherapy (this is the same technology as SBRT, for simplicity SABR is used throughout this report)
HCC	hepatocellular carcinoma		
HCV	hepatitis C virus		
HIFU	high-intensity focused ultrasound	SBRT	stereotactic body radiotherapy (this is the same technology as SABR, see comment above)
HR	hazard ratio		
HRQOL	health-related quality of life		
ICU	intensive care unit	SD	standard deviation
IRE	irreversible electroporation	SE	standard error
KM	Kaplan–Meier	SIRT	selective internal radiation therapy
MWA	microwave ablation		
NICE	National Institute for Health and Care Excellence	TACE	transarterial chemoembolisation
NMA	network meta-analysis	TTP	time to progression
OS	overall survival	VOI	value of information
PAI	percutaneous acetic acid injection		

List of supplementary material

Report Supplementary Material 1 Full search strategies

Report Supplementary Material 2 Schoenfeld residuals

Report Supplementary Material 3 Reasons for inclusion and exclusion of RCTs in the NMA

Report Supplementary Material 4 Data tables for NMAs

Report Supplementary Material 5 NMA results

Supplementary material can be found on the NIHR Journals Library report page (<https://doi.org/10.3310/GK5221>).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

Plain language summary

Hepatocellular carcinoma is the most common type of primary liver cancer. There are a range of different treatments available for patients with early hepatocellular carcinoma. We looked for clinical trials in patients with small tumours (up to 3 cm) that compared different treatments. We brought together and analysed the results of these trials to see which treatments were most effective in terms of survival, progression, side effects and quality of life.

Overall, the evidence has limitations; many trials had few patients and were of poor quality. Most were from China or Japan, where the common causes of liver disease and treatments available differ from those in the United Kingdom. The results of our analyses were very uncertain so we cannot be sure which treatment is the best overall.

We did find that three treatments – radiofrequency ablation, microwave ablation and surgery – were generally more effective than percutaneous ethanol injection and percutaneous acid injection. There was not enough evidence to be certain which treatment was better when radiofrequency ablation was compared with laser ablation, microwave ablation, proton beam therapy or surgery. We found only poor-quality, non-randomised trials on high-intensity focused ultrasound, cryoablation and irreversible electroporation. There was very little evidence on treatments that combined radiofrequency ablation with other therapies. We found no studies that compared electrochemotherapy, histotripsy, stereotactic ablative radiotherapy or wider radiotherapy techniques with other treatments. Only two studies reported data on quality of life or patient satisfaction.

We discussed the findings with patients and clinical experts. Stereotactic ablative radiotherapy was highlighted as a treatment that requires further research; however, it is only appropriate for certain subgroups of patients. Feasibility studies could inform future clinical trials by exploring issues such as whether patients are willing to take part in a trial or find the treatments acceptable.

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 \leq 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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Chapter 1 Background

Over the last decade, liver cancer incidence has increased by 45% in the UK and is projected to rise further to 15 cases per 100,000 people by 2035.¹ Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer.² Between 1997 and 2017 the incidence of HCC in the UK increased by 5.9% a year on average.³ Primary liver cancer frequently arises on a background of chronic liver disease, and around 90% of cases of HCC are associated with a known underlying aetiology.² Globally, hepatitis B virus (HBV) infection is the most common cause of primary liver cancer, but aetiology varies between regions and countries.⁴ In the UK, the majority of HCC is associated with the development of cirrhosis, which is most often a consequence of alcohol-related liver disease or non-alcoholic fatty liver disease. Around one-third of patients with cirrhosis develop HCC.² Risk increases with the severity of the underlying liver disease in cirrhotic patients,² such that patients developing HCC often have advanced liver disease and a significant risk of developing liver failure.

Hepatocellular carcinoma is often asymptomatic until late in its disease course, and the prognosis of HCC patients presenting with symptoms is poor.⁵ Recognising the importance of early HCC diagnosis in patients with cirrhosis, the National Institute for Health and Care Excellence (NICE) recommends regular surveillance ultrasound scans intended to diagnose small HCCs so that they can be treated.⁶ The Barcelona Clinic Liver Cancer (BCLC) staging system defines very early-stage HCC as a single tumour < 2 cm, preserved liver function and performance status of 0; early-stage disease is defined as a single tumour of any size or up to three tumours ≤ 3 cm, preserved liver function and performance status of 0. Patients with multinodular disease and/or larger tumours would be categorised as having intermediate, advanced or terminal-stage disease (also depending on liver function and performance status).² Patients with good liver function who are diagnosed with HCC at an early stage can be offered surgical and non-surgical interventions with curative intent; in general, these patients have favourable 5-year survival rates.² However, if patients have signs of advanced cirrhosis with the development of portal hypertension, this restricts the use of liver resection as a treatment option.⁷ While liver transplantation is associated with reduced HCC recurrence compared with other treatments, transplantation is limited by availability.⁸ Consequently, ablative therapies are frequently used in patients with small HCCs.

A range of ablative and non-surgical therapies is available for treating small HCC tumours in patients with very early or early-stage disease and preserved liver function. The main methods used are microwave ablation (MWA) and radiofrequency ablation (RFA). Alternative methods of ablation include percutaneous ethanol injection (PEI) or percutaneous acetic acid injection (PAI), irreversible electroporation (IRE), laser ablation and cryoablation. Stereotactic ablative radiotherapy [SABR; the term stereotactic body radiotherapy (SBRT) is also used for this technology, but for simplicity SABR is used throughout this report] is emerging as an alternative to invasive ablation and has recently been commissioned as a treatment option by NHS England.⁹ Non-ablative approaches, which achieve cure much less frequently, include transarterial (chemo-) embolisation [TA(C)E] and selective internal radiation therapy (SIRT).

However, there has been no definitive assessment of these therapies. NICE guidance comprises overviews of interventional procedures based on rapid reviews, rather than a full systematic assessment of the different treatment options.¹⁰⁻¹² Scoping searches identified four Cochrane Reviews of ablative and minimally invasive therapies that appeared to have populations relevant to this research question; these generally found few or no randomised controlled trials (RCTs), low-quality evidence and a high risk of bias (RoB).¹³⁻¹⁶ While some network meta-analyses (NMAs) have been completed, these did not include all relevant therapies and could not assess all relevant outcomes.¹⁷⁻¹⁹ The evidence base is large, but the majority of studies are small and of poor quality. It is also important to consider the applicability of the research evidence to the UK population, since the aetiology of HCC differs between European and Asian populations;²⁰ many primary studies of interventions for HCC have been undertaken in

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Asia. Therefore, a thorough systematic evaluation of the existing research evidence was required to inform UK clinical practice and the design of future effectiveness and cost-effectiveness studies of emerging treatments.

Chapter 2 Aim and objectives

The aim of this project was to evaluate and compare the effectiveness of ablative and non-surgical therapies for patients with HCC whose tumours are small (up to 3 cm).

The key objectives were:

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

Chapter 3 Methods

The systematic reviews were conducted following the Centre for Reviews and Dissemination (CRD) guidance on undertaking systematic reviews²¹ and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.^{22,23} The protocol is registered on PROSPERO, the international prospective register of systematic reviews in health and social care; registration number CRD42020221357.

Systematic review of randomised controlled trials

Search strategy for identification of randomised controlled trials

A comprehensive, systematic search of bibliographic databases and trial registers was undertaken to identify RCTs of ablative and non-surgical therapies for the treatment of early/small (≤ 3 cm diameter) HCCs. The search strategy was developed in Ovid MEDLINE by an information specialist (MH) with input from the review team. The strategy combined relevant text word searches for terms that appear in the titles or abstracts of database records, with relevant subject headings (e.g. MeSH terms). The strategy consisted of a set of terms for early/small HCC combined with terms for each of the ablative and non-surgical therapies. The MEDLINE search strategy was adapted for use in all other resources searched.

Searches were limited to RCTs using validated study design search filters where available. Retrieval was restricted to articles published from 2000 onwards, as clinical advice confirmed that practice has evolved over the past 20 years and techniques have changed over time. In addition, the natural history and treatment of the underlying liver disease have also changed over the last 20 years, including antiviral therapies for HBV/hepatitis C virus (HCV); therefore, overall outcomes will have changed over this period. Language limits were not applied to the strategy.

The following databases were searched on 3 February 2021:

- MEDLINE ALL (Ovid)
- Embase (Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Science Citation Index (Web of Science).

Relevant systematic reviews were also sought, in order to check their reference lists for additional relevant studies. The following systematic review databases were searched on 3 February 2021:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (CRD databases)
- International Health Technology Assessment database
- Epistemonikos
- International Prospective Register of Systematic Reviews (PROSPERO).

At our first advisory group meeting on 15 February 2021, a few additional non-surgical therapies were suggested for inclusion in the review: electrochemotherapy (ECT), histotripsy and wider radiotherapy techniques. Therefore, all of the databases listed above were searched again on 17–18 March 2021 using terms for the condition taken from the original searches (devised by MH), with further terms for additional therapies (devised by HF). The records retrieved from these searches were deduplicated against the original search results in EndNote™ 20 (Clarivate Analytics, Philadelphia, PA, USA).

Information on studies in progress and unpublished research was sought by searching ClinicalTrials.gov and the European Union Clinical Trials Register on 27 April 2021, using terms for early/small HCC only. These searches were devised and performed by an information specialist (HF). As trial registers have limited search interfaces which are not designed for expert searches, terms for the condition were searched for without listing any of the interventions, to capture as many relevant records as possible. The search of ClinicalTrials.gov was limited to 'interventional studies', and both registers were limited to trials first posted from 2010 onwards, since the main purpose of searching clinical trial registers was to identify ongoing trials. Clinical advisors were consulted about relevant studies they were aware of.

Search results were imported into EndNote 20 and deduplicated. MEDLINE search strategies are presented in [Appendix 1.1](#). Search strategies for other databases are presented in [Report Supplementary Material 1](#).

Inclusion criteria

Participants

Patients diagnosed with HCC with tumour size up to 3 cm (studies with mixed populations were considered if the data for patients with tumour size up to 3 cm could be extracted separately), who were suitable for treatment with ablative or non-surgical therapies. Key participant subgroups considered included:

- size of tumour
- number of tumours (single or multiple lesions)
- disease stage
- cirrhosis and severity (Child–Pugh A or B)
- liver disease (HBV/HCV, other)
- prior HCC treatment
- study location.

Interventions

Any ablative or non-surgical therapy, including:

- RFA
- MWA
- laser ablation
- high-intensity focused ultrasound (HIFU)
- cryoablation
- PEI
- PAI
- IRE
- TACE
- transarterial embolisation
- SIRT
- ECT
- histotripsy
- SABR
- wider radiotherapy techniques.

Comparators

The project aimed to evaluate the comparative effectiveness of all of the therapies listed above, so no specific comparator therapy was considered; any comparator was eligible for inclusion, including ablative, minimally invasive or more invasive interventions. Studies comparing a relevant therapy versus surgical resection were also included. Studies comparing different methods of undertaking the same intervention were not eligible for inclusion (e.g. conventional temperature control RFA vs. impedance

control RFA, RFA under ultrasound guidance vs. RFA under computed tomography guidance); studies had to compare two different therapies.

Outcomes

The outcomes of interest were:

- overall survival (OS)
- progression-free survival (PFS)
- time to progression (TTP)
- recurrence
- serious adverse events (AEs)
- intervention-specific AEs (e.g. pneumothorax, post-ablation syndrome, post-embolisation syndrome, thermoablative injury, pain, haemorrhage or bile leak)
- quality of life.

Where reported, outcomes of economic relevance were recorded, including healthcare costs and duration of hospital stay.

Study design

Randomised controlled trials were eligible for inclusion.

Study selection and data extraction

Studies were initially assessed for relevance using titles and abstracts. As the database searches were expected to be extensive, a single reviewer screened each identified title/abstract, and 10% of records were checked by another reviewer. Full-text articles were independently screened by two reviewers for final inclusion. Any disagreements were resolved through discussion and, where necessary, consultation with a third reviewer. Foreign-language studies were translated and assessed for inclusion. Studies only available as conference abstracts were identified and attempts were made to contact authors for further data to enable them to be assessed for inclusion in the review.

A data extraction form was developed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), piloted on a sample of studies and refined. Data on intervention, comparator and patient characteristics and results were extracted by one reviewer (SS-H or ES) and checked by a second reviewer (RW). Any discrepancies were resolved by discussion. Foreign-language studies were data extracted by a native speaker and discussed at a meeting with a second reviewer (RW). Authors of conference abstracts were contacted for further information; data were extracted using only the abstract when authors did not respond.

For all outcomes, data were extracted from publications either as hazard ratios (HRs) for survival outcomes, or as relative risks (RRs) for dichotomous outcomes, and in all cases with their corresponding 95% confidence intervals (CIs) or standard errors (SEs).

For survival outcomes, where studies did not report HRs and their variances, Kaplan–Meier (KM) data, including the numbers at risk, were extracted using methods reported by Guyot *et al.*²⁴ and HRs were computed using the reconstructed individual patient data. If a study did not report the numbers at risk, the p-value for the log-rank test was used to calculate the HR and its corresponding variance using methods described by Irvine *et al.*²⁵

In the instance where neither HRs were reported nor KM plots were provided, HRs and SEs were back-calculated using the reported survival rates and the p-value of the log-rank test with the log-rank test.²⁶

Critical appraisal

Risk of bias in RCTs was assessed using the latest version of the Cochrane RoB tool.²⁷ RoB assessment was undertaken by one reviewer (SS-H or ES) and independently checked by a second reviewer (RW). Any disagreements were resolved through consensus.

Network meta-analysis

Feasibility assessment

Randomised controlled trials were mapped according to interventions included, outcomes reported, trial size and quality, to determine the overall extent of the RCT evidence. Trials were grouped according to identified subgroups (e.g. tumour size and stage), where appropriate. Key interventions and comparisons of interventions where existing RCT data are absent, limited or of poor quality were identified. The mapping was used to determine whether NMA of the RCTs was feasible.

Networks of treatment comparisons were drawn for each outcome to check that they were connected. Not all RCTs reported data that could be used; only studies with usable data were included in the networks.

Included data

Network meta-analyses were conducted for four outcomes: OS, PFS, overall recurrence, and local recurrence. For OS and PFS, only contrast-level data were available in the form of HRs. For overall recurrence and local recurrence, both contrast-level and arm-level data were available. Data for both HRs and RRs were synthesised on the log scale, by log-transforming estimates and their CIs from studies.

For OS and PFS, summary effect estimates from the NMAs were presented as HRs and their corresponding 95% credible intervals (CrIs), whereas overall and local recurrence estimates were presented as RRs and their corresponding 95% CrIs.

Any deviation from proportional hazards was tested for, and the Schoenfeld residuals, survival curves and piecewise hazards visually inspected. If there is strong evidence that the proportional hazards assumption does not hold, or the simpler models initially considered do not fit the data well, more complex, time-varying models that account for non-proportional hazards should be considered, if sufficient data are available. However, data were limited, so this was not possible. Consequently, appropriate caution with the results is expressed, where appropriate.

Network meta-analysis

Network meta-analyses were conducted in a Bayesian framework using Markov chain Monte Carlo techniques. For the aggregate RCT data (HRs and RRs), contrast-based models proposed by Dias *et al.*, which appropriately account for correlations in trials with more than two arms, were used.²⁸⁻³⁰ All four outcomes were modelled using a normal likelihood with an identity link.³⁰ Where arm-level data were available for overall and local recurrence, the binomial likelihood, logit link model suggested by Warn *et al.*³¹ was also fitted to prove comparability of the results.

All analyses were carried out using the GeMTC package³² in R (version 4.1.2).

To account for the correlation between the relative effects in three-arm trials³³ the covariance between differences taken with respect to the same control arm was calculated using the equation:

$$\text{Cov}(y_{ab}, y_{ac}) = \frac{\text{Var}(y_{ab}) + \text{Var}(y_{ac}) - \text{Var}(y_{bc})}{2} \quad (1)$$

Fixed-effect (FE) and random-effects (RE) models were fitted. Models were sampled for 100,000 iterations over four chains after an initial burn-in of 50,000 iterations. Model convergence was assessed through visual inspection of Brook–Gelman–Rubin diagnostic and history plots.³⁴

For the RE models, the choice of prior distributions for the between-study standard deviation (SD) was explored. A half-normal (0, 0.19²) and a uniform (0, 3) prior distribution were considered. As a sensitivity analysis, a half-normal (0, 0.50²) prior was also used for the between-study heterogeneity.³⁵

Models were compared based on their deviance information criteria (DIC), and the model with the smallest DIC was selected as the base-case analysis.^{36,37} Differences < 3 were not considered meaningful, and the simplest model was selected. Where a FE model was selected, results for the RE models were also presented as a sensitivity analysis.

In networks with loops formed by independent studies (i.e. where different studies provided direct and indirect evidence for the same comparison), inconsistency (i.e. conflict between the direct and indirect evidence) was checked by comparing the model fit and between-study heterogeneity from the NMA models versus the corresponding unrelated mean effects (inconsistency) models.^{28,38} Where inconsistency was identified, it was explored by inspecting the characteristics of the included studies (participant and design characteristics) that may contribute to inconsistency. Where feasible, node-split models were fitted to provide further evidence of the location and impact of potential inconsistency.³⁹

Where judged appropriate, NMA was used to assess and rank interventions by comparative effectiveness. Where feasible, the potential impact of additional evidence on the NMAs was investigated using threshold analysis.^{40,41}

Threshold analysis

Threshold analysis^{40,41} was conducted at the contrast level to examine the impact of potential changes to the evidence on each treatment contrast to identify which treatment comparisons lacked robust RCT evidence. Threshold analysis represents a robust statistical alternative to qualitative assessment of the robustness of evidence. It is a novel statistical approach that can be used to investigate which comparisons in a NMA have estimated relative effects which might not be robust to changes in the observed evidence due to either possible bias, sampling variation or relevance.^{40,41} Threshold analysis uses formal statistical methods to quantify precisely how much the results of a NMA could vary (due to changes in the amount of data, or due to potential bias) before any conclusion changes (e.g. changes to the ranking of an intervention), by examining what the smallest changes to the available data required to alter a conclusion are. It can therefore be used to identify which interventions, or comparisons of interventions, have the most robust evidence, and which interventions would benefit from further trials.

Threshold analysis was carried out using the `nmathresh` package⁴⁰ in R (version 4.1.2). Results of the threshold analysis are presented graphically as forest plots and threshold tables. The results have been used to identify interventions and comparisons where non-randomised evidence should be sought for further review, based on the sensitivity shown by the comparison with potential additional evidence.

Following clinical advice, comparisons that included PAI and PEI were excluded from the threshold analysis to restrict attention to interventions considered relevant to current practice.

Systematic review of non-randomised evidence

Results of the mapping exercise, NMAs and threshold analyses were used to identify interventions or comparisons where non-randomised evidence might usefully add to the RCT evidence or potentially

resolve uncertainty (see [Systematic review of RCTs](#), [Network meta-analysis results](#) and [Threshold analysis of RCT networks](#)). This identified and classified evidence for interventions:

1. with no RCT evidence
2. with limited RCT evidence (e.g. only one or two trials, or <50 or <100 patients in total)
3. where RCT evidence is very heterogeneous (e.g. very different results across trials)
4. where RCT evidence is highly uncertain (e.g. wide CIs or uncertain ranking in NMAs, as identified by the threshold analysis)
5. where RCT evidence is of low or uncertain quality, or at ROB.

The advisory group was consulted to identify interventions of particular practical interest where RCT evidence was lacking. A distinction was made between comparisons without any current RCT evidence (i.e. where an intervention of interest was disconnected from the main network) and comparisons with imprecise or non-robust RCT evidence.

This targeted approach was used because preliminary searches suggested that the quantity of non-randomised evidence was too large to be fully reviewed within the time and resource available for this project; furthermore, this would be of limited value as much of the non-randomised evidence is likely to be of insufficient quality for inclusion in any analysis.

For the interventions identified for further investigation by our classification and by the advisory group, targeted database searching and screening were performed.

Search strategy for identification of non-RCTs

Searches were undertaken to identify non-randomised studies of selected interventions for early/small (≤ 3 cm diameter) HCC, where RCT evidence was not available. The search strategy consisted of terms for small or early HCC combined with terms for the selected interventions (HIFU, cryoablation, IRE, ECT, histotripsy, SABR and wider radiotherapy techniques). Relevant subject headings alongside text word searches in the title and abstracts of records were included in the search strategy. To allow comprehensive retrieval of non-randomised studies, the search was not restricted by study type.⁴² The strategy was limited to articles published from the year 2000 onwards. Language limits were not applied.

The searches were carried out on 28 July 2021. The following databases were searched: MEDLINE (Ovid), Embase (Ovid), CENTRAL (Wiley) and the Science Citation Index (Web of Science, Clarivate). EndNote 20 was used to manage and deduplicate the search results.

Although conference abstracts were due to be identified via a search of the Conference Proceedings Citation Index – Science, a pragmatic decision to not search this database was taken due to a lack of time and resources to screen and follow up ongoing studies reported as conference abstracts. Similarly, conference abstracts were removed from the search results retrieved in Embase.

MEDLINE search strategies are presented in [Appendix 1.2](#). Search strategies for other databases are presented in [Report Supplementary Material 1](#).

Searches were also undertaken to identify studies of selected interventions for comparisons where additional evidence could plausibly change the NMA conclusions, as identified by the threshold analysis. The search strategy consisted of terms for small or early HCC combined with terms for the selected interventions (RFA, MWA and laser ablation, compared with each other or with surgical resection). Relevant subject headings alongside text word searches in the title and abstracts of records were included in the search strategy. The strategy was limited to articles published from the year 2000 onwards, and animal studies were removed where possible. Language limits were not applied.

The searches were carried out on 24 August 2021. The following databases were searched: MEDLINE (Ovid), Embase (Ovid), CENTRAL (Wiley) and the Science Citation Index (Web of Science, Clarivate). EndNote 20 was used to manage and deduplicate the search results.

MEDLINE search strategies are presented in [Appendix 1.3](#). Search strategies for other databases are presented in [Report Supplementary Material 1](#).

Inclusion criteria

Participants

Patients diagnosed with HCC with tumour size up to 3 cm (studies with mixed populations were considered if the data for patients with tumour size up to 3 cm could be extracted separately), who were suitable for treatment with ablative or non-surgical therapies. Studies of patients with recurrent HCC were excluded, as clinical advisors confirmed that it was not appropriate to synthesise the results of these studies with the studies of HCC patients included in the networks.

Interventions

Informed by the systematic review of RCTs and results of the NMAs and threshold analyses (see [Systematic review of RCTs](#), [Network meta-analysis results](#) and [Threshold analysis of RCT networks](#)), ablative or non-surgical therapies of particular practical interest where RCT evidence was lacking were sought; these were interventions where either RCT evidence was not available, or where additional evidence could plausibly change the NMA result, as identified by the threshold analysis. The specific interventions were:

- RFA
- MWA
- laser ablation
- HIFU
- cryoablation
- IRE
- ECT
- histotripsy
- SABR
- wider radiotherapy techniques.

Comparators

The project aimed to evaluate the comparative effectiveness of all the therapies listed above, so no specific comparator therapy was considered; any comparator was eligible for inclusion, including ablative, minimally invasive or more invasive interventions. Studies comparing a relevant therapy versus surgical resection were also included. Studies comparing different methods of undertaking the same intervention were not eligible for inclusion (e.g. conventional temperature control RFA vs. impedance control RFA; RFA under ultrasound guidance vs. RFA under computed tomography guidance); studies had to compare two different therapies.

Outcomes

The outcomes of interest were:

- OS
- PFS
- TTP
- quality of life.

Studies only reporting response and AE results were excluded from the review of non-RCTs as these outcomes were not relevant for the NMAs.

Study design

Only prospective non-randomised studies that compared two or more eligible therapies were included; studies of single therapies were excluded.

Study selection and data extraction

Consistent with the review of RCTs, titles and abstracts were screened by a single reviewer, with 10% of records checked by another reviewer. Full-text articles were independently screened by two reviewers for final inclusion. Any disagreements were resolved through discussion and, where necessary, consultation with a third reviewer. Foreign-language studies were translated and assessed for inclusion. Studies only available as conference abstracts were assessed based on the limited data available and were included if there were sufficient data reported on the relevant outcomes.

The data extraction form developed using Microsoft Excel for the review of RCTs was modified for the review of non-RCTs. Data on intervention, comparator and patient characteristics and results were extracted by one reviewer (RW or ES) and independently checked by a second reviewer (ES or RW). Any discrepancies were resolved by discussion. Foreign-language studies were data extracted by a native speaker and discussed at a meeting with a second reviewer (RW). Where studies were only reported as conference abstracts, data were extracted using the limited data available. Where possible, HRs and their variances were extracted by one reviewer and checked by a second reviewer. When the HRs were not available, KM data were extracted using methods reported by Guyot *et al.*²⁴ If neither HRs nor KM data were available, survival rates and p-values for the log-rank test were extracted.

Critical appraisal

A validity assessment tool was developed, piloted on a sample of studies and refined. Validity assessment was undertaken by one reviewer (RW or ES) and independently checked by a second reviewer (ES or RW). Any disagreements were resolved through consensus. The most important quality assessment criteria were selected, based on their potential impact on the overall validity of the studies, and an overall RoB judgement was made for each study; important criteria were those relating to the participant inclusion criteria, appropriateness of treatment allocation, similarity of treatment groups at baseline and whether missing outcome data were balanced across treatment groups.

Updated network meta-analysis

For non-randomised studies that were of sufficient quality, the NMA and threshold analyses were repeated after pooling (without any adjustments) the non-randomised evidence with the RCT evidence, to assess whether estimates were improved.

The updated NMA was conducted using the methods detailed in *Network meta-analysis*.

Updated threshold analysis

A threshold analysis was conducted on the results for the updated NMAs using both RCT and non-randomised evidence to explore the robustness of the updated results.

The updated threshold analysis was conducted using methods detailed in *Threshold analysis*.

Chapter 4 Results

Systematic review of RCTs

The electronic searches identified a total of 7550 records after deduplication between databases; 6774 records were identified from the original searches of bibliographic databases undertaken on 3–4 February 2021, 655 from the searches for studies of ECT, histotripsy and wider radiotherapy techniques undertaken on 17–18 March 2021, and 121 from the trial register searches undertaken on 27 April 2021. One additional record was identified from screening reference lists of relevant systematic reviews. Clinical advisors were not aware of any additional RCTs not identified in the electronic searches.

Two hundred potentially relevant studies were ordered for full paper screening. Twenty-seven full papers were unavailable as they were only reported as conference abstracts or clinical trial register records; study authors were e-mailed (where contact details could be found) and authors of six records confirmed that they were either duplicate reports or did not meet our inclusion criteria. One hundred and seventy-three full papers were screened; 138 were excluded at the full paper stage and are listed in [Appendix 2](#), along with the reasons for their exclusion. [Figure 1](#) presents the flow of studies through the study selection process.

Characteristics of RCTs included in the review

Details of the 37 RCTs that were included in the systematic review are presented in [Table 1](#). One RCT was ongoing and therefore no results were available for data extraction. The characteristics and results of the other 36 RCTs were extracted into an Excel spreadsheet.

Fifteen of the 36 completed RCTs restricted inclusion criteria to HCC patients with tumour size up to 3 cm in diameter.^{43–57} Six RCTs included patients with tumours up to 4 cm in diameter,^{58–63} 12 RCTs included patients with tumours up to 5 cm in diameter^{64–75} and one RCT included patients with tumours up to 7 cm in diameter.⁷⁶ One RCT did not report specific tumour size criteria but included patients with small HCCs,⁷⁷ and one RCT included patients within BCLC stages 0–B.⁷⁸ The RCTs that included patients with larger tumours (>3 cm diameter) were included in the review if they reported separate results for the subgroup of patients with a tumour diameter up to 3 cm or, in the case of three RCTs, if a clear majority of patients had tumours < 3 cm in diameter.^{60,63,71} Three RCTs included patients with recurrent/residual tumours ≤ 3 cm.^{51,74,75} Sample sizes ranged from 30 to 308 patients.

The majority of RCTs were conducted in Asian countries, which has implications for the generalisability of results to the UK population. HCC in European patients is more likely to be caused by alcohol or hepatitis C, whereas in Asia it is more likely to be caused by hepatitis B. The natural history of these diseases is different and treatment options for the underlying liver disease differ. RCTs were conducted in China ($n = 17$), Japan ($n = 7$), Taiwan ($n = 4$), South Korea ($n = 1$), Egypt ($n = 2$), Italy ($n = 4$), Italy and Germany ($n = 1$) and Switzerland and France ($n = 1$).

The most frequently assessed ablative/non-surgical therapy was RFA, either alone or in combination with TACE, PEI, iodine-131 metuximab, iodine-125 or chemotherapy. [Table 2](#) shows the comparisons made in the included RCTs. The majority of RCTs assessed OS, progression-/disease-free survival and/or recurrence, along with response and AEs. A few RCTs presented economic outcomes. Only one RCT assessed patient satisfaction.

Quality of RCTs included in the review

Risk of bias was assessed for each of the main study outcomes using the Cochrane RoB tool, resulting in 58 assessments for the 35 included RCTs for which RoB could be assessed; two RCTs did not have a RoB assessment as they were either ongoing⁸⁰ or did not report any relevant outcomes for the subgroup of

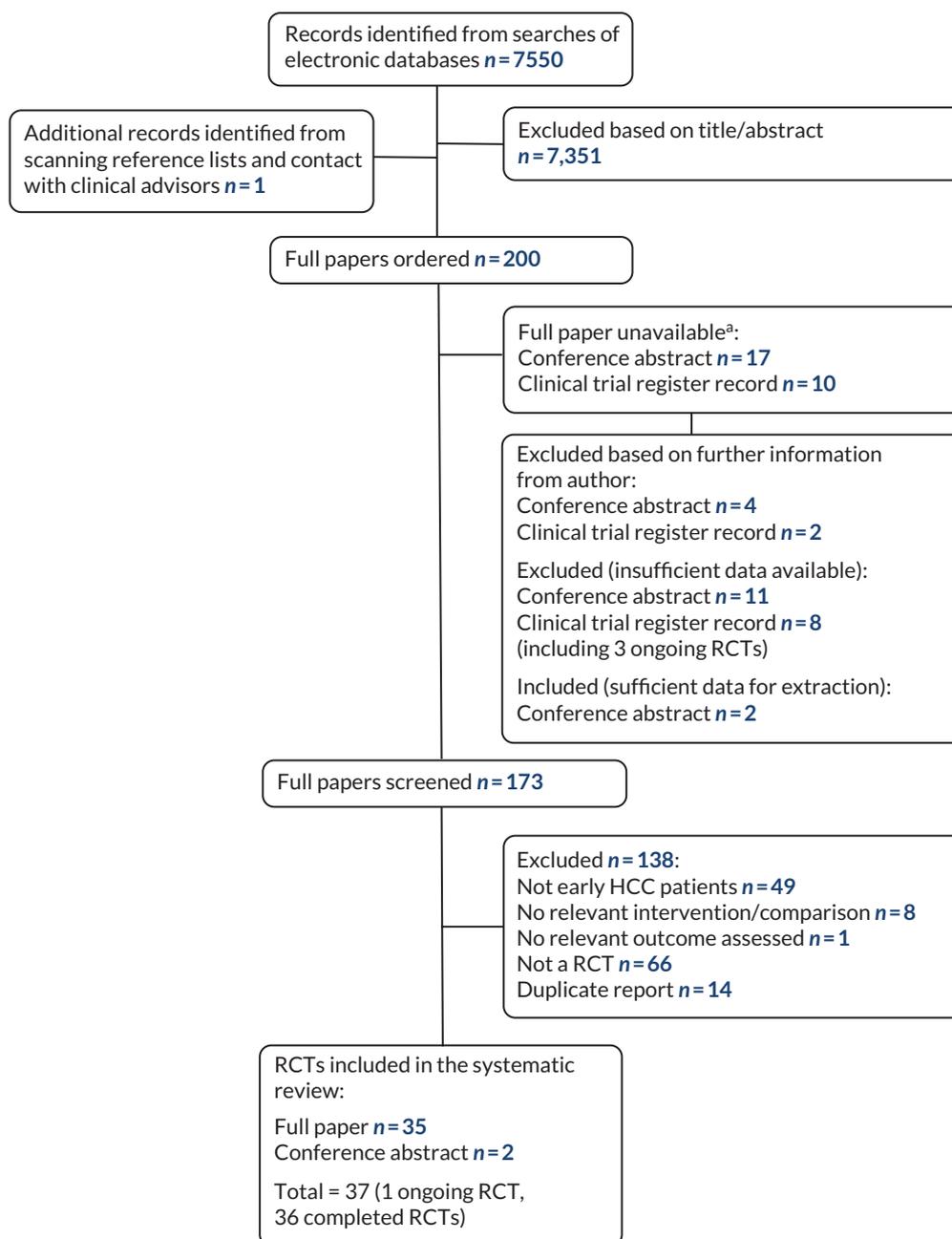


FIGURE 1 Flow diagram of the study selection process (RCTs).

^aWhere possible, authors were contacted for further information.

patients with tumours ≤ 3 cm.⁵⁸ Results of the RoB assessment for the most relevant outcome assessed are presented in [Table 3](#). Results for each of the main study outcomes are presented in [Appendix 3](#). Two RCTs were only reported as conference abstracts; therefore, some questions had a 'no information' response owing to the limited reporting, resulting in a high RoB for the domain and the study overall.^{43,50}

Generally, methods were poorly reported. There was either a high RoB or some concerns arising from the randomisation process in 20/35 of the RCTs assessed. Most RCTs had a low RoB for domains relating to deviations from the intended intervention (27/35), missing outcome data (24/35) and selective outcome reporting (34/35 had a low RoB for the most relevant outcome). All RCTs had a low RoB relating to measurement of the outcome, using computerised tomography (CT) (or magnetic

TABLE 1 RCTs included in the systematic review

Study	Location	Participant information	Intervention	Comparator
Abdelaziz, 2014 ⁶⁴	Egypt	111 patients (with 128 tumours) \leq 5 cm; subgroup of 87 tumours \leq 3 cm	RFA	MWA
Aikata, 2006 (abstract) ⁴³	Not reported (authors from Japan)	44 patients with tumours $<$ 3 cm	RFA + TACE	RFA alone
Azab, 2011 ⁶⁵	Egypt	90 patients (with 98 tumours) \leq 5 cm; subgroup of 48 tumours \leq 3 cm	PEI + RFA	RFA alone PEI alone
Bian, 2014 ⁷⁸	China	127 patients with BCLC stage 0–B; subgroup of 78 patients with tumours $<$ 3 cm	RFA + iodine-131 metuximab	RFA alone
Brunello, 2008 ⁴⁴	Italy	139 patients with tumours \leq 3 cm	RFA	PEI
Chen, 2005 (reported in Chinese) ⁶⁶	China	86 patients with tumours \leq 5 cm; subgroup of 47 patients with tumours \leq 3 cm	RFA + PEI	RFA alone
Chen, 2005 (reported in Chinese) ⁶⁷	China	132 patients with tumours \leq 5 cm; subgroup of 55 patients with tumours \leq 3 cm	Resection	RFA
Chen, 2006 ⁶⁸	China	180 patients with tumours \leq 5 cm; subgroup of 79 patients with tumours \leq 3 cm	Percutaneous local ablative therapy	Partial hepatectomy
Chen, 2014 ⁴⁵	China	136 patients with tumours \leq 3 cm	RFA + iodine-125	RFA alone
Fang, 2014 ⁴⁶	China	120 patients with tumours \leq 3 cm	RFA	Hepatectomy
Feng, 2012 ⁵⁸	China	168 patients with tumours $<$ 4 cm; subgroup of 56 patients with tumours \leq 2 cm	RFA	Surgical resection
Ferrari, 2007 ⁷⁷	Not reported (authors from Italy)	81 patients with tumours \leq 4 cm; subgroup of 28 patients with tumours \leq 2.5 cm	Laser ablation	RFA
Gan, 2004 (reported in Chinese) ⁴⁷	China	38 patients with tumours \leq 3 cm	RFA alone	RFA + chemotherapy
Giorgio, 2011 ⁴⁸	Italy	285 patients with tumours \leq 3 cm	RFA	PEI
Huang, 2005 ⁴⁹	Taiwan	82 patients with tumours \leq 3 cm	PEI	Resection
Huang, 2010 ⁶⁹	China	230 patients with tumours \leq 5 cm; subgroup of 159 patients with tumours \leq 3 cm	RFA	Resection
Huo, 2003 ⁷⁰	Taiwan	108 patients with tumours \leq 5 cm; subgroup of 55 patients with tumours \leq 3 cm	Sequential TACE and PAI	PAI alone
Izumi, 2019 (abstract) ⁵⁰	Japan	308 patients with tumours \leq 3 cm	RFA	Surgery
Kim, 2020 ⁵¹	South Korea	144 patients with recurrent/residual tumours $<$ 3 cm	Proton beam radiotherapy	RFA
Koda, 2001 ⁵²	Japan	52 patients with tumours $<$ 3 cm	TACE + PEI	PEI alone
Lencioni, 2003 ⁷¹	Not reported (authors from Italy and Germany)	104 patients with tumours \leq 5 cm (large proportion had tumours \leq 3 cm)	PEI	RFA
Lin, 2004 ⁵⁹	Not reported (authors from Taiwan)	157 patients with tumours \leq 4 cm; subgroup of 114 patients with tumours \leq 3 cm	RFA	Low-dose PEI High-dose PEI

continued

TABLE 1 RCTs included in the systematic review (*continued*)

Study	Location	Participant information	Intervention	Comparator
Lin, 2005 ⁵³	Taiwan	187 patients with tumours \leq 3 cm	RFA	PEI PAI
Liu, 2016 ⁷²	China	200 patients with tumours \leq 5 cm; subgroup of 135 patients with tumours \leq 3 cm	Partial hepatectomy	TACE + RFA
Mizuki, 2010 ⁶⁰	Japan	30 patients with tumours \leq 4 cm (large proportion had tumours \leq 3 cm)	PEI alone	TACE + PEI
Ng, 2017 ⁷⁹	China	218 patients with tumours \leq 5 cm; subgroup of 55 patients with tumours \leq 2 cm	Resection	RFA
Orlacchio, 2014 ⁶¹	Italy	30 patients with tumours \leq 4 cm (mean tumour size 2.4 cm)	Laser ablation	RFA
Peng, 2012 ⁷⁴	China	139 patients with recurrent HCC tumours \leq 5 cm; subgroup of 87 patients with tumours \leq 3 cm	RFA + TACE	RFA alone
Shibata, 2002 ⁶²	Japan	72 patients (with 94 tumours) $<$ 4 cm; subgroup of 88 tumours \leq 3 cm	RFA	MWA
Shibata, 2009 ⁵⁴	Japan	89 patients with tumours \leq 3 cm	RFA + TACE	RFA alone
Shiina, 2005 ⁵⁵	Japan	232 patients with tumours \leq 3 cm	RFA	PEI
Vietti Violi, 2018 ⁶³	Switzerland and France	152 patients with tumours \leq 4 cm (mean tumour size 1.8 cm, $<$ 8% patients had tumours $>$ 3 cm)	MWA	RFA
Xia, 2020 ⁷⁵	China	240 patients with recurrent HCC tumours \leq 5 cm; subgroup of 159 patients with tumours \leq 3 cm	RFA	Repeat hepatectomy
Yan, 2016 ⁵⁶	China	120 patients with tumours \leq 3 cm	Resection	MWA + sorafenib
Zhang, 2007 ⁷⁶	China	133 patients with tumours \leq 7 cm; subgroup of 60 patients with tumours \leq 3 cm	RFA + PEI	RFA alone
Zhu, 2021 (protocol) ⁸⁰	China	Ongoing RCT	RFA	Laparoscopic hepatectomy
Zou, 2017 ⁵⁷	China	74 patients with tumours \leq 3 cm	Laser ablation	RFA

resonance imaging) for assessment of tumour response, progression and recurrence. The overall judgement of RoB was low for 9 RCTs and high for 12 RCTs, and there were some concerns for 14 RCTs.

Results of RCTs included in the review

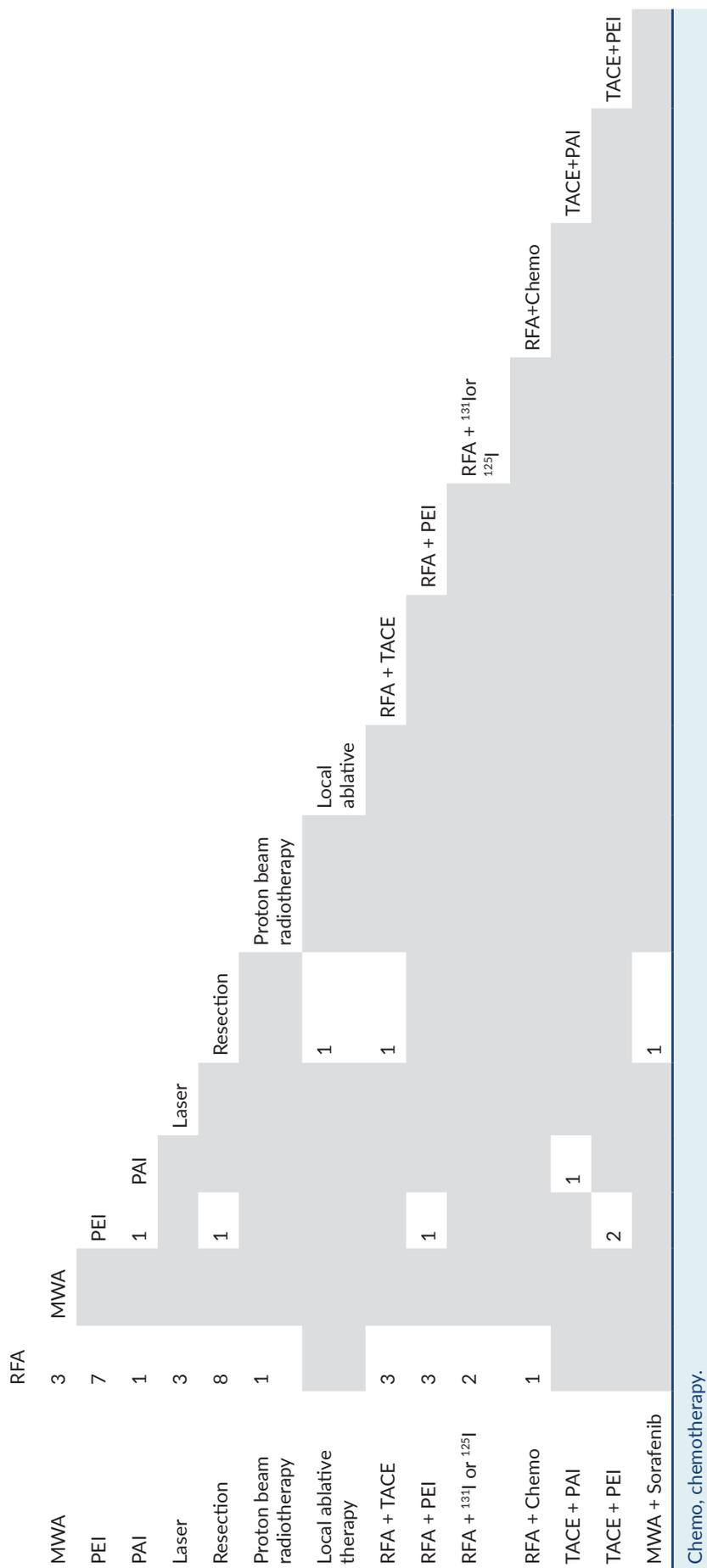
A table of study characteristics and results is presented in [Appendix 4](#).

Radiofrequency ablation versus microwave ablation

Three RCTs compared RFA with MWA. One was assessed as having a high RoB⁶⁴ and the other two as having some concerns.^{62,63} One RCT included 152 participants with tumours up to 4 cm but only a small minority of patients had tumours $>$ 3 cm.⁶³ The other two RCTs only reported the number of tumours \leq 3 cm ($n = 87$ and $n = 88$) rather than the number of patients.^{62,64}

Only one RCT (with some RoB concerns) reported OS and recurrence outcomes.⁶³ OS was similar between the two treatment groups at 2 years (RFA 84% vs. MWA 86%). More patients in the RFA group had experienced recurrence (local tumour progression) at 2 years (12% vs. 6%; RR 1.62, 95% CI 0.66 to

TABLE 2 Number of RCTs making each comparison



RESULTS

TABLE 3 Risk of bias assessment results (RCTs)

Trial	ROB arising from the randomisation process	ROB due to deviations from the intended intervention	ROB due to missing outcome data	ROB in measurement of the outcome	ROB in selection of the reported result	Overall judgement of ROB
Abdelaziz, 2014 ⁶⁴	High	Low	Low	Low	Low	High
Aikata, 2006 (abstract) ⁴³	Some concerns	High	High	Low	Low	High
Azab, 2011 ⁶⁵	Some concerns	Low	Low	Low	Low	Some concerns
Bian, 2014 ⁷⁸	Some concerns	Low	Low	Low	Low	Some concerns
Brunello, 2008 ⁴⁴	Low	Low	Low	Low	Low	Low
Chen, 2005 ⁶⁷	Some concerns	Low	Low	Low	Low	Some concerns
Chen, 2005 ⁶⁶	Some concerns	Low	High	Low	Low	High
Chen, 2006 ⁶⁸	Low	High	Low	Low	Low	High
Chen, 2014 ⁴⁵	Low	Low	Low	Low	Low	Low
Fang, 2014 ⁴⁶	Some concerns	Low	Low	Low	Low	Some concerns
Ferrari, 2007 ⁷⁷	Some concerns	Low	Low	Low	Low	Some concerns
Gan, 2004 ⁴⁷	Some concerns	Low	High	Low	Low	High
Giorgio, 2011 ⁴⁸	Low	High	High	Low	Low	High
Huang, 2005 ⁴⁹	High	High	High	Low	Low	High
Huang, 2010 ⁶⁹	Low	Low	High	Low	Low	High
Huo, 2003 ⁷⁰	High	Low	High	Low	Low	High
Izumi, 2019 (abstract) ⁵⁰	Some concerns	High	High	Low	Some concerns	High
Kim, 2020 ⁵¹	Some concerns	Low	Low	Low	Low	Some concerns
Koda, 2001 ⁵²	Low	Low	Low	Low	Low	Low
Lencioni, 2003 ⁷¹	Low	Low	Low	Low	Low	Low
Lin, 2004 ⁵⁹	Low	Low	Low	Low	Low	Low
Lin, 2005 ⁵³	Some concerns	Low	Low	Low	Low	Some concerns
Liu, 2016 ⁷²	Some concerns	Low	Low	Low	Low	Some concerns
Mizuki, 2010 ⁶⁰	Low	Some concerns	Some concerns	Low	Low	Some concerns
Ng, 2017 ⁷⁹	Low	Low	Low	Low	Low	Low
Orlacchio, 2014 ⁶¹	Some concerns	Low	Some concerns	Low	Low	Some concerns

TABLE 3 Risk of bias assessment results (RCTs) (continued)

Trial	ROB arising from the randomisation process	ROB due to deviations from the intended intervention	ROB due to missing outcome data	ROB in measurement of the outcome	ROB in selection of the reported result	Overall judgement of ROB
Peng, 2012 ⁷⁴	Low	Low	Low	Low	Low	Low
Shibata, 2002 ⁶²	Low	Low	Some concerns	Low	Low	Some concerns
Shibata, 2009 ⁵⁴	High	Low	Low	Low	Low	High
Shiina, 2005 ⁵⁵	Some concerns	Low	Low	Low	Low	Some concerns
Vietti Violi, 2018 ⁶³	Low	Some concerns	Low	Low	Low	Some concerns
Xia, 2020 ⁷⁵	Low	Low	Low	Low	Low	Low
Yan, 2016 ⁵⁶	High	Some concerns	Low	Low	Low	High
Zhang, 2007 ⁷⁶	Low	Low	Low	Low	Low	Low
Zou, 2017 ⁵⁷	Some concerns	Low	Low	Low	Low	Some concerns
Total	High: 5 Some concerns: 15 Low: 15	High: 5 Some concerns: 3 Low: 27	High: 8 Some concerns: 3 Low: 24	Low: 35	Some concerns: 1 Low: 34	High: 12 Some concerns: 14 Low: 9

3.94), but the median TTP was longer after RFA than after MWA (16 months vs. 12 months; HR 0.72, 95% CI 0.44 to 1.18).

There was a high rate of complete response or complete ablation of tumours in both the RFA and MWA arms in all three RCTs. A slightly higher proportion of HCC nodules showed complete response after RFA in one RCT (96% vs. 89%),⁶² whereas in the other two RCTs the rates were similar between treatment arms.

One RCT reported a higher rate of major complications with MWA than with RFA (RFA 3% vs. MWA 11%).⁶² Another RCT reported that grade IV AEs only occurred in the MWA arm (0 vs. 2%), but more grade III (3% vs. 0%) and grade I–II (11.5% vs. 5%) AEs occurred in the RFA arm.⁶³ The RCT at high RoB reported that there were no major complications in either group.⁶⁴

Radiofrequency ablation versus percutaneous ethanol injection

Seven RCTs compared RFA with PEI ($n = 1061$ patients in six RCTs; the other RCT included 48 tumours). Three RCTs had a low RoB,^{44,59,71} three were judged to have some concerns^{53,55,65} and one had a high RoB.⁴⁸ One RCT included two different PEI arms with either a low dose or a high dose of PEI.⁵⁹ One RCT compared RFA versus PEI versus RFA in combination with PEI; the results of the combined RFA + PEI group are reported in the relevant sections below.⁶⁵ One RCT included patients with tumours ≤ 5 cm, but a large proportion had tumours ≤ 3 cm.⁷¹

Six of the seven RCTs reported OS (see [Table 4](#)).^{44,48,53,55,59,71} OS was better after treatment with RFA in four of the RCTs, which were at low RoB^{59,71} or had some concerns.^{53,55} OS was similar between groups in one high-quality RCT⁴⁴ and one low-quality RCT.⁴⁸

TABLE 4 Radiofrequency ablation vs. PEI – OS

	RFA	PEI	High-dose PEI	Study
1 year	95%	95%	-	Giorgio, 2011
	100%	96%	-	Lencioni, 2003
	1–2 cm: 96% / 2.1–3 cm: 89%	1–2 cm: 94% / 2.1–3 cm: 84%	1–2 cm: 93% / 2.1–3 cm: 83%	Lin, 2004
	93%	88%	-	Lin, 2005
2 years	90%	83%	-	Giorgio, 2011
	98%	88%	-	Lencioni, 2003
	1–2 cm: 84% / 2.1–3 cm: 78%	1–2 cm: 78% / 2.1–3 cm: 70%	1–2 cm: 80% / 2.1–3 cm: 71%	Lin, 2004
	81%	66%	-	Lin, 2005
3 years	26 deaths/70 patients	28 deaths/69 patients	-	Brunello, 2008
	83%	78%	-	Giorgio, 2011
	1–2 cm: 78% / 2.1–3 cm: 73%	1–2 cm: 70% / 2.1–3 cm: 62%	1–2 cm: 72% / 2.1–3 cm: 64%	Lin, 2004
	74%	51%	-	Lin, 2005
4 years	73%	70%	-	Giorgio, 2011
	74%	57%	-	Shiina, 2005
5 years	70%	68%	-	Giorgio, 2011

Event-free survival (survival free of local recurrence, new HCC and extrahepatic metastases) was also higher after RFA than after PEI in one high-quality RCT (2-year rate: 64% vs. 43%).⁷¹ Two RCTs (one high quality,⁵⁹ one with some concerns⁵³) reported that cancer-free survival was higher after RFA than after PEI at 1, 2 and 3 years [e.g. 3-year rate (tumours 2.1–3 cm): RFA 40% vs. low-dose PEI 30% vs. high-dose PEI 32%⁵⁹].

Five RCTs reported recurrence^{44,48,53,55,71} or local tumour progression.⁵⁹ The outcome measures reported differed between RCTs (e.g. distant intrahepatic recurrence,⁴⁴ local recurrence,^{48,71} etc). In the five better-quality RCTs (low RoB or some concerns), recurrence or local tumour progression occurred in more patients in the groups that received PEI,^{44,53,55,59,71} although the difference was only small in one RCT (distant intrahepatic recurrence: RFA 32/70 vs. PEI 35/69⁴⁴). One of these RCTs reported results by tumour size. Local tumour progression was similar between groups for smaller tumours (1–2 cm diameter) (3-year rate: RFA 9% vs. low-dose PEI 13% vs. high-dose PEI 12%), but it occurred in more patients with larger tumours (2.1–3 cm) after PEI treatment (RFA 18% vs. low-dose PEI 37% vs. high-dose PEI 33%).⁵⁹ In one low-quality RCT, the rate of local recurrence was similar between the two arms (5-year rate: RFA 11.7% vs. PEI 12.8%).⁴⁸

Four RCTs reported a higher proportion of patients achieving complete response or complete ablation with RFA treatment than with PEI treatment.^{44,53,65,71}

Findings on AEs were mixed, with some RCTs reporting worse AEs after RFA^{53,55,59,71} and others reporting similar rates between treatment groups.^{44,48} One high-quality RCT⁴⁴ and one low-quality RCT⁴⁸ reported a similar rate of major complications in each arm (RFA 2/70 vs. PEI 2/69;⁴⁴ RFA 0.9% vs. PEI 1.9%⁴⁸). The rate of treatment-emergent AEs was also similar in the high-quality RCT (RFA 14.3% vs. PEI 17.4%).⁴⁴ In two RCTs, serious AEs were uncommon but only occurred in the RFA group (1.9% vs. 0;⁵⁹ 4.8% vs. 0⁵³). AEs were also worse in the RFA group in the other two RCTs (RFA 32 vs. PEI 19 events;⁷¹ RFA 5.1% vs. PEI 2.6% grade ≥ III events⁵⁵). One RCT reported only that there were no mortalities related to either treatment.⁶⁵

Five RCTs reported economic outcomes.^{44,48,53,55,59} Two RCTs reported the direct medical costs of the procedures (see [Appendix 4](#) for details).^{44,48} Three RCTs reported average length of hospital stay, which was considerably longer for patients who received RFA in two RCTs (RFA 4.2 days vs. PEI 1.7 days;⁵³ RFA 4.4 days vs. low-dose PEI 1.6 days vs. high-dose PEI 2.1 days⁵⁹), but considerably longer for patients who received PEI in one RCT (RFA 10.8 days vs. PEI 26.1 days⁵⁵).

Radiofrequency ablation versus percutaneous acid injection

Only one RCT compared RFA with PAI, and it was judged to have some RoB concerns ($n = 187$ patients).⁵³ OS was better in the RFA arm than the PAI arm (3-year survival: 74% vs. 53%; 10/62 deaths vs. 15/63 deaths). Cancer-free survival (3-year rate: 43% vs. 23%) and recurrence (3-year rate: 14% vs. 31%; 8 vs. 17 local recurrence events) were also better after treatment with RFA. Complete response was achieved in a similar proportion of tumours in each group (RFA 96.1% vs. PAI 92.4%). However, three serious AEs occurred in the RFA group (4.8% of patients) and none in the PAI group. Mean length of hospital stay was longer for patients who received RFA than for those receiving PAI (4.2 days vs. 2.2 days).

Radiofrequency ablation versus laser ablation

Three RCTs compared RFA with laser ablation, with all three assessed as having some RoB concerns ($n = 132$ patients).^{57,61,77} One RCT included patients with tumours ≤ 4 cm, but the mean tumour size was 2.4 cm.⁶¹ One RCT included a subgroup of patients with tumours ≤ 2.5 cm.⁷⁷

Only one of the RCTs reported survival or progression outcomes.⁶¹ There were no deaths in either treatment group, but PFS (1-year rate: RFA 86% vs. laser ablation 54%) and local disease progression (2/15 patients vs. 6/15 patients) were better in the RFA group than the laser ablation group.

Two RCTs reported complete response or complete ablation. In one RCT the proportion of tumours with complete ablation was higher in the RFA arm after both one procedure (86.7% vs. 66.7% of nodules) and two procedures (93% vs. 87%).⁶¹ In the other RCT the complete response rate was similar between arms (RFA 92.3% vs. laser ablation 88.6%).⁵⁷

One RCT measured patient satisfaction, using a self-made satisfaction questionnaire that included intraoperative discomfort, postoperative therapy effects, adverse reactions and physical recovery.⁵⁷ There was greater satisfaction with the laser ablation treatment than with RFA [great satisfaction (score 61–100 out of 100): RFA 64.1% vs. laser ablation 85.7%]. 30.8% of patients were dissatisfied (score < 60) after RFA, compared with just 5.7% of patients who received laser ablation.

All three RCTs reported AE results. One reported considerably more AEs (intra- or post-procedural) in patients who received RFA (93.3% vs. 13.3%), although there were no major complications in either arm.⁶¹ In one RCT, postoperative rates of fever, nausea, vomiting, diarrhoea, abdominal pain and skin rash were similar between the two treatments.⁵⁷ The other RCT reported no major or minor complications during the procedures in either group.⁷⁷

Radiofrequency ablation versus resection

Seven completed RCTs compared RFA with surgical resection ($n = 912$ patients).^{46,50,58,67,69,75,79} One ongoing RCT was also identified.⁸⁰ One RCT did not report any data for the relevant subgroup (HCC ≤ 2 cm; the full population included patients with tumours < 4 cm, and the proportion with tumours ≤ 3 cm was not stated) and so RoB was not assessed.⁵⁸ Another RCT, which was judged to have some RoB concerns, did not report any relevant data for the ≤ 3 cm subgroup other than a KM curve.⁶⁷ Of the remaining RCTs, two were judged to have low RoB,^{75,79} two had high RoB^{50,69} and one had some concerns.⁴⁶ One of the RCTs recruited patients with recurrent HCC.⁷⁵

Four RCTs reported OS,^{46,69,75,79} with mixed findings. In one high-quality RCT⁷⁹ and one low-quality RCT,⁶⁹ OS at 1, 3 and 5 years was better after surgical resection [5-year rate: RFA 69% vs. resection 76%;⁷⁹

5-year rate: RFA 61.4%/45.2% (solitary tumours/multifocal tumours) vs. resection 82.2%/69.2%⁶⁹]. However, the RCT with some RoB concerns reported slightly better OS at 1, 2 and 3 years in the group that received RFA (3-year rate: 82.5% vs. 77.5%).⁴⁶ The high-quality RCT of recurrent HCC found that the two treatments were similar [HR (RFA vs. resection) 1.05, 95% CI 0.67 to 1.65].⁷⁵

There were also mixed findings from the four RCTs that measured disease- or recurrence-free survival.^{46,50,75,79} Recurrence-free survival was similar between treatment groups in one low-quality RCT (3-year rate: RFA 47.7% vs. surgery 49.8%; HR 0.96)⁵⁰ and the high-quality RCT of recurrent HCC patients (repeat-recurrence-free survival: HR 1.07, 95% CI 0.71 to 1.6⁷⁵). The other high-quality RCT reported better disease-free survival after resection (5-year rate: 46% vs. 52%).⁷⁹ However, the disease-free survival rate was higher for patients who received RFA in the RCT with some RoB concerns (3-year rate: 55.4% vs. 41.3%).⁴⁶

Only the RCT with some RoB concerns reported recurrence of HCC, with a similar proportion of patients experiencing recurrence in the RFA group as in the hepatectomy group (22/60 vs. 21/60).⁴⁶ This was also the only RCT to report on response, with a similar rate of complete tumour treatment after RFA as after surgery (57/60 vs. 58/60).

There were limited data on AEs reported. One RCT reported that postoperative complications (RFA 2/60 vs. resection 17/60), major complications (1/60 vs. 14/60) and serious pain requiring analgesia (3/60 vs. 43/60) were all more common after surgery than after RFA.⁴⁶ Four RCTs reported that there was no mortality related to the treatment or within the hospital admission period in either arm.^{46,50,58,69}

Two RCTs reported average length of hospital stay, which was shorter for patients receiving RFA than resection in both RCTs (4 days vs. 7 days;⁷⁹ 4.3 days vs. 11.8 days⁴⁶). Length of intensive care unit (ICU) stay was also shorter after RFA (0 days vs. 6 days).⁴⁶

Radiofrequency ablation versus proton beam radiotherapy

One RCT of patients with recurrent or residual tumours compared RFA with proton beam radiotherapy and was judged to have some RoB concerns ($n = 144$ patients).⁵¹ OS was similar between the treatment groups (4-year rate: RFA 77.0% vs. proton beam radiotherapy 75.4%; HR at 2 years 1.07, 95% CI 0.58 to 1.98). PFS was also similar between treatment groups, with a median of 13.4 months after proton beam radiotherapy and 13.7 months after RFA. The rate of PFS was the same at 2 years (31.9% vs. 31.9%; HR 0.99, 95% CI 0.70 to 1.41), slightly higher after proton beam therapy at 3 years (17.9% vs. 26.3%), with a smaller difference between groups at 4 years (12.6% vs. 18.7%). The total number of progression events was greater in the RFA group (62/72 vs. 56/72). There were nine (16%) AEs at grade III or above in the RFA group compared with none in the proton beam radiotherapy group.

Radiofrequency ablation versus radiofrequency ablation + transarterial chemoembolisation

Three RCTs compared RFA alone versus RFA combined with TACE ($n = 220$ patients).^{43,54,74} One included patients with recurrent HCC and was judged to be at low RoB.⁷⁴ The other two RCTs were at high RoB,^{43,54} although one was only reported as a conference abstract, with very limited reporting of methods.⁴³

All three RCTs reported OS. In the high-quality RCT of patients with recurrent HCC, OS was better at 1 and 3 years after RFA combined with TACE (3-year rate: RFA 60% vs. RFA + TACE 70%), but was the same in both arms at 5 years (50% vs. 50%).⁷⁴ Similarly, in one low-quality RCT, survival was better in the combined treatment arm at 2 years (88.8% vs. 100%) but similar by 3 and 4 years (4-year rate: RFA 74% vs. RFA + TACE 72.7%).⁵⁴ Overall the total number of deaths was similar between treatment arms in this RCT (5/46 vs. 6/43). However, in the other low-quality RCT, OS was better after treatment with RFA combined with TACE at 2 and 3 years (3-year rate: 73.9% vs. 84%), but similar at 1 year (RFA: 100% vs. RFA + TACE: 95.2%).⁴³

Recurrence-free survival was higher after RFA combined with TACE in the high-quality RCT of patients with recurrent HCC (5-year rate: 26% vs. 48%).⁷⁴ One low-quality RCT reported higher local PFS in the combined treatment group at 2 years (74.1% vs. 81.1%) but a higher rate in the RFA-alone group at 3 and 4 years (4-year rate: 61.7% vs. 55.8%).⁵⁴ However, event-free survival (time from the beginning of treatment to last follow-up CT examination, local tumour progression, new lesions in the liver, distant metastasis, or death) was better after the combined treatment at 2, 3 and 4 years (4-year rate: 29.7% vs. 36.6%).

The two low-quality RCTs^{43,54} both reported a similar rate of local tumour progression in both treatment groups (3-year rate: 8.7% vs. 9.5%;⁴³ 3-year rate: 14.4% vs. 17.6%⁵⁴). Only one RCT reported response, with 100% of patients achieving complete response in both arms.⁵⁴ The rate of major complications was the same between treatment groups in the two low-quality RCTs.^{43,54}

Radiofrequency ablation versus radiofrequency ablation + percutaneous ethanol injection

Three RCTs compared RFA treatment alone versus RFA combined with PEI ($n \geq 147$ patients).^{65,66,76} One was judged to have a low RoB,⁷⁶ one some concerns⁶⁵ and one a high RoB.⁶⁶

Overall survival was reported by two RCTs (one high quality and one low quality).^{66,76} Both reported higher OS after treatment with RFA combined with PEI than after RFA alone (5-year rate: RFA 50.2% vs. RFA + PEI 55.3%;⁷⁶ 2-year rate: RFA 64.9% vs. RFA + PEI 79.0%⁶⁶). In the low-quality RCT there was also more HCC recurrence after RFA treatment alone (2-year rate: 34.1% vs. 20.9%).⁶⁶

Two RCTs reported data on response.^{65,76} In both RCTs the rate of complete ablation was higher after one treatment of RFA combined with PEI than after one session of RFA alone. After two sessions of treatment (if necessary), the rate was similar between groups in the high-quality RCT⁷⁶ but remained higher in the RFA + PEI group in the RCT with some concerns (87.5% vs. 100%⁶⁵).

Very limited data on AEs were reported. The two lower-quality RCTs reported that there were no serious AEs⁶⁶ or mortalities related to treatment⁶⁵ in either arm.

Radiofrequency ablation versus radiofrequency ablation + iodine-131 metuximab

One RCT with some RoB concerns compared RFA alone with RFA and iodine-131 metuximab but reported limited data for the relevant subgroup of patients with tumours < 3cm ($n = 78$ patients).⁷⁸ There was less recurrence in the group that received RFA combined with iodine-131 metuximab (HR 0.46, 95% CI 0.21 to 1.01). There were no serious AEs or treatment-related deaths in either group.

Radiofrequency ablation versus radiofrequency ablation + iodine-125

One RCT with a low RoB compared RFA alone versus RFA and iodine-125 ($n = 136$ patients).⁴⁵ OS was better after the combined treatment than after RFA alone (RFA: mean 70.8 months vs. RFA + iodine-125: 95.8 months; 36/68 vs. 23/68 deaths; HR 0.502, 95% CI 0.313 to 0.806). There was also less recurrence in patients who received the combined treatment (39/68 patients vs. 27/68 patients; HR 0.508, 95% CI 0.317 to 0.815; mean time to recurrence 66.8 vs. 93 months). Complete ablation was achieved in more patients with one treatment of RFA + iodine-125 than with one treatment of RFA alone, although after two treatments all participants in both arms had achieved complete ablation. There were more AEs at grade III or above after RFA combined treatment than after RFA alone (11 vs. 15 events; patient numbers not reported), although there were no procedure-related mortalities and no iodine-125 seed migration from the liver to the heart or other organs.

Radiofrequency ablation versus radiofrequency ablation + chemotherapy

One RCT with a high RoB compared RFA alone versus RFA combined with chemotherapy ($n = 38$ patients).⁴⁷ Recurrence was higher in the RFA group than in the RFA + chemotherapy group at 1 year (50% vs. 27%). There were no serious AEs in either group.

Radiofrequency ablation + transarterial chemoembolisation versus resection

One RCT compared RFA combined with TACE versus partial hepatectomy, and it was judged to have some RoB concerns ($n = 135$ patients).⁷² The paper did not report any relevant efficacy data for the subgroup of patients with tumours ≤ 3 cm. However, KM curves for OS and recurrence showed that hepatectomy was more effective than RFA + TACE. There was no 30- or 90-day mortality in either arm.

Percutaneous ethanol injection versus percutaneous acid injection

One RCT compared PEI with PAI and was judged to have some RoB concerns ($n = 187$ patients).⁵³ OS (3-year rate: PEI 51% vs. PAI 53%; number of deaths 17/62 vs. 15/63), cancer-free survival (3-year rate: 21% vs. 23%), recurrence (3-year rate 34% vs. 31%; number of events 19/55 vs. 17/58) and complete response (88.1% vs. 92.4%) were all similar between arms. No serious AEs were reported in either arm. The average length of hospital stay was also similar between PEI and PAI groups (1.7 days vs. 2.2 days).

Percutaneous ethanol injection versus resection

One RCT with high RoB compared PEI with resection ($n = 82$ patients).⁴⁹ There was a higher rate of OS in the PEI arm at 2 and 3 years (3-year rate 96.7% vs. 88.1%) but by 4 years it was similar (92.1% vs. 88.1%) and at 5 years it was higher in the resection arm (46.0% vs. 81.8%). PFS was higher after resection at 1, 2, 3 and 4 years (4-year rate: 44.6% vs. 56.2%) but was similar by 5 years (44.6% vs. 48.2%). There was more recurrence of HCC in the PEI group (18/40 vs. 15/42 patients). Three patients had adverse effects after PEI, but for the resection arm the paper only reported that there were no significant complications.

Percutaneous ethanol injection versus radiofrequency ablation + percutaneous ethanol injection

One RCT compared PEI alone versus RFA combined with PEI and was judged to have some RoB concerns ($n = 48$ tumours).⁶⁵ The only relevant data reported were on complete response. After both one and two treatment sessions, no tumours in the PEI arm had been completely ablated, compared with 93.8% and 100%, respectively, in the RFA + PEI arm. Only 81.25% of tumours in the PEI group achieved complete ablation after all sessions. There were no mortalities related to either treatment.

Percutaneous ethanol injection versus percutaneous ethanol injection + transarterial chemoembolisation

Two RCTs compared PEI alone with PEI combined with TACE ($n = 82$ patients). One had a low RoB⁵² and one had some bias concerns.⁶⁰ The two RCTs differed in their results. The high-quality RCT reported higher OS rates in the PEI + TACE arm at 1, 2 and 3 years (3-year rate: PEI 65.9% vs. PEI + TACE 80.8%), although it was similar between groups at 5 years (37.7% vs. 40.4%).⁵² Rates of local residual disease (5-year rate 39.3% vs. 19.3%) and new nodular recurrence (5-year rate 100% vs. 50.2%) were lower after the combined PEI and TACE treatment. However, the lower-quality RCT reported a longer mean OS (57.2 vs. 42.4 months) and fewer deaths (6/14 vs. 8/13) in the PEI-alone arm.⁶⁰ Recurrence was also higher in the combined treatment arm (71.4% vs. 84.6%). However, the mean length of cancer-free survival was longer after PEI + TACE (16.7 vs. 22.9 months).⁶⁰

The high-quality RCT reported two major complications (among 26 patients) in the combined treatment group and none in the PEI-alone group. Fever, continuous abdominal pain and transient increases in C-reactive protein were common AEs in both treatment groups.⁵² The other RCT reported that no serious adverse effects or complications were related to either treatment.⁶⁰

Percutaneous acid injection versus percutaneous acid injection + transarterial chemoembolisation

One RCT with a high RoB compared PAI versus sequential TACE and PAI treatment ($n = 55$ patients).⁷⁰ The rate of OS was 100% in both groups at 1 year, but at 3 years it was higher in the group that had received the combined treatment (49% vs. 73%). Data on cancer-free survival were not reported for the

subgroup of patients with tumours ≤ 3 cm (other than that there were no significant differences between treatment groups). There were no serious complications necessitating intensive care in either group.

Percutaneous local ablative therapy versus resection

One RCT with high RoB compared percutaneous local ablative therapy (RFA, followed by RFA/PEI for any residual tumour, and TACE if residual tumour still remained) with partial hepatectomy ($n = 79$ patients).⁶⁸ The paper did not report any relevant data for the subgroup of patients with tumours ≤ 3 cm, other than a KM curve. However, it reported that there were no significant differences in OS or disease-free survival between the two treatment groups for the ≤ 3 cm subgroup.

Microwave ablation + sorafenib versus resection

One RCT with a high RoB compared treatment with MWA combined with sorafenib versus surgical resection ($n = 120$ patients).⁵⁶ Rates of OS and tumour-free survival were similar between the two treatments at 1, 3 and 5 years, but mean OS was longer in the MWA + sorafenib group than the resection group (64.6 vs. 51.2 months). However, at 5 years there had been more recurrence of HCC in the MWA + sorafenib group (38.3% vs. 18.3%). Pain, fever, abdominal bleeding and infection were all experienced by considerably more patients in the resection arm than the MWA + sorafenib arm (pain: MWA + sorafenib 23.3% vs. resection 63.3%; fever: 25% vs. 48.3%; abdominal bleeding: 3.3% vs. 11%; infection: 1.7% vs. 30%).

Ongoing trials

The electronic searches for RCTs undertaken on 3 February 2021 identified four potentially relevant ongoing RCTs: the published protocol by Zhu *et al.*⁸⁰ and three clinical trial register records, for which no further information was available. The searches for studies in progress and unpublished research, undertaken on 27 April 2021, identified 121 records in ClinicalTrials.Gov and 64 records in the European Union Clinical Trials Register; there was only one further potentially relevant ongoing RCT, after deduplication between databases. Further details are presented in [Table 5](#).

TABLE 5 Table of potentially relevant ongoing RCTs

Study	Further details
Ongoing studies identified from searches of bibliographic databases for RCTs	
Zhu, 2021 ⁸⁰	Published protocol for a single centre (The Ninth People's Hospital of Chongqing, China) RCT comparing RFA vs. laparoscopic hepatectomy for small HCC (three or fewer tumours ≤ 3 cm in diameter).
ClinicalTrials.gov: NCT04727307	Clinical trial register record describing a multicentre RCT comparing atezolizumab + bevacizumab combined with RFA vs. RFA alone for small HCC (one to three nodules < 3 cm). Sponsor: University Hospital, Montpellier, France. Actual study start date: 26 January 2021. Estimated primary completion date: January 2025. Estimated study completion date: July 2027.
ClinicalTrials.gov: NCT03790059	Clinical trial register record describing a multicentre RCT comparing RFA combined with recombinant human adenovirus Type 5 (H101) injection vs. RFA alone for small HCC (single lesion ≤ 3 cm in diameter). Sponsor: Southwest Hospital, China. Study start date: October 2016. Estimated primary completion date: September 2020. Estimated study completion date: September 2020.
ClinicalTrials.gov: NCT04235660	Clinical trial register record describing a single-centre pilot RCT comparing Y90 radioembolisation vs. stereotactic body radiation therapy for solitary early-stage (≤ 3 cm) HCC. Sponsor: Indiana University. Actual study start date: 22 July 2020. Estimated primary completion date: May 2024. Estimated study completion date: May 2024.
Studies identified from searches of ClinicalTrials.Gov and the European Union Clinical Trials Register for ongoing RCTs	
ClinicalTrials.gov: NCT04663035	Clinical trial register record describing a single-centre RCT comparing ablation followed by tislelizumab (immunotherapy) vs. ablation alone for early recurrent HCC. Sponsor: Sun Yat-sen University. Actual study start date: 21 December 2020. Estimated primary completion date: December 2023. Estimated study completion date: December 2025.

Network meta-analysis results

Randomised controlled trials assessing the clinical effectiveness of ablative and non-surgical therapies for patients with early or very early HCC have been discussed and summarised in [Systematic review of RCTs](#). Four NMA models were produced, for the outcomes OS, PFS and overall recurrence and local recurrence.

Of the 37 RCTs described in [Systematic review of RCTs](#), six did not report any relevant data for the subgroup of patients with tumours ≤ 3 cm that could be included in the NMA^{57,58,62,64,65,78} and one was ongoing, so no results were available.⁸⁰ A further three RCTs of patients with recurrent/residual HCC were not included.^{51,74,75} Not all the resulting 27 RCTs included in the NMAs reported data for all four NMA outcomes; which RCTs reported for each outcome, as well as the type of data reported, are presented in [Report Supplementary Material 3](#).

Due to the small number of RCTs in each network, there was little evidence to inform the between-study heterogeneity. The uniform (0,3) prior distribution was considered in exploratory analyses and found to be too influential on the results. The half-normal (0, 0.19²) was used instead, as it expresses the prior belief that 95% of trials will give HRs within a factor of 2 from the estimated mean HR.²⁸ Results estimated using the half-normal (0, 0.50²) prior distribution are also reported.

Results for checks on the proportional hazards assumption are presented in [Report Supplementary Material 2](#). Schoenfeld residuals⁸¹ were calculated for RCTs that reported the numbers at risk for the included KM curve. For RCTs that did not report the numbers at risk,^{46,77,82} the proportional hazards assumption was assessed by visual inspection of the KM curves. For two trials (Aikata *et al.*⁴³ and Izumi *et al.*⁵⁰) the proportional hazards assumption could not be tested as there were no KM curves available.

There were four RCTs for which the KM curves for OS crossed over,^{46,48,52,70} which suggests that there may be some concerns about the proportional hazards assumption; however, for all other RCTs there was no statistical evidence that the assumption was violated. The validity of the NMAs depends on the proportional hazards assumption being correct, and more complex models with non-proportional hazards could not be fitted due to limitations of the data. Therefore, results should be interpreted with caution.

Overall survival

Data

Of the 27 RCTs that reported relevant data, 16 were included in the NMA for OS. Eleven RCTs were excluded from the NMA: two^{47,50} did not report OS data, and eight^{49,56,59,60,66-68,71} reported data that would require strong assumptions to be made in order to calculate log-HRs required for the NMA; Orlicchio *et al.* (2014)⁶¹ was also not included in the NMA as both arms in the trial reported zero deaths. Further details about the inclusion/exclusion of studies and how the evidence reported in the studies was transformed to a form suitable for NMA are summarised in the [Report Supplementary Material 3](#).

The network diagram for OS is presented in [Figure 2](#). Fifteen two-arm trials and one three-arm trial provided evidence on 11 interventions. A summary of the data used for the NMA is provided in [Report Supplementary Material 4](#).

Model selection and consistency checking

Model fit parameters for the FE and RE models are presented in [Report Supplementary Material 5](#). All three models fitted the data well, but as the difference in the DICs between the FE and RE models was < 3 , the simpler FE model was chosen.

The 95% CrI for the RE model using the half-normal (0, 0.50²) prior was almost twice as wide as the 95% CrI for the model using half-normal (0, 0.19²), evidence that the priors for heterogeneity are

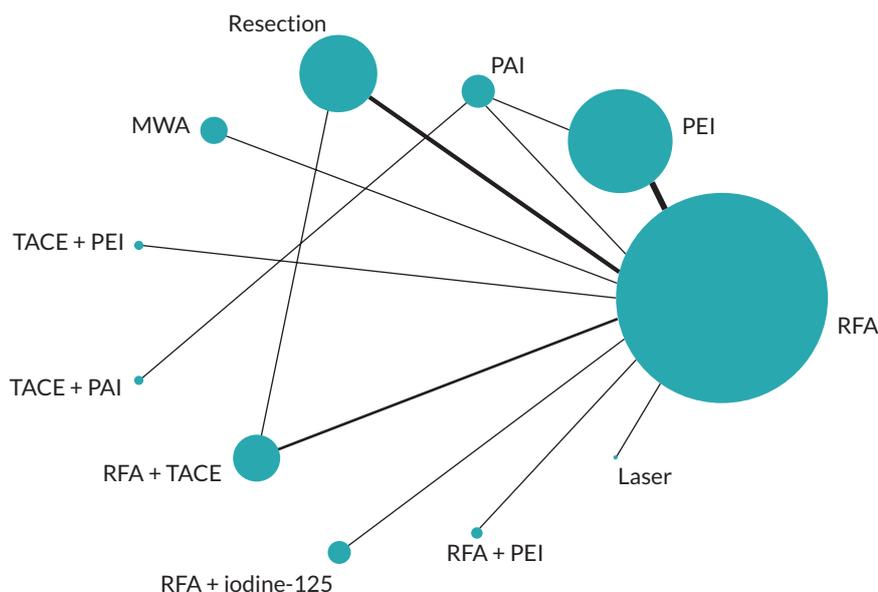


FIGURE 2 Network diagram for OS.

Treatment nodes in the network diagram are scaled proportional to the number of patients who receive a particular treatment. The widths of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison.

influential due to few studies being included for each comparison in the network. Plots for the prior and posterior distributions of the between-study heterogeneity for the RE models are presented in [Report Supplementary Material 5](#).

There was no evidence to suggest inconsistency in the network. Details of the inconsistency check and node-splitting results are presented in [Report Supplementary Material 5](#).

Model results

Hazard ratios for OS for all treatments compared with RFA are presented in [Figure 3](#).

There was evidence to suggest that PEI worsens OS compared with RFA, and that RFA + iodine-125 improves OS compared with RFA (see [Figure 3](#)). There was also evidence to suggest that PEI worsens OS compared with resection, and that RFA + iodine-125 improves survival compared with PEI, PAI, TACE + PAI, RFA + TACE, and laser. There was insufficient evidence to suggest a difference in OS for all other treatment comparisons.

Hazard ratios comparing all treatment groups against each other for FE and RE models are reported in [Report Supplementary Material 5](#). Results for RE models displayed more uncertainty than the FE model, where results estimated using the wider half-normal (0, 0.50²) prior were more uncertain compared with results estimated using a half-normal (0, 0.19²) prior.

The mean and median ranks for each treatment, with their corresponding 95% CrIs, are presented in [Table 6](#). RFA + iodine-125 had the highest probability of being ranked the best treatment. However, there was a high level of uncertainty in treatment rankings; all treatments apart from RFA + iodine-125 displayed very wide CrIs. In fact, MWA, RFA + PEI, and TACE + PEI had 95% CrIs that included all 11 potential treatment ranks.

The treatment rank plot for OS (see [Figure 4](#)) also shows that RFA + iodine-125 had the highest probability of being the best treatment; however, the uncertainty in treatment ranks is also evident, as the probability of all other treatment ranks is < 50%.

RESULTS

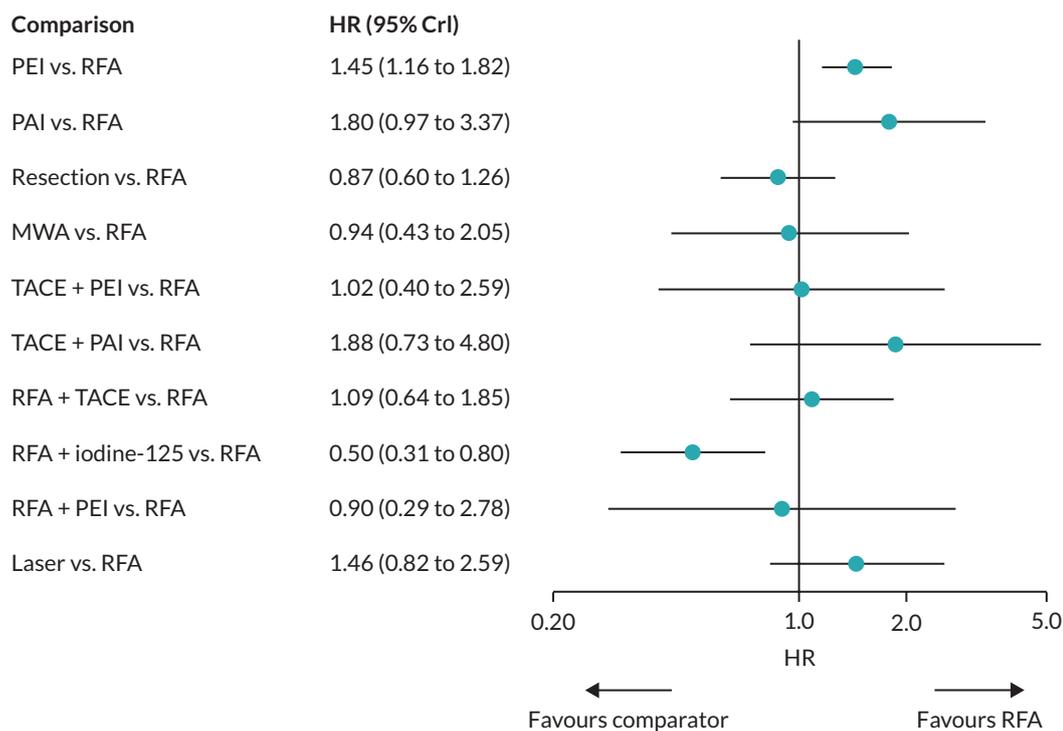


FIGURE 3 Plot of HRs for OS compared with RFA for the FE model. HRs < 1 favour the comparator treatment over RFA.

TABLE 6 Mean and median treatment ranks for the FE model, with corresponding 95% CrIs for OS, sorted by mean rank out of 11 treatments

Treatments	Mean rank	Median rank	95% CrI for the rank
RFA + iodine-125	1.42	1	(1.00 to 3.00)
Resection	3.84	4	(2.00 to 7.00)
MWA	4.81	4	(1.00 to 11.00)
RFA + PEI	4.82	4	(1.00 to 11.00)
RFA	4.98	5	(3.00 to 7.00)
TACE + PEI	5.42	5	(1.00 to 11.00)
RFA + TACE	5.90	6	(2.00 to 10.00)
Laser	8.07	8	(3.00 to 11.00)
PEI	8.28	8	(6.00 to 11.00)
TACE + PAI	9.11	10	(3.00 to 11.00)
PAI	9.34	10	(5.00 to 11.00)

Progression-free survival

Data

Of the 27 RCTs that reported relevant data, six were included in the NMA for PFS. Twenty-one RCTs were excluded from the NMA: 14^{43-45,47,48,52,55,66,67,69,70,72,76,77} did not report PFS data, and five^{49,56,59,60,68} reported data that would require strong assumptions to be made in order to calculate log-HRs required for the NMA; a further two^{61,63} were excluded as they only reported local disease-free survival/PFS. Details about the inclusion/exclusion of studies and how the evidence reported in the studies was transformed into a form suitable for NMA are summarised in [Report Supplementary Material 3](#).

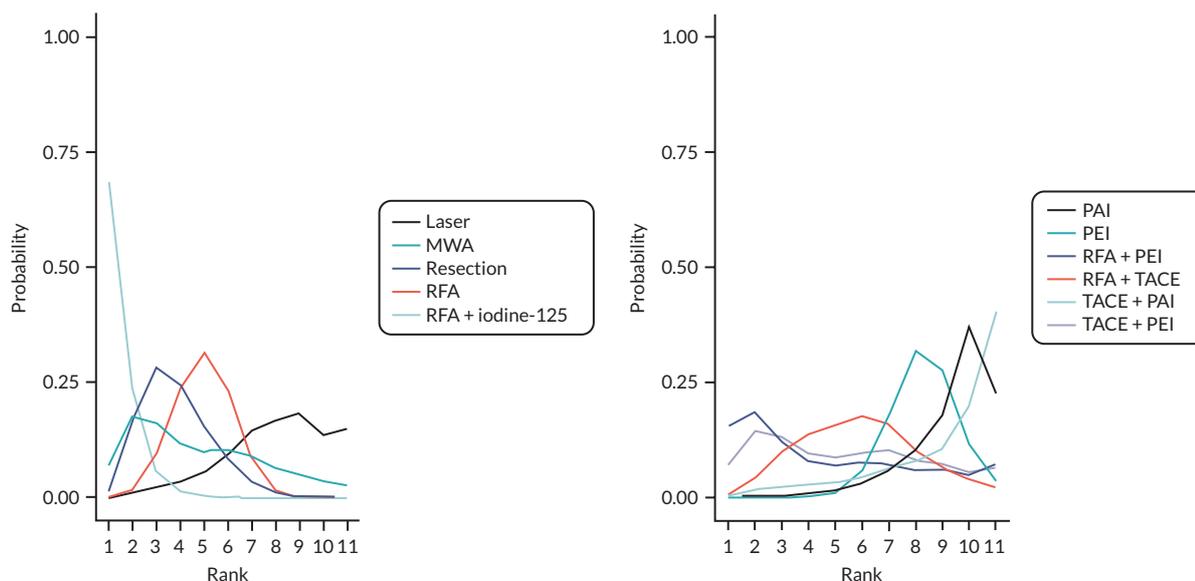


FIGURE 4 Rank plot for OS for the FE model.

The network diagram for PFS is presented in [Figure 5](#). Five two-arm trials and one three-arm trial provided evidence on six interventions. A summary of the data used for the NMA is provided in [Report Supplementary Material 4](#).

Model selection and consistency checking

Model fit parameters for the FE and RE models are presented in [Report Supplementary Material 5](#). All three models fit the data well, but as the difference in DICs between the fixed and RE models was < 3 , the simpler FE model was chosen.

The between-study heterogeneity was low for the two RE models; however, the 95% CrI for the model using the half-normal $(0, 0.50^2)$ prior was almost twice as wide as the 95% CrI for the model using the half-normal $(0, 0.19^2)$ prior, evidence that the priors for heterogeneity are influential due to few studies

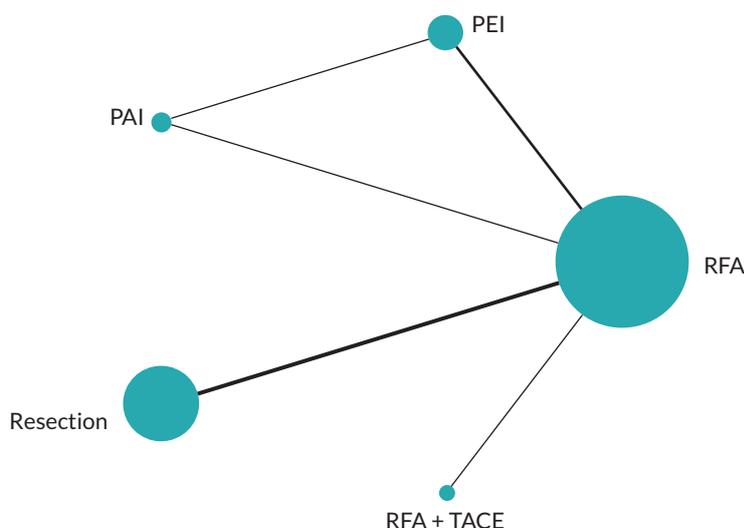


FIGURE 5 Network diagram for PFS.

Treatment nodes in the network diagram are scaled proportional to the number of patients who receive a particular treatment. The widths of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison.

RESULTS

being included in the network. Plots for the prior and posterior distributions of the between-study heterogeneity for the RE models are presented in [Report Supplementary Material 5](#).

There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons – the single loop is formed by a three-arm study.⁵³

Model results

Hazard ratios for PFS for all treatments compared with RFA are presented in [Figure 6](#).

There was evidence to suggest that PEI and PAI are associated with worse PFS compared with RFA (see [Figure 6](#)). There was insufficient evidence to suggest a difference in PFS for all other treatment comparisons.

Hazard ratios comparing all treatment groups against each other for FE and RE models are reported in [Report Supplementary Material 5](#). Results for RE models displayed more uncertainty compared with the FE model, where results estimated using the wider half-normal (0, 0.50²) prior were more uncertain compared with results estimated using a half-normal (0, 0.19²) prior.

The treatment rank plot for PFS is presented in [Figure 7](#), and the mean and median ranks for each treatment, with their corresponding 95% CrIs are presented in [Table 7](#). RFA + TACE had the highest probability to be ranked the best treatment. However, there was a high level of uncertainty in the treatment ranking – all treatments displayed wide CrIs for ranks.

Overall recurrence

Data

Of the 27 RCTs that reported relevant data, seven were included in the NMA for overall recurrence. Twenty RCTs were excluded from the NMA: 19^{43,48,50,52-54,59,61,63,66-72,76,77,79} did not report overall recurrence data, and one reported distant recurrence.⁴⁴ Details about the inclusion/exclusion of RCTs and how the evidence reported was transformed into a form suitable for NMA are summarised in [Report Supplementary Material 3](#).

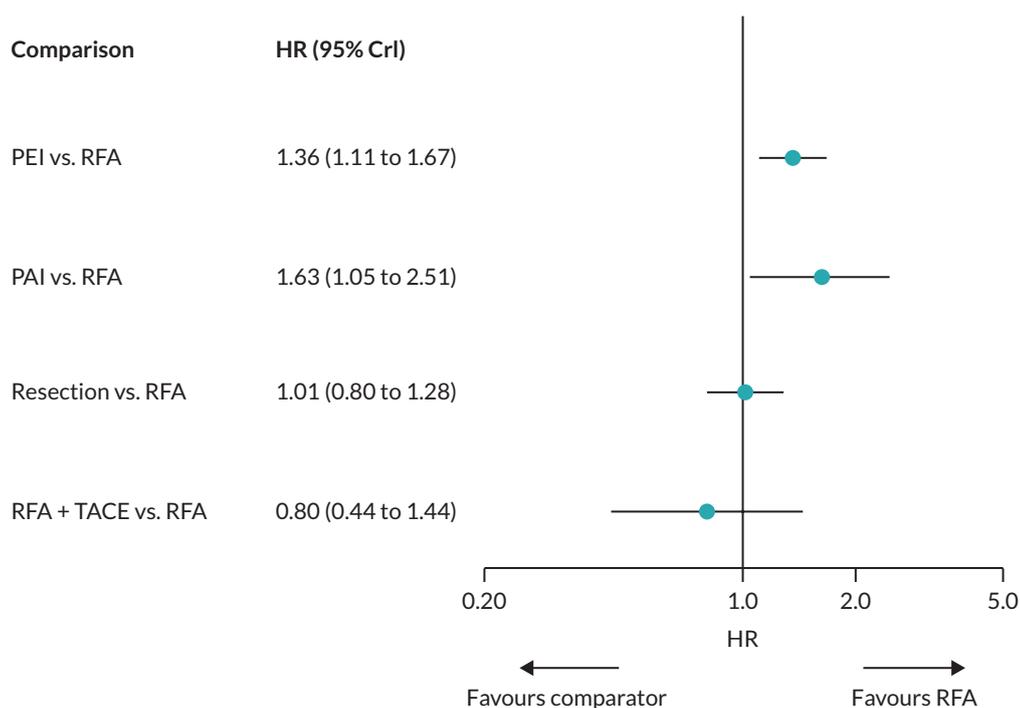


FIGURE 6 Plot of HRs for PFS compared with RFA for the FE model. HRs < 1 favour the comparator treatment over RFA.

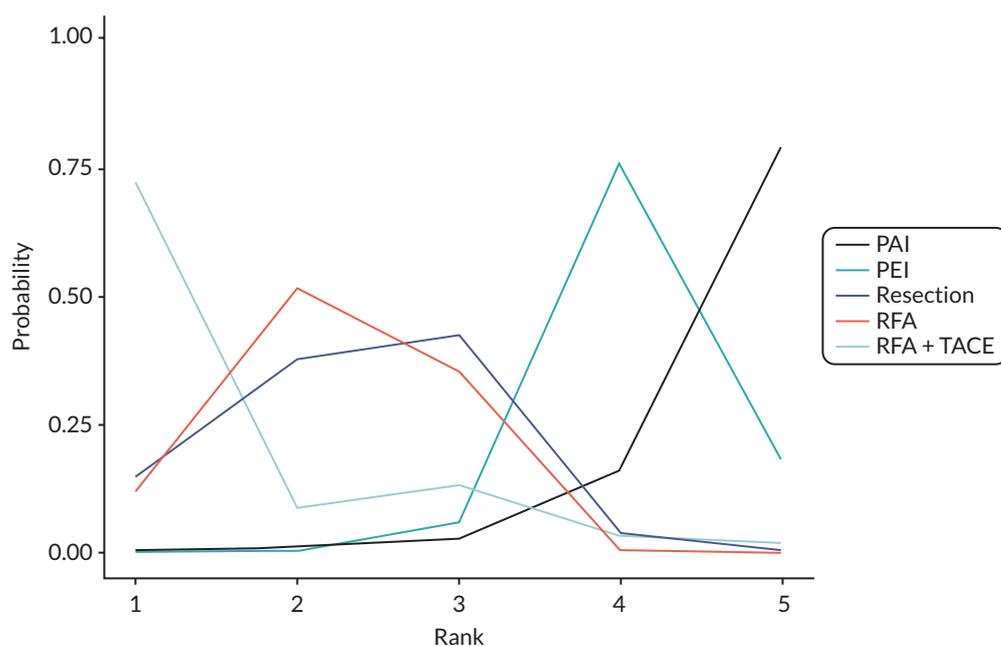


FIGURE 7 Rank plot for PFS for the FE model

TABLE 7 Mean and median ranks for the FE model, with the corresponding 95% CrIs for PFS, sorted by mean rank out of five treatments

Treatments	Mean rank	Median rank	95% CrI for the rank
RFA + TACE	1.53	1	(1.00 to 4.00)
RFA	2.24	2	(1.00 to 3.00)
Resection	2.38	2	(1.00 to 4.00)
PEI	4.12	4	(3.00 to 5.00)
PAI	4.73	5	(3.00 to 5.00)

The network diagram for overall recurrence is presented in [Figure 8](#). Seven two-arm RCTs provided evidence on seven interventions. A summary of the data used for the NMA is provided in [Report Supplementary Material 4](#).

Model selection and consistency checking

Model fit parameters for the FE and RE models are presented in [Report Supplementary Material 5](#). All three models fit the data well, but as the difference in DICs between the fixed and RE models was < 3 , the simpler FE model was chosen.

The between-study heterogeneity was low for the two RE models; however, the 95% CrI for the model using the half-normal (0, 0.50²) prior was almost twice as wide as the 95% CrI for the model using the half-normal (0, 0.19²) prior, evidence that the priors for heterogeneity are influential due to few studies being included in the network. Plots for the prior and posterior distributions of the between-study heterogeneity for the RE models are presented in [Report Supplementary Material 5](#).

There was no evidence to suggest inconsistency in the network. Details of the inconsistency check and node-splitting results are presented in [Report Supplementary Material 5](#).

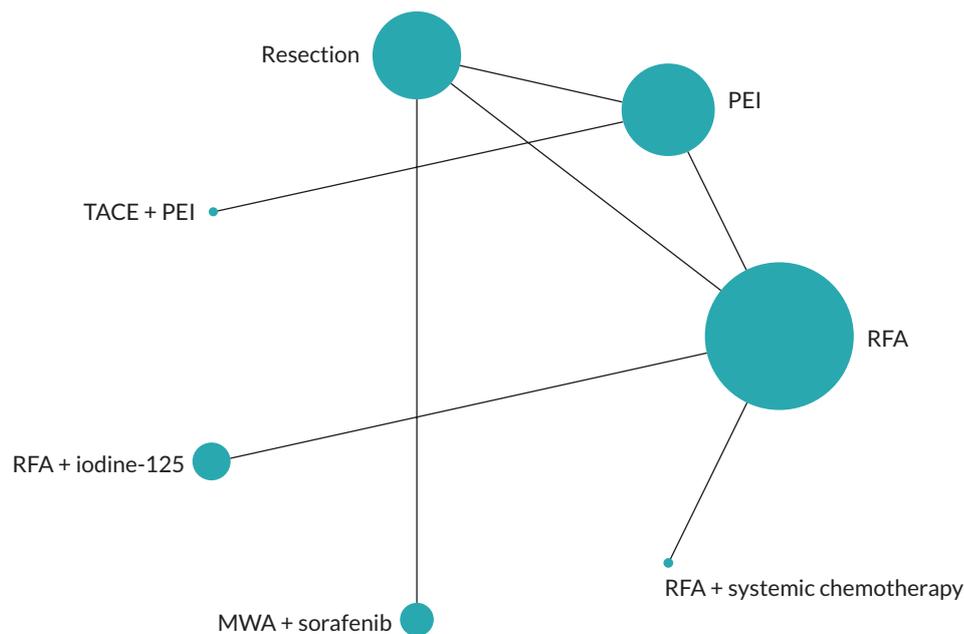


FIGURE 8 Network diagram for overall recurrence.

Treatment nodes in the network diagram are scaled proportional to the number of patients who receive a particular treatment. The widths of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison.

Model results

Relative risks for overall recurrence for all treatments compared with RFA are presented in [Figure 9](#).

There was evidence to suggest that PEI increases the risk of overall recurrence compared with RFA (see [Figure 9](#)), and that RFA + iodine-125 decreases the risk of overall recurrence compared with RFA. The 95% CrIs of these estimates are very close to the 'null' effect.

There was evidence to suggest that RFA + iodine-125 decreases the risk of overall recurrence compared with PEI and TACE + PEI.

There was evidence to suggest that MWA + sorafenib increases the risk of overall recurrence compared with resection, and that RFA + iodine-125 and RFA + systemic chemotherapy decrease the risk of overall recurrence compared with MWA + sorafenib. There was insufficient evidence to suggest a difference in overall recurrence for all other treatment comparisons.

Relative risks comparing all treatment groups against each other for FE and RE models are reported in [Report Supplementary Material 5](#). Alternative models using arm-level data gave similar results. Results for RE models displayed more uncertainty compared with the FE model, where results estimated using the wider half-normal (0, 0.50²) prior were more uncertain compared with results estimated using a half-normal (0, 0.19²) prior.

The treatment rank plot for overall recurrence is presented in [Figure 10](#), and the mean and median ranks for each treatment, with their corresponding 95% CrIs, are presented in [Table 8](#). RFA + systemic chemotherapy had the highest probability of being ranked the best. There was a high level of uncertainty in treatment rankings – all treatment ranks displayed wide CrIs.

Local recurrence

Data

Of the 27 RCTs that reported relevant data, 10 were included in the NMA for local recurrence.

Seventeen [44-47,49,50,55,56,60,67-70,72,76,77,79](#) did not report local recurrence data and were therefore excluded

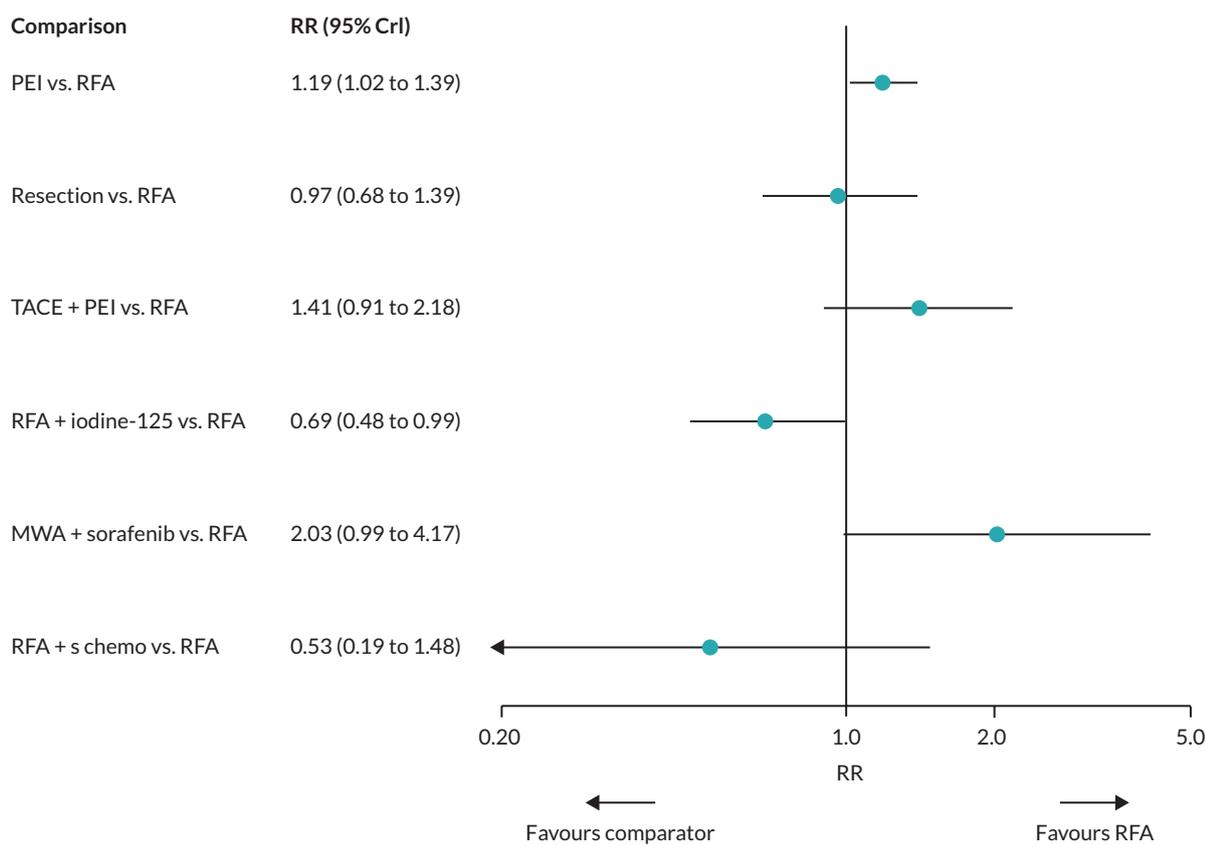


FIGURE 9 Plot of RRs for overall recurrence compared with RFA for the FE model. RRs < 1 favour the comparator treatment over RFA.

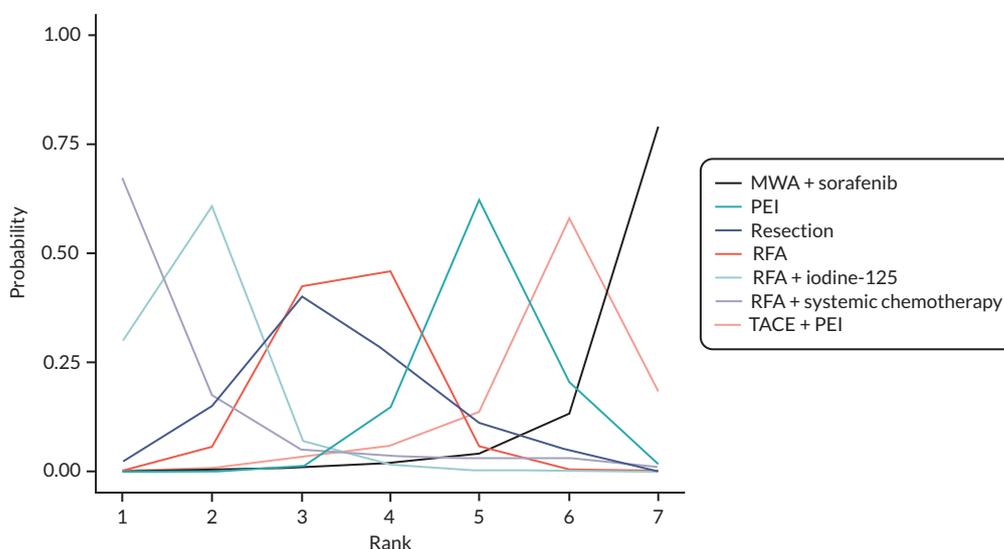


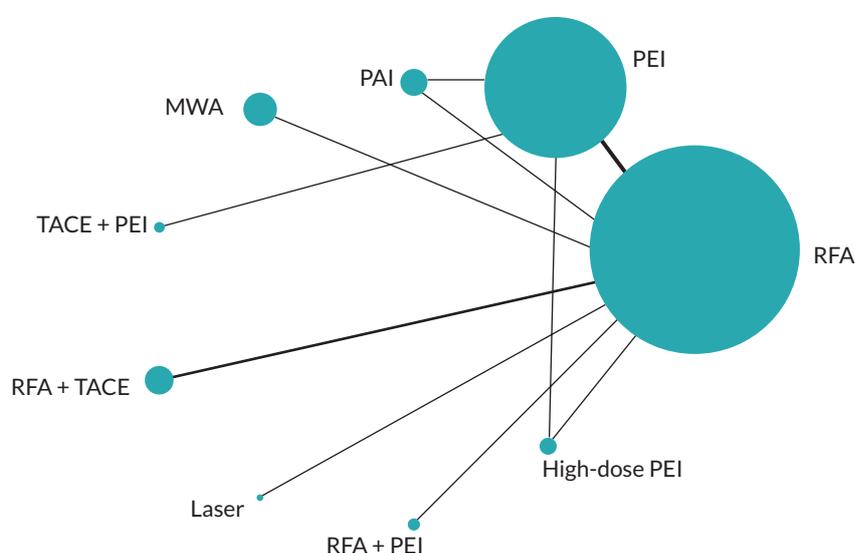
FIGURE 10 Rank plot for overall recurrence for the FE model.

from the NMA. Details about the inclusion/exclusion of RCTs and how the evidence reported was transformed into a form suitable for NMA are summarised in [Report Supplementary Material 3](#).

The network diagram for overall recurrence is presented in [Figure 11](#). Eight two-arm and two three-arm RCTs provided evidence on nine interventions. A summary of the data used for the NMA is provided in [Report Supplementary Material 4](#).

TABLE 8 Mean and median ranks for the FE model, with corresponding 95% CrIs for overall recurrence, sorted by mean rank, out of seven treatments

Treatments	Mean rank	Median rank	95% CrI for the rank
RFA + systemic chemotherapy	1.70	1	(1.00 to 6.00)
RFA + iodine-125	1.81	2	(1.00 to 3.00)
Resection	3.44	3	(2.00 to 6.00)
RFA	3.52	4	(2.00 to 5.00)
PEI	5.06	5	(4.00 to 6.00)
TACE + PEI	5.79	6	(3.00 to 7.00)
MWA + sorafenib	6.67	7	(4.00 to 7.00)

**FIGURE 11** Network diagram for local recurrence.

Treatment nodes in the network diagram are scaled proportional to the number of patients who receive a particular treatment. The widths of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison.

Model selection and inconsistency checking

Model fit parameters for the FE and RE models are presented in [Report Supplementary Material 5](#). All three models fit the data well, but as the difference in DICs between the FE and RE models was < 3, a simpler FE model was chosen.

The between-study heterogeneity was low and consistent for the two RE models. However, the 95% CrI for the model using the half-normal (0, 0.50²) prior was twice as wide as the 95% CrI for the model using the half-normal (0, 0.19²). Plots for the prior and posterior distribution of the between-study heterogeneity for the RE models are presented in [Report Supplementary Material 5](#).

There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons – the two loops in the network are formed by two separate three-arm studies.^{53,59}

Model results

Relative risks for local recurrence for all treatments compared with RFA are presented in [Figure 12](#).

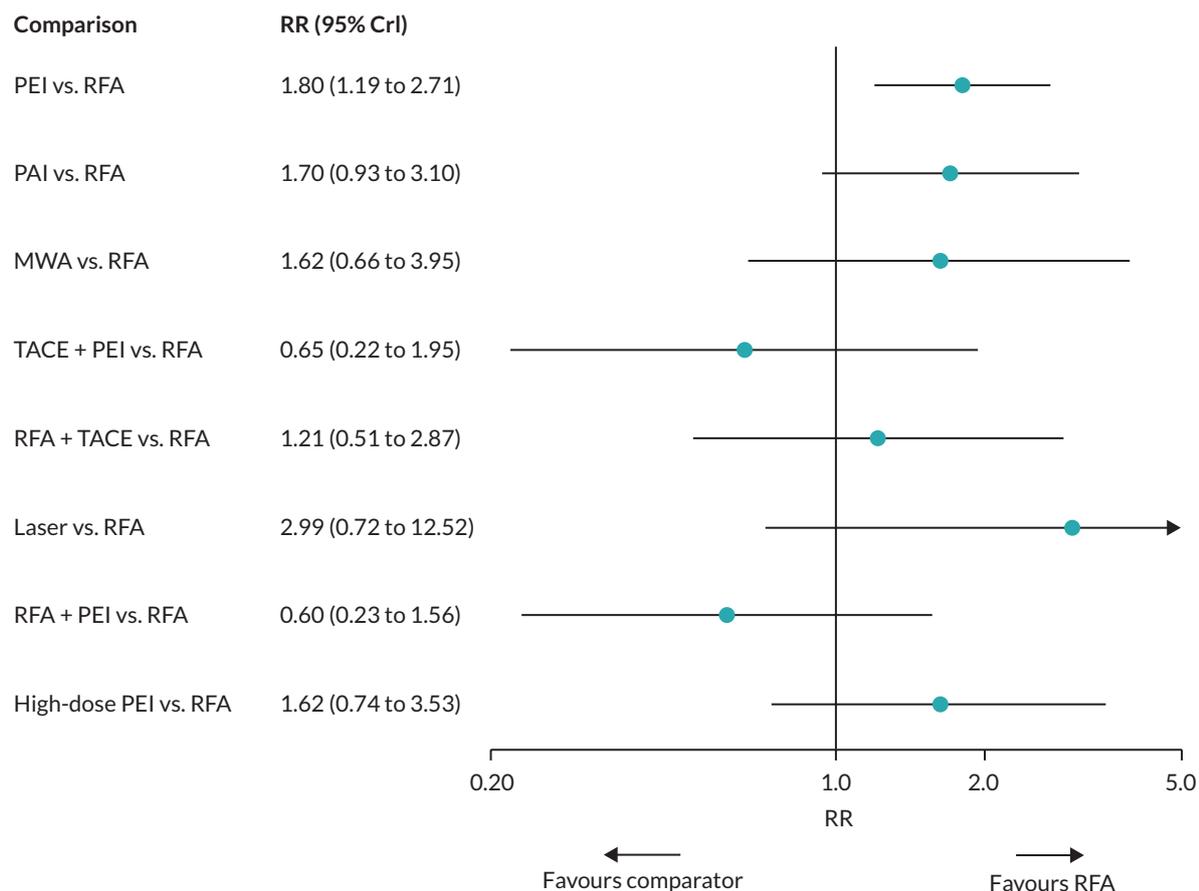


FIGURE 12 Plot of RRs for local recurrence compared with RFA for the FE model. RRs < 1 favour the comparator treatment over RFA.

There was evidence to suggest that PEI increases the risk of local recurrence compared with RFA (see [Figure 12](#)), and that RFA + PEI decreases the risk of local recurrence compared with PEI. There was insufficient evidence to suggest a difference in local recurrence for all other treatment comparisons.

Relative risks comparing all treatment groups against each other for FE and RE models are reported in [Report Supplementary Material 5](#). Alternative models using arm-level data gave similar results. Results for RE models displayed more uncertainty compared with the FE model, where results estimated using the wider half-normal (0, 0.50²) prior were more uncertain compared with results estimated using a half-normal (0, 0.19²) prior.

The treatment rank plot for local recurrence is presented in [Figure 13](#), and the mean and median ranks for each treatment, with their corresponding 95% CrIs, are presented in [Table 9](#). RFA + PEI had the highest probability of being ranked the best, although this probability was < 50%. The level of uncertainty in the treatment ranks was high – all treatments, with the exception of laser for the ninth rank, had rank probabilities below 50%. All treatments also had very wide CrIs for their rank.

Threshold analysis of RCT networks

Overall survival

The forest plot for the threshold analysis is presented in [Figure 14](#).

RESULTS

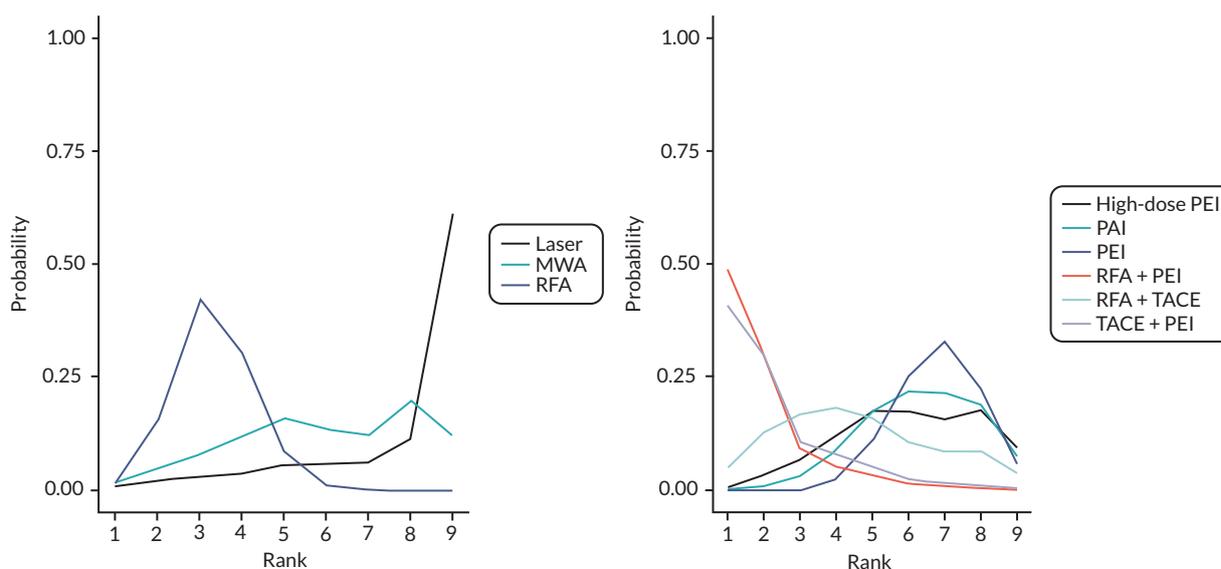


FIGURE 13 Rank plot for local recurrence for the FE model.

TABLE 9 Mean and median ranks for the FE model, with corresponding 95% CrIs for local recurrence, sorted by mean rank, out of nine treatments

Treatments	Mean rank	Median rank	95% CrI of the rank
RFA + PEI	1.96	2	(1.00 to 6.00)
TACE + PEI	2.27	2	(1.00 to 7.00)
RFA	3.33	3	(2.00 to 5.00)
RFA + TACE	4.59	4	(1.00 to 9.00)
MWA	5.98	6	(2.00 to 9.00)
High-dose PEI	6.01	6	(2.00 to 9.00)
PAI	6.33	6	(3.00 to 9.00)
PEI	6.78	7	(4.00 to 9.00)
Laser ablation	7.75	9	(2.00 to 9.00)

Credible intervals for the MWA versus RFA (5 vs. 1) comparison extend beyond the limits of the invariance intervals, suggesting that the recommended treatment is sensitive to the uncertainty in the data.

As interventions that included PEI and PAI were not considered in the threshold analysis, comparisons including those interventions – PEI versus RFA (2 vs. 1), PAI versus RFA (3 vs. 1), RFA + PEI versus PEI (10 vs. 1), PAI versus PEI (3 vs. 2), TACE + PEI versus RFA (6 vs. 2), and TACE + PAI versus PAI (6 vs. 3) – had large thresholds on the log scale. None of the comparisons had thresholds that would be sensitive to small changes in log-HRs. The thresholds and new optimum treatments, based only on relative effects, are presented in [Report Supplementary Material 5](#).

Progression-free survival

The forest plot for the threshold analysis is presented in [Figure 15](#).

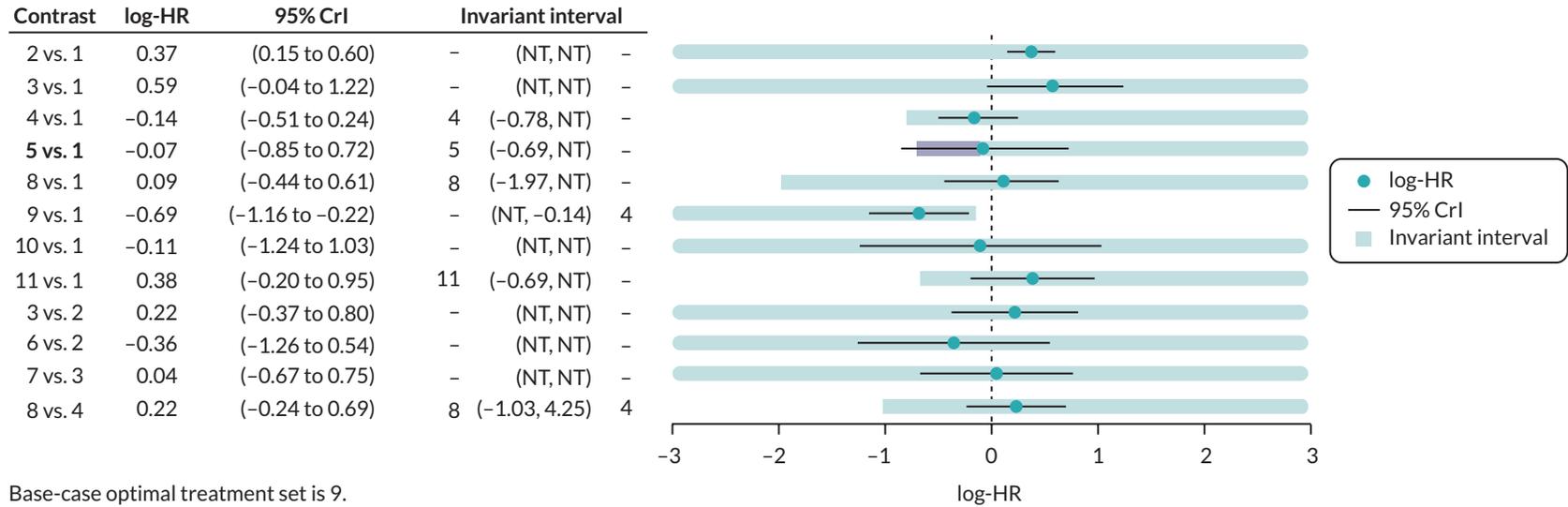


FIGURE 14 Forest plot for threshold analysis results for OS.

The light blue shaded bars represent the invariant interval; where the bars are shown in purple, CrIs for the comparison extend beyond the invariant interval.

Treatment codes: 1: RFA, 2: PEI, 3: PAI, 4: Resection, 5: MWA, 6: TACE + PEI, 7: TACE + PAI, 8: RFA + TACE, 9: RFA + iodine-125, 10: RFA + PEI, 11: Laser. The optimum treatment for this analysis was RFA + iodine-125.

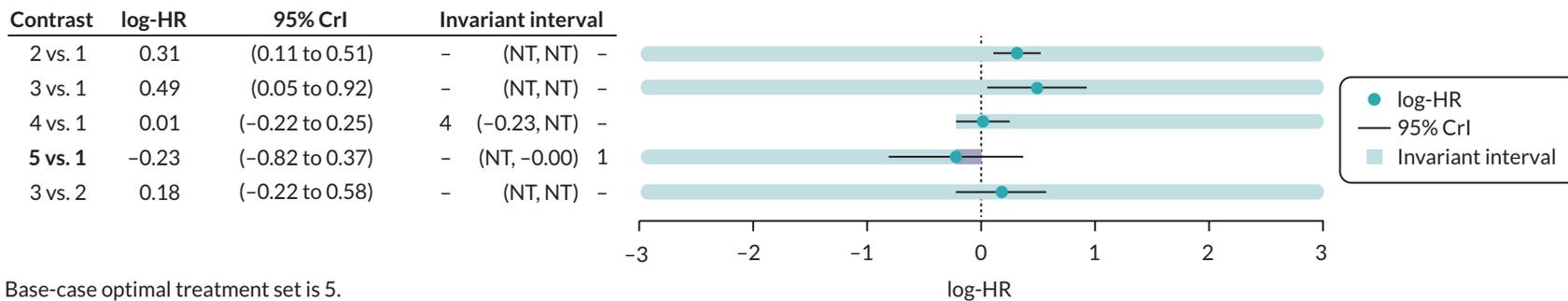


FIGURE 15 Forest plot for the threshold analysis for PFS.

The light blue shaded bars represent the invariant interval; where the bars are shown in purple, CrIs for the comparison extend beyond the invariant interval.

Treatment codes: 1: RFA, 2: PEI, 3: PAI, 4: Resection, 5: RFA + TACE. The optimum treatment for this analysis was RFA + TACE.

RESULTS

Credible intervals for the RFA + TACE versus RFA (5 vs. 1) comparison extend beyond the limits of the invariance intervals, suggesting that the recommended treatment is sensitive to the uncertainty in the data, changing the optimum treatment to RFA.

Comparisons including PEI and PAI – PEI versus RFA (2 vs. 1), PAI versus RFA (3 vs. 1), and PAI versus PEI (3 vs. 2) – had very large thresholds on the log scale. However, the negative threshold for the resection versus RFA (4 vs. 1) comparison was very small, and a change of 0.24 units on the log-HR scale in the negative direction changes the optimum treatment to resection. Thresholds and new optimum treatments, based only on relative effects, are presented in [Report Supplementary Material 5](#).

Overall recurrence

The forest plot for the threshold analysis is presented in [Figure 16](#).

Credible intervals for the RFA + iodine-125 versus RFA (5 vs. 1) and RFA + systemic chemotherapy versus RFA (7 vs. 1) comparisons extend beyond the limits of the invariance intervals, suggesting that the recommended treatment is sensitive to the uncertainty in the data.

Three comparisons – PEI versus RFA (2 vs. 1), resection versus PEI (3 vs. 2), and MWA + sorafenib versus resection (6 vs. 3) – had very large thresholds on the log scale. On the other hand, the negative threshold for the RFA + iodine-125 versus RFA (5 vs. 1) comparison was very small, and a change of 0.26 units on the log-RR scale in the negative direction changes the optimum treatment to RFA + iodine-125. Additionally, the positive threshold for RFA + systemic chemotherapy versus RFA (7 vs. 1) was very small, and a change of 0.26 units on the log-RR scale in the positive direction also changes the optimum treatment to RFA + iodine-125. Thresholds and new optimum treatments, based only on relative effects, are presented in [Report Supplementary Material 5](#).

Local recurrence

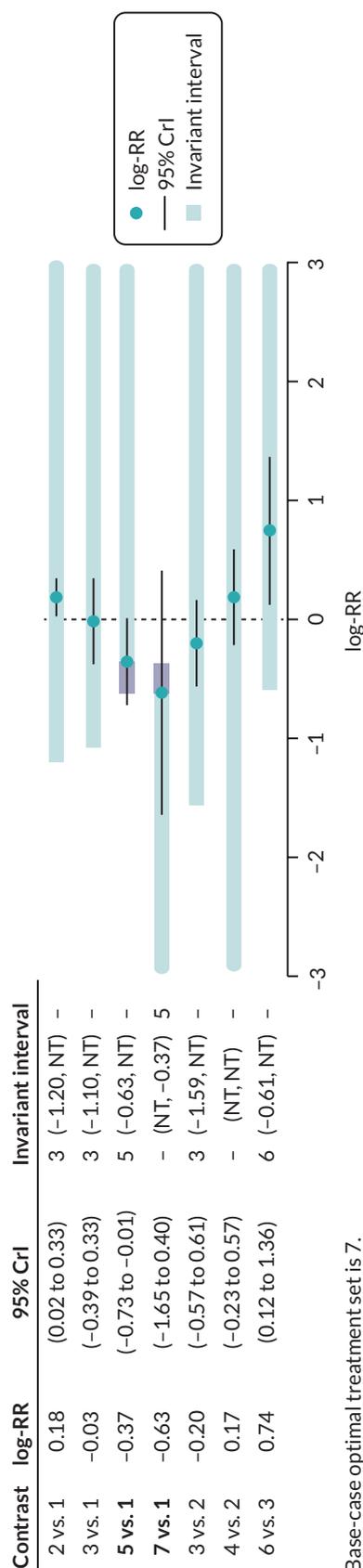
The forest plot for the threshold analysis is presented in [Figure 17](#).

Credible intervals for the MWA versus RFA (4 vs. 1), RFA + TACE versus RFA (6 vs. 1), and laser versus RFA (7 vs. 1) comparisons extend beyond the limits of the invariance intervals, suggesting that the recommended treatment is sensitive to the uncertainty in the data.

Comparisons including PEI and PAI – PEI versus RFA (2 vs. 1), PAI versus RFA (3 vs. 1), RFA + PEI versus RFA (8 vs. 1), high-dose PEI versus RFA (9 vs. 1), PAI versus PEI (3 vs. 2), TACE + PEI versus PEI (5 vs. 2), and high-dose PEI versus PEI (9 vs. 2) – had very large thresholds on the log-RR scale, as did the laser versus RFA (7 vs. 1) comparison. On the other hand, the negative threshold for the MWA versus RFA (4 vs. 1) and RFA + TACE versus RFA (6 vs. 1) comparisons was small, and changes of 0.48 and 0.19 units on the log-RR scale in the negative direction would change the optimum treatment to MWA and RFA + TACE, respectively. Thresholds and new optimum treatments, based only on relative effects, are presented in [Report Supplementary Material 5](#).

Systematic review of non-randomised evidence

The electronic searches for non-randomised studies of selected interventions, where RCT evidence was not available (HIFU, cryoablation, IRE, ECT, histotripsy, SABR and wider radiotherapy techniques) or for comparisons where the threshold analysis suggested that additional evidence could plausibly change the NMA result (RFA, MWA and laser ablation, compared with each other or surgical resection), identified a total of 8009 records after deduplication between databases. One additional record was identified from screening reference lists of relevant systematic reviews. Clinical advisors were not aware of any additional studies, other than those already identified from the electronic searches. However, clinical advisors were aware of additional unpublished data from a prospective registry of patients undergoing



Base-case optimal treatment set is 7.

FIGURE 16 Forest plot for threshold analysis results for overall recurrence.

The light blue shaded bars represent the invariant interval; where the bars extend beyond the invariant interval.

Treatment codes: 1: RFA, 2: PEI, 3: Resection, 4: TACE + PEI, 5: RFA + iodine-125, 6: MWA + sorafenib, 7: RFA + systemic chemotherapy. The optimum treatment for this analysis was RFA + systemic chemotherapy.

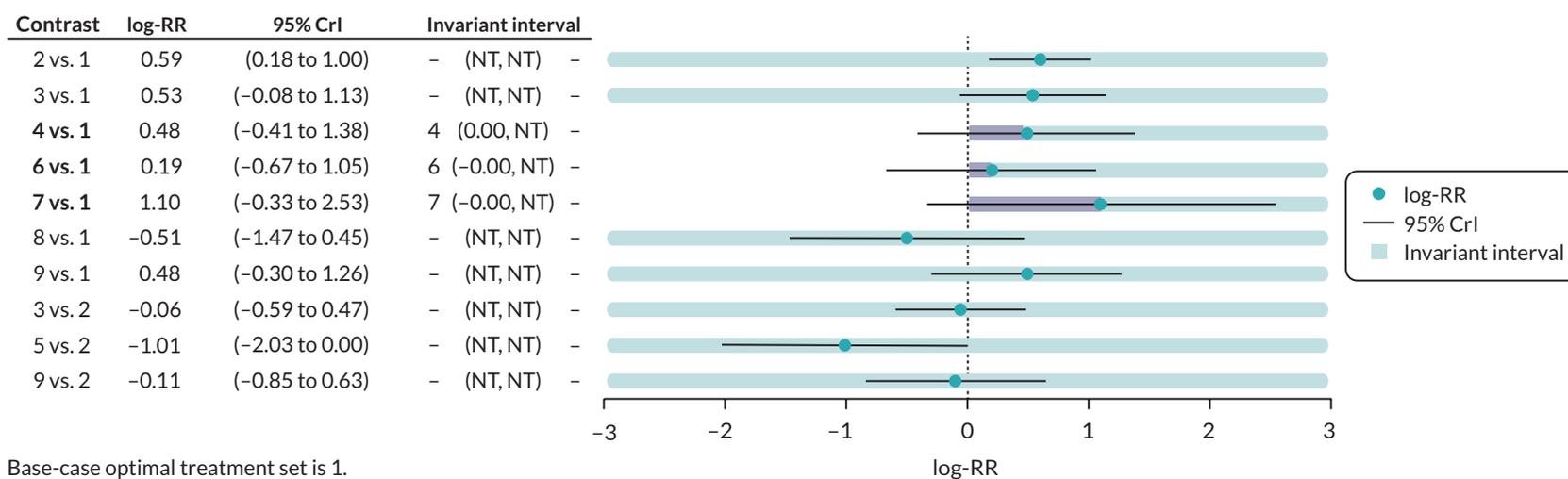


FIGURE 17 Forest plot for results of threshold analysis for local recurrence.

The light blue shaded bars represent the invariant interval; where the bars are shown in purple, CrIs for the comparison extend beyond the invariant interval.

Treatment codes: 1: RFA, 2: PEI, 3: PAI, 4: MWA, 5: TACE + PEI, 6: RFA + TACE, 7: Laser, 8: RFA + PEI, 9: High-dose PEI. The optimum treatment for this analysis was RFA.

treatment for HCC at Leeds Teaching Hospitals NHS Trust. These data were made available for use in the updated NMAs (see [Updated network meta-analyses using RCT and non-RCT evidence](#)).

Two hundred and thirty-four potentially relevant studies were ordered for full paper screening. Eight papers were unavailable as they were only reported as conference abstracts or clinical trial register records. Two hundred and twenty-six full papers were screened; 218 were excluded at the full paper stage and are listed in [Appendix 5](#), along with the reasons for their exclusion. [Figure 18](#) presents the flow of non-RCT studies through the study selection process.

Characteristics of non-randomised studies included in the review

Details of the 14 non-randomised comparative studies that were included in the systematic review are presented in [Table 10](#). Eight of the 14 studies restricted inclusion criteria to HCC patients with tumour size up to 3 cm in diameter.⁸³⁻⁹⁰ One study restricted inclusion criteria to HCC patients with tumour size up to 2 cm in diameter.⁹¹ One study included patients with tumours up to 5 cm in diameter, but reported separate results for the subgroup of patients with tumours up to 3 cm in diameter.⁹² Two studies did not report specific tumour size inclusion criteria, but in one study average tumour size was 2.15 (± 0.53)

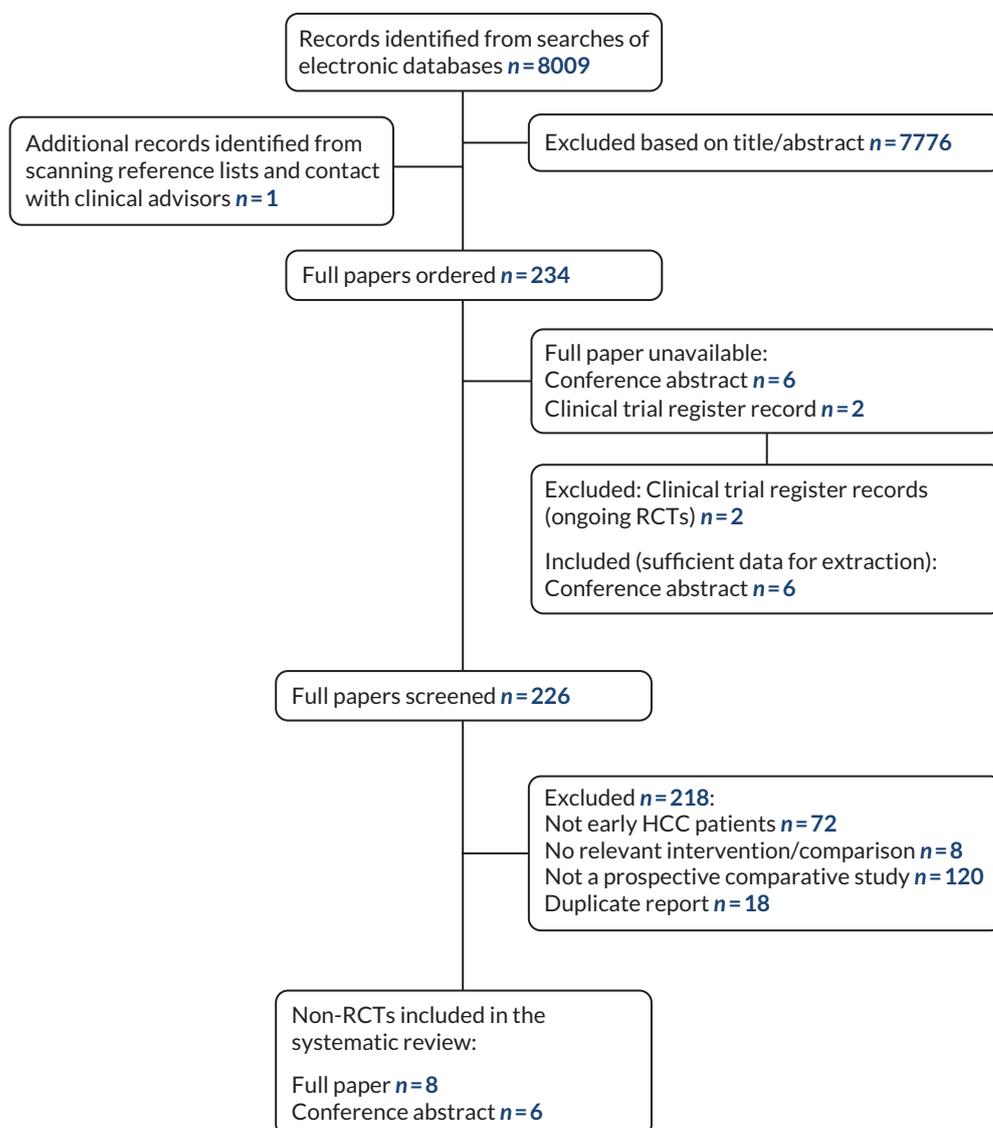


FIGURE 18 Flow diagram of the study selection process (non-RCTs).

TABLE 10 Non-RCTs included in the systematic review

Study	Location	Participant information	Intervention	Comparator
Barabino, 2016 ⁹³ (abstract)	Italy	154 patients with HCC unsuitable for percutaneous treatments or hepatic resection (average tumour size 2.15 (\pm 0.53) cm in one arm and 1.92 (\pm 0.5) cm in the other)	Laparoscopic RFA	Laparoscopic MWA
Cheung, 2013 ⁸³	China	106 patients (with 119 tumours) with < 3 cm tumours (primary or first recurrence)	HIFU	RFA
Choi, 2004 ⁸⁴ (abstract)	Korea	164 patients with \leq 3 cm tumours	RFA	Hepatic resection
Du, 2012 ⁹² (reported in Chinese)	China	116 patients with tumours \leq 5 cm; subgroup of 60 patients with tumours \leq 3 cm	RFA	Surgical resection
Ei, 2015 ⁹⁵	Japan	119 patients with < 5 cm tumours, included a few patients with tumours > 3 cm; median 2.5 cm in cryoablation group (maximum 4 cm), median 1.9 cm in RFA/MWA group (maximum 4.5 cm)	Cryoablation	RFA or MWA
Elgendi, 2014 ⁸⁵ (abstract)	Egypt	51 patients with < 3 cm tumours in locations not amenable for percutaneous route	Intraoperative RFA	Surgical resection
Elgendi, 2015 ⁹¹ (abstract)	Egypt	92 patients with < 2 cm tumours in locations not amenable for percutaneous route	Intraoperative RFA	Surgical resection
Harada, 2016 ⁹⁶	Japan	121 patients with < 5 cm tumours and portal hypertension, included a few patients with tumours > 3 cm in the resection group; mean 2.1 cm (range 0.7–5 cm)	RFA	Liver resection
Horigome, 2000 ⁸⁶	Japan	105 patients with \leq 3 cm tumours	Resection	MWA PEI
Huang, 2014 ⁸⁷	China	346 patients with \leq 3 cm tumours	RFA	Surgical resection
Peng, 2010 ⁸⁸ (abstract)	China	195 patients with \leq 3 cm tumours	RFA ($n = 79$), surgical resection ($n = 24$)	Surgical resection ($n = 75$), RFA ($n = 17$)
Qian, 2012 ⁸⁹	China	42 patients with < 3 cm tumours	MWA	RFA
Sugimoto, 2019 ⁹⁴	Japan	21 patients (with 24 tumours; median tumour size 2.03 (SD 0.44) cm in one arm and 1.73 (SD 0.67) cm in the other)	IRE	RFA
Tateishi, 2020 ⁹⁰ (abstract)	Japan	740 patients with \leq 3 cm tumours	RFA	Surgery

cm in one arm and 1.92 (\pm 0.5) cm in the other,⁹³ and the other study reported median tumour size of 2.03 (SD 0.44) cm in one arm and 1.73 (SD 0.67) cm in the other.⁹⁴ Two studies included patients with tumours up to 5 cm, but a clear majority of patients had tumours < 3 cm in diameter.^{95,96} In three of the included studies the patients had tumours unsuitable for percutaneous treatment,^{85,91,93} and one study included patients with primary or first recurrent HCC.⁸³ Study sample sizes ranged from 21 to 740 patients.

The majority of studies were conducted in Asian countries, which has implications for the generalisability of results to the UK population, as discussed in [Characteristics of RCTs included in the review](#). Studies were

TABLE 11 Number of non-RCTs making each comparison

RFA	RFA				
MWA	2	MWA			
PEI*		1	PEI ^a		
Resection	8	1	1	Resection	
HIFU	1			HIFU	
Cryoablation					Cryoablation
RFA/MWA					1 RFA/MWA
IRE	1				

a Note that PEI was included as part of a three-arm trial comparing MWA, resection and PEI; we did not search for non-RCTs of PEI.

conducted in China ($n = 5$), Japan ($n = 5$), Egypt ($n = 2$), Korea ($n = 1$) and Italy ($n = 1$). Six of the included studies were only reported as conference abstracts, and therefore limited data were available.^{84,85,88,90,91,93} While the inclusion criteria stated that only prospective studies were eligible for inclusion, for six studies it was not possible to determine whether patients were recruited prospectively or retrospectively; these studies were included to ensure that no relevant data were missed.^{83–85,91,93,95}

Table 11 shows the comparisons made in the included studies, 13 of which assessed RFA. While RFA was usually delivered via the percutaneous route, three studies assessed laparoscopic⁹³ or intraoperative RFA^{85,91} in patients with tumours unsuitable for percutaneous treatment. It should also be noted that several of the studies allocated patients to treatment groups depending on their tumour characteristics. Cheung *et al.* offered HIFU to patients with poor liver function or decompensated cirrhosis or tumours located at sites considered difficult for RFA;⁸³ Ei *et al.* allocated patients to cryoablation if tumours were in close vicinity to major veins or organs;⁹⁵ both studies by Elgendi *et al.* allocated patients depending on the location and depth of the tumour from the liver capsule;^{85,91} Harada *et al.* allocated patients depending on Child–Pugh class, tumour location and indocyanine green retention tests;⁹⁶ and Sugimoto *et al.* allocated patients depending on operator preference, tumour size, geometry and location.⁹⁴ In the study by Peng *et al.*, patients were allocated to RFA or surgical resection as the first choice, but the actual treatment received depended on the tumour location.⁸⁸

Quality of non-randomised studies included in the review

Results of the quality assessment of the non-randomised comparative studies are presented in **Table 12**. Six of the included studies were only reported as conference abstracts, and therefore there are a few 'Unclear' responses to some of the quality assessment criteria owing to the limited reporting.

Generally, methods were poorly reported. Inclusion criteria were clearly defined in 8/14 studies. The intervention was clearly described and consistently delivered in 8/14 studies and the comparator was clearly described and consistently delivered in 7/14 studies. None of the studies reported whether outcome assessors were blinded to treatment group.

Allocation to treatment groups was adequately described and appropriate in only two studies, resulting in patients having similar baseline characteristics between groups.^{87,89} As discussed in **Overall survival**, several of the studies allocated patients to treatment groups depending on their tumour characteristics. Because appropriateness of treatment allocation and similarity of treatment groups at baseline were two of the important quality assessment criteria, this resulted in the other 12 studies having a high overall RoB judgement. The study by Qian *et al.* was the only study to have a low overall RoB judgement⁸⁹

TABLE 12 Risk of bias assessment results (non-RCTs)

Trial	Inclusion criteria clearly defined ^a	Allocation to treatment groups adequately described/ appropriate ^a	Groups similar at baseline ^a	Clearly described and consistently delivered intervention	Clearly described and consistently delivered comparator	Outcomes assessors blinded	Missing outcome data balanced across groups ^a	Free from suggestion of selective reporting	Overall judgement of ROB
Barabino, 2016 ⁹³ (abstract)	No	No	No	No	No	Unclear	Unclear	Unclear	High
Cheung, 2013 ⁸³	Yes	No	No	Yes	Yes	Unclear	Unclear	Yes	High
Choi, 2004 ⁸⁴ (abstract)	No	No	Unclear	No	No	Unclear	Unclear	Unclear	High
Du, 2012 ⁹² (Chinese)	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Yes	High
Ei, 2015 ⁹⁵	Yes	No	No	Yes	No	Unclear	Yes	Yes	High
Elgendi, 2014 ⁸⁵ (abstract)	No	No	Unclear	No	No	Unclear	Unclear	Unclear	High
Elgendi, 2015 ⁹¹ (abstract)	No	No	Unclear	No	No	Unclear	Unclear	Unclear	High
Harada, 2016 ⁸⁶	Yes	No	No	Yes	Yes	Unclear	Yes	Yes	High
Horigome, 2000 ⁸⁶	No	No	No	Yes	Yes	Unclear	Yes	Yes	High
Huang, 2014 ⁸⁷	Yes	Yes	Yes	Yes	Yes	Yes for HRQoL, unclear for survival/ AE	Unclear	Yes	Unclear
Peng, 2010 ⁸⁸ (abstract)	No	No	Unclear	No	No	Unclear	Unclear	Unclear	High
Qian, 2012 ⁸⁹	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Low
Sugimoto, 2019 ⁹⁴	Yes	No	No	Yes	Yes	Unclear	Unclear	Yes	High
Tateishi, 2020 ⁹⁰ (abstract)	Yes	No	No	No	No	Unclear	Unclear	Yes	High
Total	Yes: 8 No: 6 Unclear: 0	Yes: 2 No: 12 Unclear: 0	Yes: 2 No: 7 Unclear: 5	Yes: 8 No: 6 Unclear: 0	Yes: 7 No: 7 Unclear: 0	Yes: 0 No: 0 Unclear: 14	Yes: 5 No: 0 Unclear: 9	Yes: 9 No: 0 Unclear: 5	High: 12 Low: 1 Unclear: 1

^a Important criteria: if 'No' then overall ROB = high; if 'Unclear' then overall ROB = unclear; if 'Yes' then overall ROB = low.
HRQoL, health-related quality of life.

and the study by Huang *et al.* had an unclear overall RoB judgement, as it was unclear whether missing outcome data were balanced across treatment groups.⁸⁷

Results of non-randomised studies included in the review

A table of study characteristics and results is presented in [Appendix 6](#). In view of the high RoB of 12 of the 14 included studies – differences in baseline characteristics between treatment groups and treatment allocation being dependent on tumour characteristics for several studies – the results below should be interpreted with caution. The non-randomised nature of these studies and the possibility that some studies may have been undertaken retrospectively mean that these results are less reliable than those of the RCTs described in [Results of RCTs included in the review](#).

Radiofrequency ablation versus microwave ablation

Two non-randomised studies compared RFA with MWA. One study was assessed as having a low RoB ($n = 42$ patients).⁸⁹ The other study was only reported as a conference abstract and had a high RoB ($n = 154$ patients).⁹³ The conference abstract did not report participant inclusion criteria relating to tumour size or the maximum tumour size of the included participants, but the mean size was 2.15 cm in the MWA arm and 1.92 cm in the RFA arm. Patients were unsuitable for percutaneous treatments; the interventions assessed were laparoscopic RFA and laparoscopic MWA.

Only the low-quality study reported OS and disease-free survival rates, which were both higher after laparoscopic RFA than after laparoscopic MWA at 5 years (OS 50% vs. 37%; disease-free survival 19% vs. 12%).⁹³ However, local tumour progression occurred in more patients in the RFA group than in the MWA group in the low-quality study (21.2% vs. 8.3%) and was similar between groups in the high-quality study (RFA 15% vs. MWA 18.2%). The proportion of patients with a new intrahepatic tumour was also higher in the RFA group than in the MWA group in the high-quality study (20% vs. 4.5%).

Both studies reported that around 95% of patients achieved complete ablation in both arms. After a second treatment, 100% of patients achieved complete ablation in the high-quality study.⁸⁹

The low-quality study reported a similar rate of major complications in both arms (RFA 1% vs. MWA 2%) and no treatment-related deaths in either group.⁹³ The high-quality study reported only that there were no skin burns, tumour seeding or treatment-related deaths in either group.⁸⁹

Radiofrequency ablation versus resection

Eight non-randomised studies compared RFA with resection ($n = 1769$ patients). Seven of the studies had a high RoB^{84,85,88,90–92,96} and one had an unclear RoB.⁸⁷ Five of the studies with a high RoB were only reported as conference abstracts.^{84,85,88,90,91} One study included tumours up to 5 cm in the resection group, but the mean tumour size in this group was 2.1 cm.⁹⁶ In four of the studies the treatment received was decided on the basis of patient characteristics (e.g. tumour location) and either there were baseline differences between groups or it was not clearly reported whether this was the case.^{85,88,91,96} In one of these studies, group allocation determined which of the two treatments was given as the first choice, but the final decision was based on tumour location.⁸⁸ In three of the other studies, allocation to treatment groups was not adequately described and either there were baseline differences between groups or it was unclear whether this was the case.^{84,90,92} Only one study reported similar baseline characteristics between treatment groups.⁸⁷

Five of the eight studies reported 1- and 3-year OS rates. In most of these studies, survival was similar between groups at 1 year,^{84,85,91,96} although it was slightly higher in the RFA group in one study (RFA 95.9% vs. resection 90.1%).⁸⁸ At later time points, findings were more mixed. Three studies reported a higher OS rate in the resection arm at 3 years (RFA vs. resection: 73.9% vs. 83.0%,⁸⁴ 74% vs 81%⁸⁵ and 76% vs. 83%⁹¹), but it remained similar in one study (84.5% vs. 84.1%⁹⁶) and was higher in the RFA arm in the other study (75.8% vs. 63.7%⁸⁸). Two studies also reported higher survival rates after RFA at 4 (70.7% vs. 55.5%⁸⁸) or 5 years (50.6% vs. 37.1%⁹⁶).

RESULTS

Two studies reported recurrence-free survival. In one study it was higher after resection at 1, 3 and 5 years (5-year rate 4.8% vs. 42.9%).⁹⁶ In the other study it was similar at 1 year (RFA 74.1% vs. resection 75.9%) but higher after resection at 3 years (40.2% vs. 54.7%).⁸⁴

Findings on recurrence were also mixed. In two studies, recurrence (local and distant/remote) was experienced by more patients in the RFA group (local or distant 85% vs. 42%;⁹⁶ local 11.3% vs. 2.0%; remote 53.7% vs. 45.3%⁸⁴). Another two studies reported similar relapse or recurrence rates between groups (1-year relapse rate: RFA 12.9% vs. resection 13.8%;⁹² 3-year recurrence rate: RFA 61.7% vs. resection 66%; adjusted HR 0.89, 95% CI 0.72 to 1.1⁹⁰). Two studies reported that no tumours showed local progression or recurrence during the follow-up period in either group.^{85,91}

Only two studies reported the complete ablation/resection rate, which was 100% in both treatment arms.^{85,91} One study reported quality-of-life outcomes, measured using the FACT-Hep questionnaire.⁸⁷ Patients in the RFA group had significantly better HRQoL total scores than those in the resection group after 3, 6, 12, 24 and 36 months.

Data on AEs were limited. Two studies reported a considerably higher rate of total AEs and AEs at grade III or above on the Clavien–Dindo scale after resection.^{87,96} While one study reported no hospital deaths in either group,⁸⁷ one study reported one hospital death occurring secondary to sepsis in the resection group (RFA 0/40 vs. resection 1/81⁹⁶), and another study reported two cases of treatment-related mortality in the resection group (RFA 0/103 vs. resection 2/92⁸⁸). Two conference abstracts reported only that complication rates were 'comparable' between groups.^{85,91}

The average length of hospital stay was approximately twice as long after resection as after RFA in two studies.^{87,96} One of the studies also reported that the RFA group experienced a shorter procedure (RFA 44.0 vs. resection 166.5 minutes) and lower blood transfusion rates.⁹⁶

Microwave ablation versus resection

One non-randomised study with a high RoB compared MWA with resection ($n = 105$ patients).⁸⁶ It also included a treatment arm that received PEI. Fewer patients experienced recurrence after MWA than after resection (MWA 38% vs. resection 72%). No data were reported on survival outcomes or AEs.

High-intensity focused ultrasound versus radiofrequency ablation

One non-randomised study with a high RoB compared HIFU with RFA ($n = 106$ patients).⁸³ Included patients had primary HCC or first recurrence. Treatment was allocated on the basis of patient characteristics (liver function, decompensated cirrhosis or tumour location), so the groups were not similar at baseline. OS was similar between arms at 1 and 3 years (1 year: HIFU 97.4% vs. RFA 94.6%; 3 years: 81.2% vs. 79.8%). Disease-free survival was also similar at 1 year (HIFU 63.6% vs. RFA 62.4%) but lower in the HIFU group at 3 years (25.9% vs. 34.1%). Complete response was slightly higher in the RFA arm (87.2% vs. 94.9%). More patients in the HIFU group than the RFA group experienced AEs (21.3% vs. 8.5%). However, the rates of AEs at grade III or above on the Clavien–Dindo scale was similar in both groups (HIFU 3/47 vs. RFA 4/59). Patients in the HIFU group had a shorter length of hospital stay than those in the RFA group (median 4 vs. 6 days).

Cryoablation versus radiofrequency ablation or microwave ablation

One non-randomised study with a high RoB compared cryoablation with a group that received either RFA or MWA ($n = 119$ patients).⁹⁵ Results were not reported separately for patients receiving RFA and those receiving MWA. Patients with HCCs up to 5 cm were eligible, but the median tumour size was 2.5 cm in the cryoablation group and 1.9 cm in the RFA/MWA group. Treatment was allocated based on tumour location, so there were baseline differences between the groups.

Overall survival and local recurrence were reported separately for patients with tumours up to 2 cm and patients with tumours over 2 cm. In the ≤ 2 cm subgroup, the 2-year OS rate was slightly higher

in the RFA/MWA group (88% vs. 95%) and the 2-year local recurrence rate was similar in both groups (cryoablation 19% vs. RFA/MWA 23%). OS was similar between groups in the > 2 cm subgroup (cryoablation 86% vs. RFA/MWA 85%), but local recurrence occurred in considerably more patients who underwent RFA or MWA than patients who underwent cryoablation (21% vs. 56%).

The 2-year local recurrence-free survival rate (for all tumour sizes) was higher in the cryoablation group (80% vs. 68%). Initial recurrence at other sites of the liver was similar between groups (cryoablation 38% vs. RFA/MWA 34%). Two patients suffered distant metastases in the bone or lung; both were in the cryoablation group.

There was a similar total rate of AEs in the two groups (cryoablation 6/55 vs. RFA/MWA 7/64) and a similar proportion of patients had AEs at grade III or above on the Clavien–Dindo scale (3/55 vs. 3/64). There was no in-hospital mortality in either group. Operative time was longer in the cryoablation group (median 180 vs. 132 minutes). The median length of hospital stay was 8 days in both groups.

Irreversible electroporation versus radiofrequency ablation

One non-randomised study with a high RoB compared IRE with RFA ($n = 21$ patients).⁹⁴ The maximum tumour size was not reported, but the median size was 2.03 cm in the IRE group and 1.73 cm in the RFA group. Treatment was allocated based on operator preference, tumour size, geometry and location, so there were baseline differences between groups. This study aimed to assess temporal changes in systemic immune responses between these two different types of ablation, and the only relevant data reported were on local tumour progression at 6 months. Local tumour progression was experienced by 1 of 10 patients in the IRE group and 0 of 11 patients in the RFA group.

Ongoing trials

The electronic searches for non-randomised trials identified two potentially relevant ongoing RCTs that were not identified in the RCT searches (described in [Ongoing trials](#)). Further details are presented in [Table 13](#).

Updated network meta-analyses using RCT and non-RCT evidence

Of the 14 non-randomised studies that were included in the systematic review, two^{87,89} could be included in the updated NMAs. Huang (2014) reported data that could be incorporated in the NMAs for OS and PFS,⁸⁷ while Qian (2012) reported data that could be incorporated in the NMA for PFS.⁸⁹

Data from a prospective registry of patients undergoing treatment for HCC were made available to the research team by a research group at Leeds Teaching Hospitals NHS Trust (Dr Tze Wah, Leeds Teaching Hospitals NHS Trust, 5 October 2021, personal communication). This contained data for 303 patients who had received either RFA, MWA, IRE or cryoablation for primary HCC. Most patients received RFA, with a smaller number receiving MWA. Very few patients received IRE or cryoablation. Data were unpublished at the time of our analysis, but have been submitted for publication.

TABLE 13 Table of potentially relevant ongoing RCTs (identified from non-RCT searches)

Study	Further details
ChiCTR2000039404	Clinical trial register record describing a single-centre RCT comparing SBRT vs. RFA for ≤ 2 cm small HCC. Registered 2020.
ClinicalTrials.gov: NCT04891874	Clinical trial register record describing a single-centre RCT comparing adjuvant SBRT after surgery vs. surgery alone for early-stage HCC with microvascular invasion and narrow resection margin. Sponsor: Eastern Hepatobiliary Surgery Hospital, China. Trial status: Completed, last update posted 10 September 2021.

Data from the Leeds patients were reported for numerous outcomes. There were sufficient data for inclusion in NMAs for OS, PFS, and local recurrence.

As there was no new evidence for overall recurrence, no updated NMAs or threshold analyses were conducted for this outcome.

Overall survival

Data

The network diagram for OS is presented in [Figure 19](#). In addition to the randomised studies included in the NMA in [Overall survival](#), one two-arm and one three-arm study provided non-randomised evidence for one new intervention in addition to three interventions already included in the network. A summary of the additional non-randomised evidence included in the NMA is provided in [Report Supplementary Material 4](#).

Model selection and inconsistency checking

Model fit parameters for the FE and RE models are presented in [Report Supplementary Material 5](#). All three models fit the data well, but as the difference in the DICs between the FE and RE models was < 3 , the simpler FE model was chosen.

The 95% CrI for the model using the half-normal $(0, 0.50^2)$ prior was wider than the 95% CrI for the model using the half-normal $(0, 0.19^2)$. This shows that the estimate of between-study heterogeneity is sensitive to the level of prior heterogeneity assumed due to few studies being included for each comparison in the network. Plots for the prior and posterior distributions of the between-study heterogeneity for the RE models are presented in [Report Supplementary Material 5](#). There was no evidence to suggest inconsistency in the network. Details of the inconsistency check and node-splitting results are presented in [Report Supplementary Material 5](#).

Model results

Hazard ratios for OS for all treatments compared with RFA are presented in [Figure 20](#).

The results for the NMA were not very different from the results from the NMA comparing only randomised evidence (see [Model results](#)). With the addition of non-randomised studies there was also

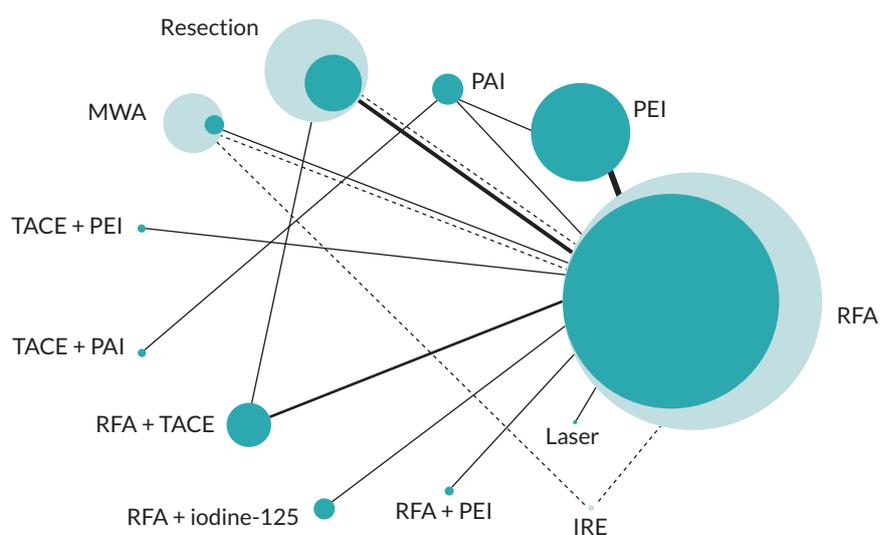


FIGURE 19 Network diagram for OS.

Treatment nodes in the network diagram are scaled proportional to the number of patients who receive a particular treatment. The widths of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. The light blue circles represent the number of patients who receive a particular treatment in both randomised and non-randomised studies, and dashed lines represent comparisons that are added to the network by non-randomised evidence.

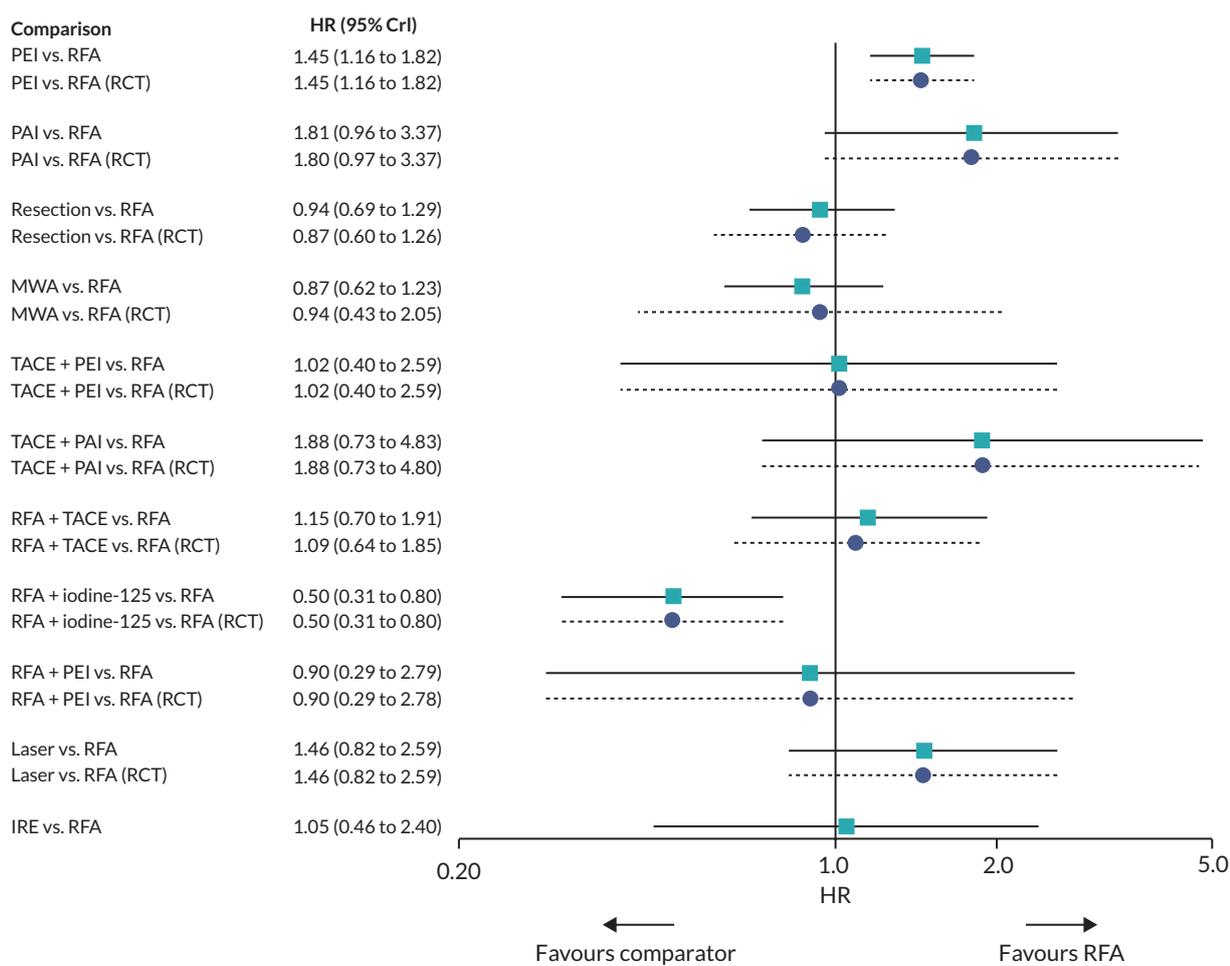


FIGURE 20 Plot of HRs for OS compared with RFA for the FE model. HRs < 1 favour the comparator treatment over RFA.

evidence to suggest that RFA + iodine-125 improves survival compared with resection. There was also evidence to suggest that MWA improves survival compared with PEI and PAI. HRs comparing all treatment groups against each other for FE and RE models are reported in [Report Supplementary Material 5](#).

The mean and median ranks for each treatment, with their corresponding 95% CrIs, are presented in [Table 14](#). RFA + iodine-125 had the highest probability of being ranked the best treatment. However, as seen for NMAs including only randomised evidence (see [Model results](#)), there was a high level of uncertainty in treatment rankings, also visible in the treatment rank plots (see [Figure 21](#)).

Progression-free survival

Data

The network diagram for PFS is presented in [Figure 22](#). In addition to the randomised studies included in the NMA in [Progression-free survival](#), two two-arm and one three-arm study provided non-randomised evidence for two new interventions in addition to two interventions already included in the network. A summary of the additional non-randomised evidence included in the NMA is provided in [Report Supplementary Material 4](#).

TABLE 14 Mean and median treatment ranks for the FE model, with corresponding 95% CrIs for OS, sorted by mean rank out of 12 treatments

Treatments	Mean rank	Median rank	95% CrI of the rank
RFA + iodine-125	1.40	1	(1.00 to 3.00)
MWA	4.10	4	(2.00 to 8.00)
Resection	4.76	5	(2.00 to 8.00)
RFA + PEI	5.19	4	(1.00 to 12.00)
RFA	5.46	5	(3.00 to 8.00)
TACE + PEI	5.88	6	(1.00 to 12.00)
IRE	6.08	6	(1.00 to 12.00)
RFA + TACE	6.94	7	(2.00 to 12.00)
Laser	8.86	9	(3.00 to 12.00)
PEI	9.14	9	(7.00 to 12.00)
TACE + PAI	9.95	11	(3.00 to 12.00)
PAI	10.23	11	(5.00 to 12.00)

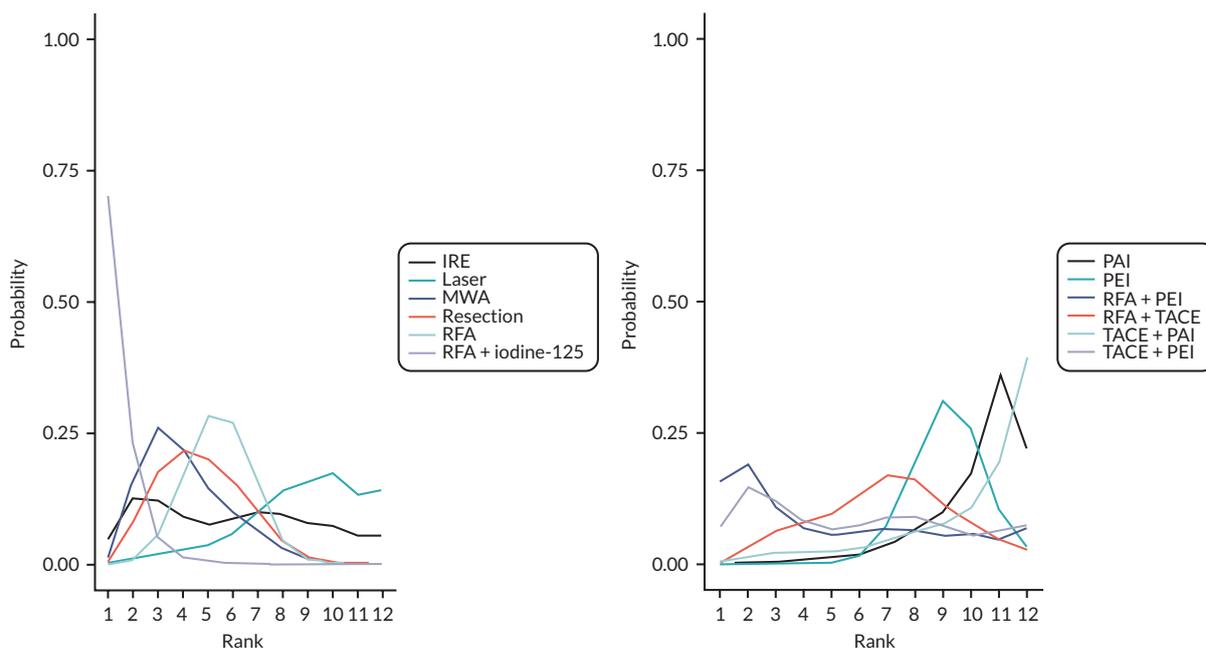


FIGURE 21 Rank plot for OS for the FE model

Model selection and consistency checking

Model fit parameters for the FE and RE models are presented in [Report Supplementary Material 5](#). All three models fit the data well, but as the difference in the DICs between the FE and RE models was < 3, the simpler FE model was chosen.

The between-study heterogeneity was low for the two RE models. However, the 95% CrI for the model using the half-normal (0, 0.50²) prior was wider than the 95% CrI for the model using the half-normal (0, 0.19²) indicating that the estimate of between-study heterogeneity is sensitive to the level of prior heterogeneity assumed due to few studies being included for each comparison in the network.

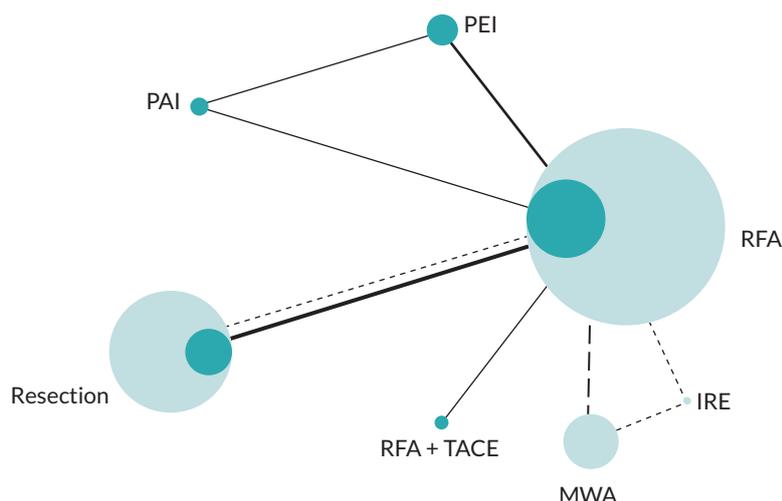


FIGURE 22 Network diagram for PFS.

Treatment nodes in the network diagram are scaled proportional to the number of patients who receive a particular treatment. The widths of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. The light blue circles represent the number of patients who receive a particular treatment in both randomised and non-randomised studies, and dashed lines represent comparisons that are added to the network by non-randomised evidence.

There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons – the two loops are formed by two three-arm studies, one of which is the work at Leeds Teaching Hospitals NHS Trust described above (Dr Tze Wah, personal communication).⁵³

Model results

HRs for PFS for all treatments compared with RFA are presented in [Figure 23](#).

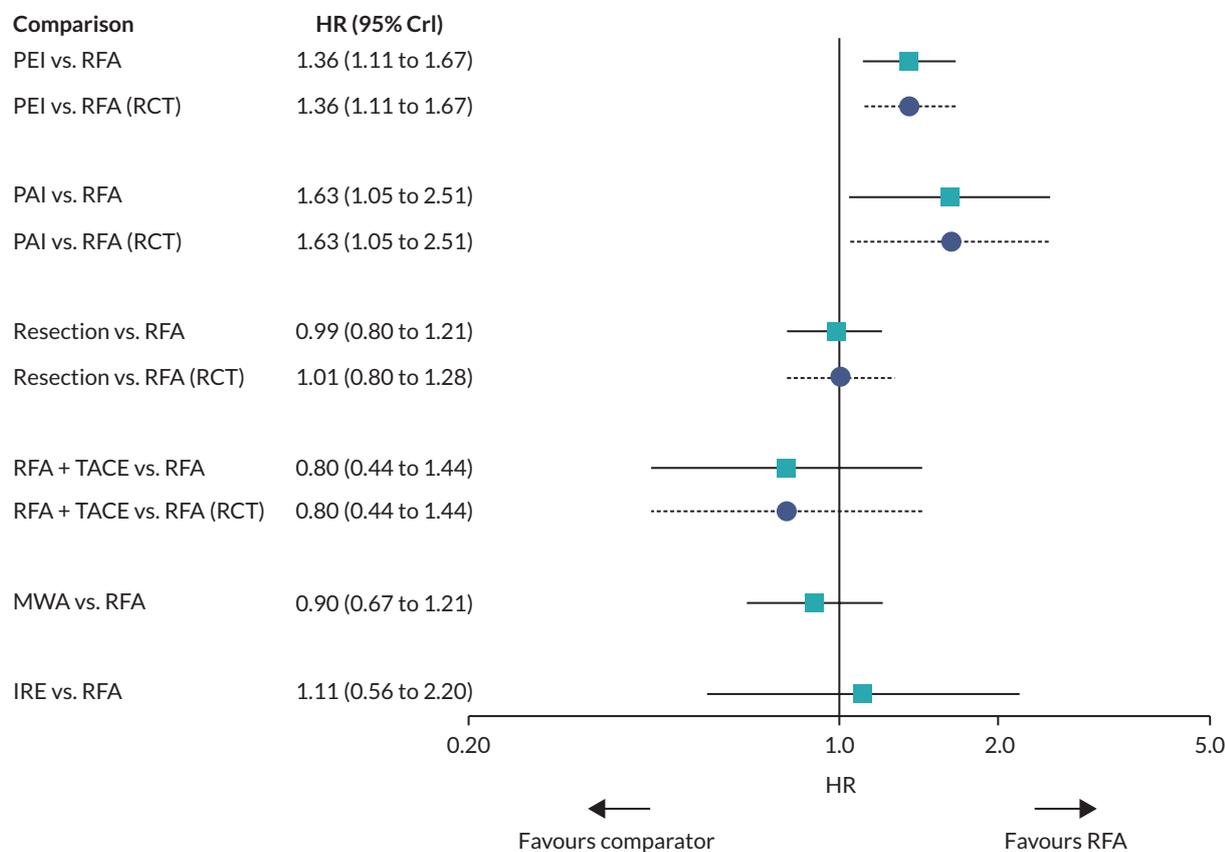


FIGURE 23 Plot of HRs for PFS compared with RFA for the FE model.

HRs < 1 favour the comparator treatment over RFA.

Similar to the NMA using only RCT evidence (see *Model selection and consistency checking*), there was evidence to suggest that PEI and PAI worsen PFS compared with RFA. However, with the addition of the non-randomised studies, there was also evidence to suggest that resection and MWA improved PFS compared with PEI and PAI. HRs comparing all treatment groups against each other for FE and RE models are reported in [Report Supplementary Material 5](#).

The treatment rank plot for PFS is presented in [Figure 24](#), and the mean and median ranks for each treatment, with their corresponding 95% CrIs, are presented in [Table 15](#). RFA + TACE had the highest probability to be ranked the best treatment. However, there was a high level of uncertainty in the treatment ranking – all treatments displayed wide CrIs for ranks.

Local recurrence

Data

The network diagram for local recurrence is presented in [Figure 25](#). In addition to the randomised studies included in the NMA in *Overall recurrence*, one three-arm study provided non-randomised evidence for one new intervention in addition to two interventions already included in the network. A summary of the additional non-randomised evidence included in the NMA is provided in [Report Supplementary Material 4](#).

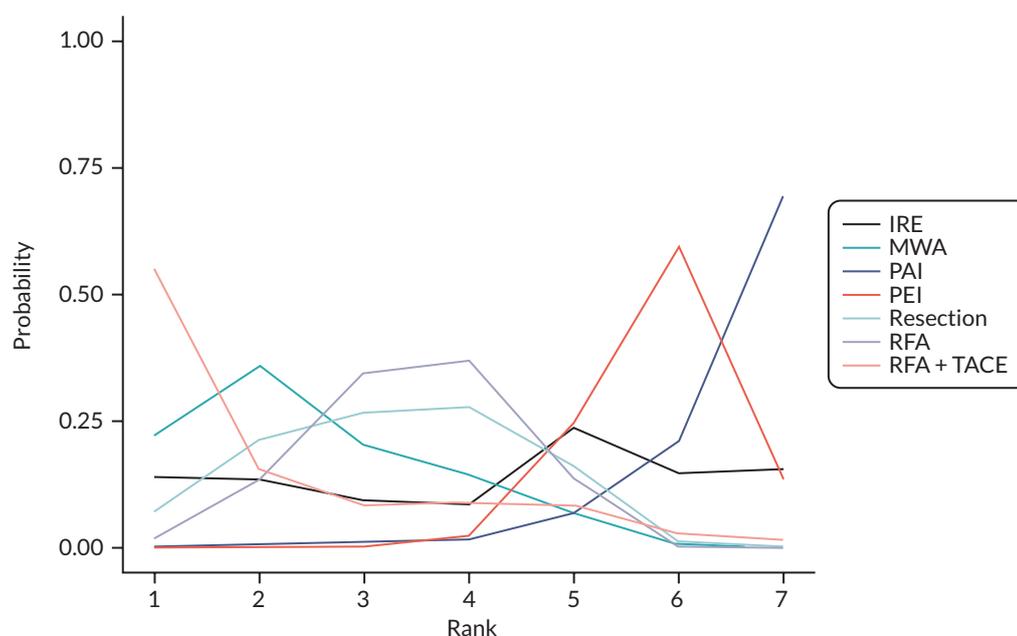


FIGURE 24 Rank plot for PFS for the FE model.

TABLE 15 Mean and median ranks, with corresponding 95% CrIs for PFS for the FE model, sorted by mean rank

Treatments	Mean rank	Median rank	95% CrI
RFA + TACE	2.14	1	(1.00 to 6.00)
MWA	2.50	2	(1.00 to 5.00)
Resection	3.28	3	(1.00 to 5.00)
RFA	3.48	4	(2.00 to 5.00)
IRE	4.21	5	(1.00 to 7.00)
PEI	5.83	6	(4.00 to 7.00)
PAI	6.55	7	(4.00 to 7.00)

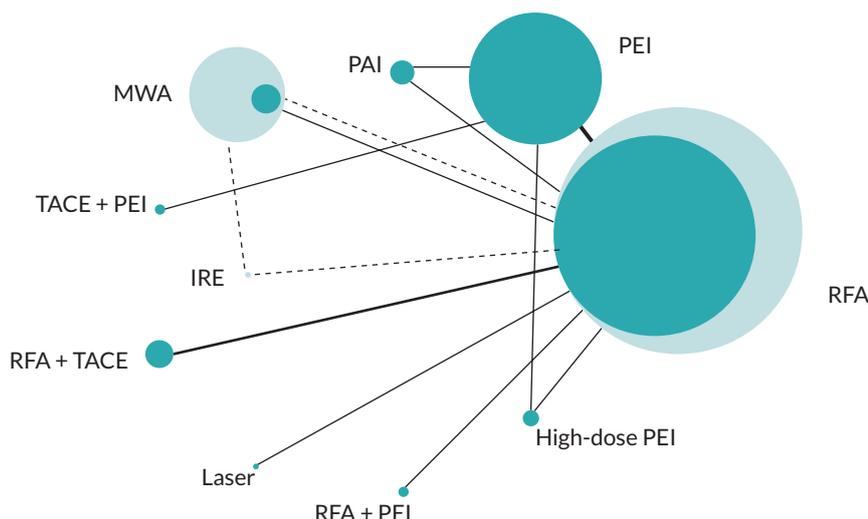


FIGURE 25 Network diagram for local recurrence.

Treatment nodes in the network diagram are scaled proportional to the number of patients who receive a particular treatment. The widths of the lines joining two nodes are weighted according to the number of studies that provide evidence on that comparison. The light blue circles represent the number of patients who receive a particular treatment in both randomised and non-randomised studies, and dashed lines represent comparisons that are added to the network by non-randomised evidence.

Model selection and inconsistency checking

Model fit parameters for the three models are reported in [Report Supplementary Material 5](#). All three models fit the data well. The between-study heterogeneity was low and consistent for the two RE models. However, the 95% CrI for the model using the half-normal (0, 0.50²) prior was wider than the 95% CrI for the model using the half-normal (0, 0.19²).

As the difference in the DICs between the FE and RE models was < 3, the simpler FE model was chosen. Plots for the prior and posterior distributions of the between-study heterogeneity for the RE models are presented in [Report Supplementary Material 5](#).

There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons; the three loops in the network are formed by three separate three-arm studies.

Model results

Relative risks for local recurrence for all treatments compared with RFA are presented in [Figure 26](#).

Similar to the NMA using only RCT evidence (see [Model results](#)), there was evidence to suggest that PEI increased the risk of local recurrence compared with RFA, and that RFA + PEI decreased the risk of local recurrence compared with PEI. However, with the addition of non-randomised studies, there was also now evidence to suggest that IRE increased the risk of local recurrence compared with RFA and RFA + PEI, although the CrIs for both comparisons were very wide. RRs comparing all treatment groups against each other for FE and RE models are reported in [Report Supplementary Material 5](#).

The treatment rank plot for local recurrence is presented in [Figure 27](#), and the mean and median ranks for each treatment, with their corresponding 95% CrIs, are presented in [Table 16](#). There was a high level of uncertainty in treatment ranks; all treatments had rank probabilities below 50% for all treatment ranks.

Updated threshold analysis

Overall survival

The forest plot for the threshold analysis is presented in [Figure 28](#).

RESULTS

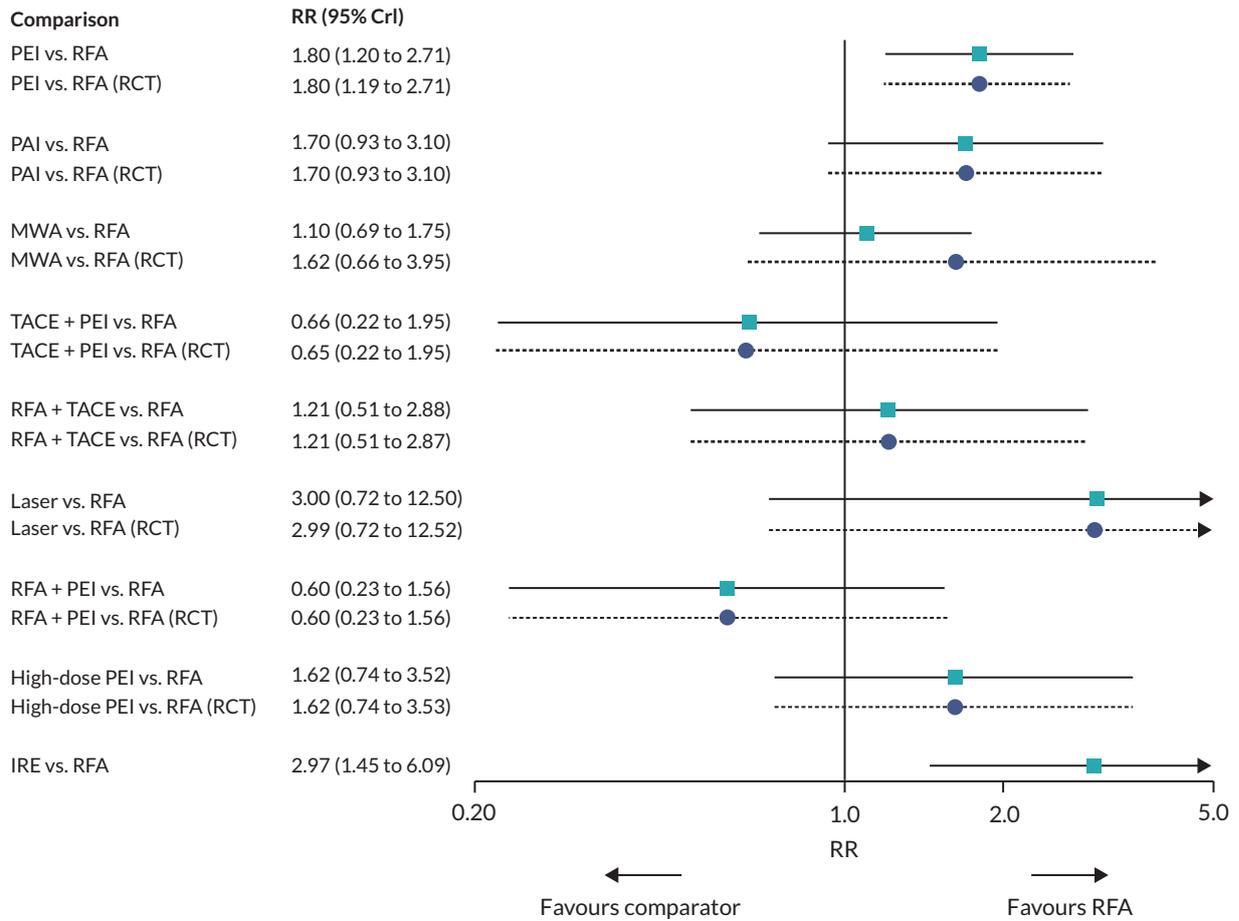


FIGURE 26 Plot of RRs for local recurrence compared with RFA for the FE model. RRs < 1 favour the comparator treatment over RFA.

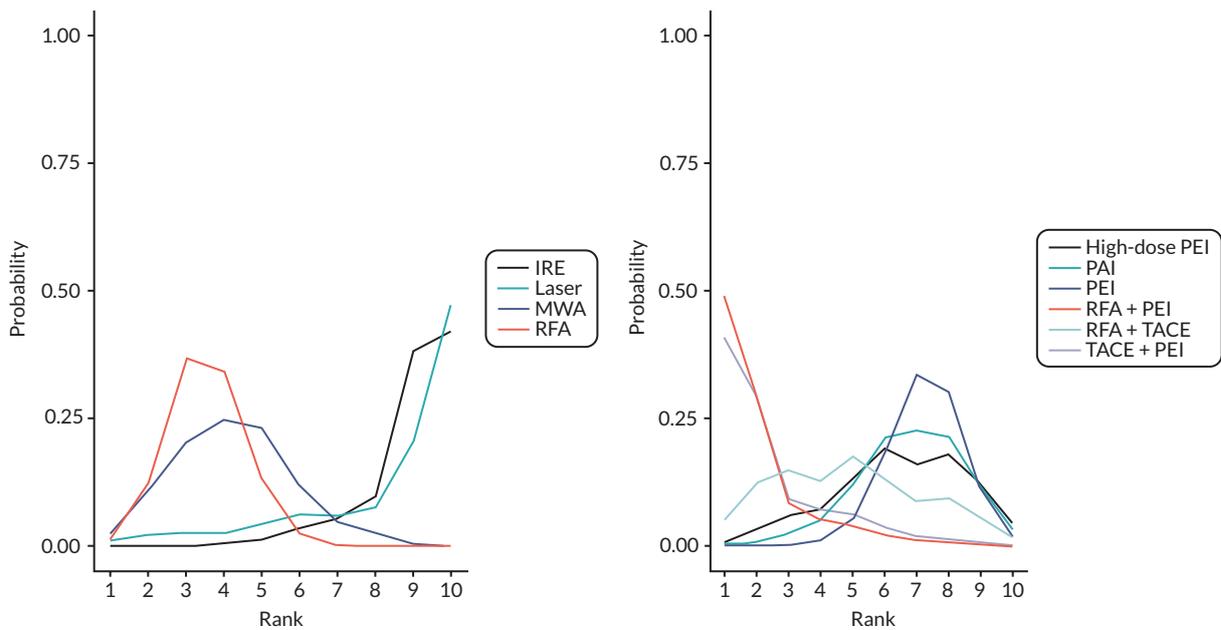


FIGURE 27 Rank plot for local recurrence for the FE model.

TABLE 16 Mean and median ranks, with corresponding 95% CrIs, for local recurrence, sorted by mean rank, for the FE model

Treatments	Mean rank	Median rank	95% CrI
RFA + PEI	2.03	2	(1.00 to 6.00)
TACE + PEI	2.38	2	(1.00 to 7.00)
RFA	3.53	3	(2.00 to 5.00)
MWA	4.23	4	(2.00 to 8.00)
RFA + TACE	4.90	5	(1.00 to 9.00)
High-dose PEI	6.45	7	(2.00 to 10.00)
PAI	6.78	7	(3.00 to 10.00)
PEI	7.25	7	(5.00 to 9.00)
Laser	8.40	9	(2.00 to 10.00)
IRE	9.05	9	(6.00 to 10.00)

Interventions that included PEI and PAI were not considered in the threshold analysis, and therefore comparisons including those interventions – PEI versus RFA (2 vs. 1), PAI versus RFA (3 vs. 1), RFA + PEI versus RFA (10 vs. 1), PAI versus PEI (3 vs. 2), TACE + PEI versus PEI (6 vs. 2), and TACE + PAI versus PAI (7 vs. 3) – had very large thresholds on the log scale. The following comparisons also had very large thresholds on the log scale: RFA + TACE versus RFA (8 vs. 1), IRE versus RFA (11 vs. 1). None of the other comparisons have thresholds that indicate estimates are sensitive to small changes in log-HRs. The thresholds and new optimum treatments, based only on relative effects, are presented in [Report Supplementary Material 5](#).

Progression-free survival

The forest plot for the threshold analysis is presented in [Figure 29](#).

Credible intervals for the RFA + TACE versus RFA (5 vs. 1), MWA versus RFA (6 vs. 1), and IRE versus RFA (7 vs. 1) comparisons extend beyond the limits of the invariance intervals, suggesting that the recommended treatment is sensitive to the uncertainty in the data, changing the optimum treatment to MWA for the RFA + TACE versus RFA and MWA versus RFA comparisons and to IRE for the IRE versus RFA comparison.

Three comparisons that included PEI and PAI – PEI versus RFA (2 vs. 1), PAI versus RFA (3 vs. 1), and PAI versus PEI (3 vs. 2) – had very large thresholds on the log scale. The negative threshold for the resection versus RFA comparison (4 vs. 1) was very small, and a change of 0.21 units on the log-HR scale in the negative direction changes the optimum treatment to resection. The positive threshold for the RFA + TACE versus RFA comparison (5 vs. 1) was very small, and a change of 0.12 units in the positive direction changes the optimum treatment to MWA. Similarly, the negative threshold for the MWA versus RFA comparison (6 vs. 1) was very small, and a change of 0.13 units in the negative direction changes the optimum treatment to MWA.

Thresholds and new optimum treatments, based only on relative effects, are presented in [Report Supplementary Material 5](#).

Local recurrence

The forest plot for the threshold analysis is presented in [Figure 30](#).

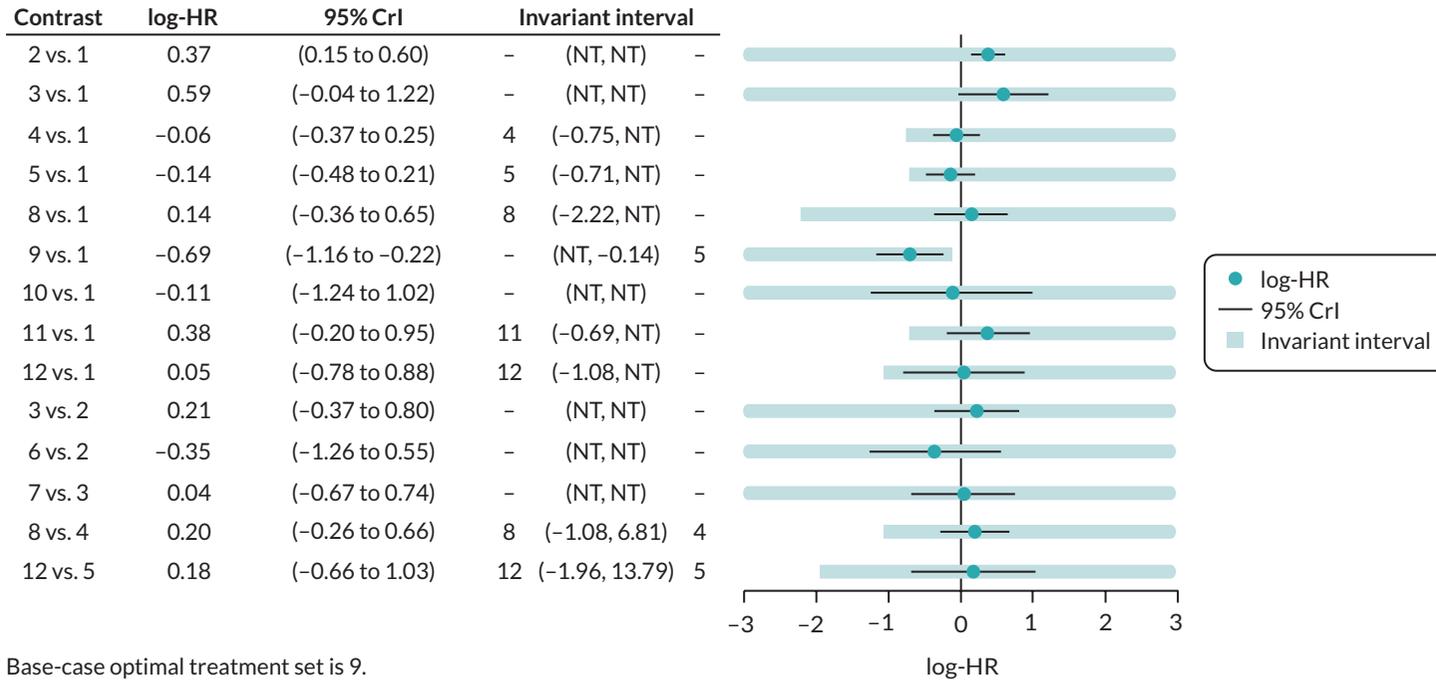


FIGURE 28 Forest plot for threshold analysis results for OS for the updated NMA.

Treatment codes: 1: RFA, 2: PEI, 3: PAI, 4: Resection, 5: MWA, 6: TACE + PEI, 7: TACE + PAI, 8: RFA + TACE, 9: RFA + iodine-125, 10: RFA + PEI, 11: Laser, 12: IRE. The optimum treatment for this analysis was RFA + iodine-125.

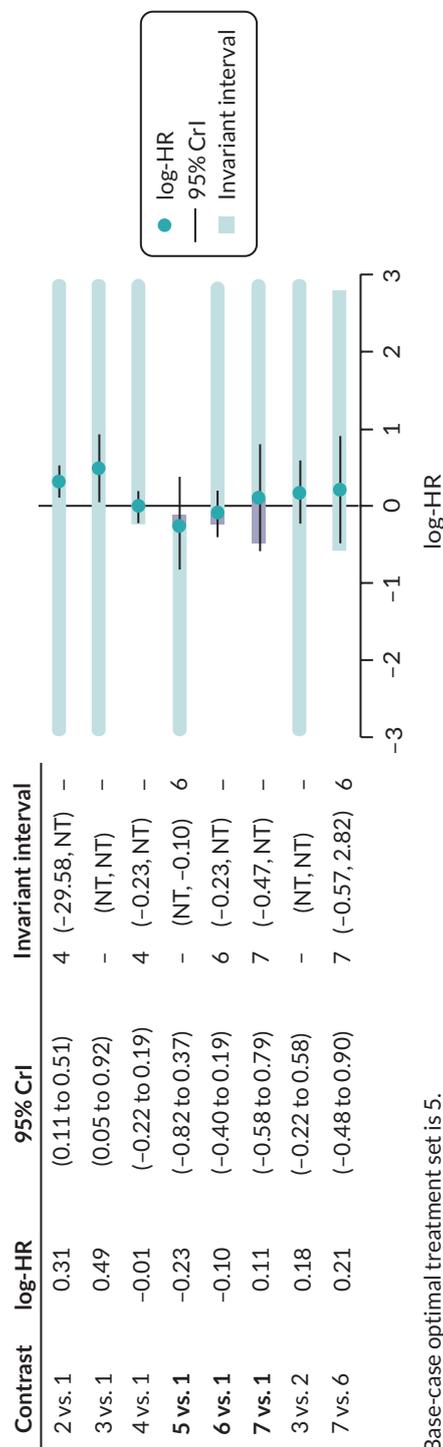


FIGURE 29 Forest plot for the threshold analysis for PFS for the updated NMA. The light blue shaded bars represent the invariant interval; where the bars are shown in purple, CrIs for the comparison extend beyond the invariant interval. Treatment codes: 1: RFA, 2: PEI, 3: PAI, 4: Resection, 5: RFA + TACE, 6: MWA, 7: IRE. The optimum treatment for this analysis was RFA + TACE.

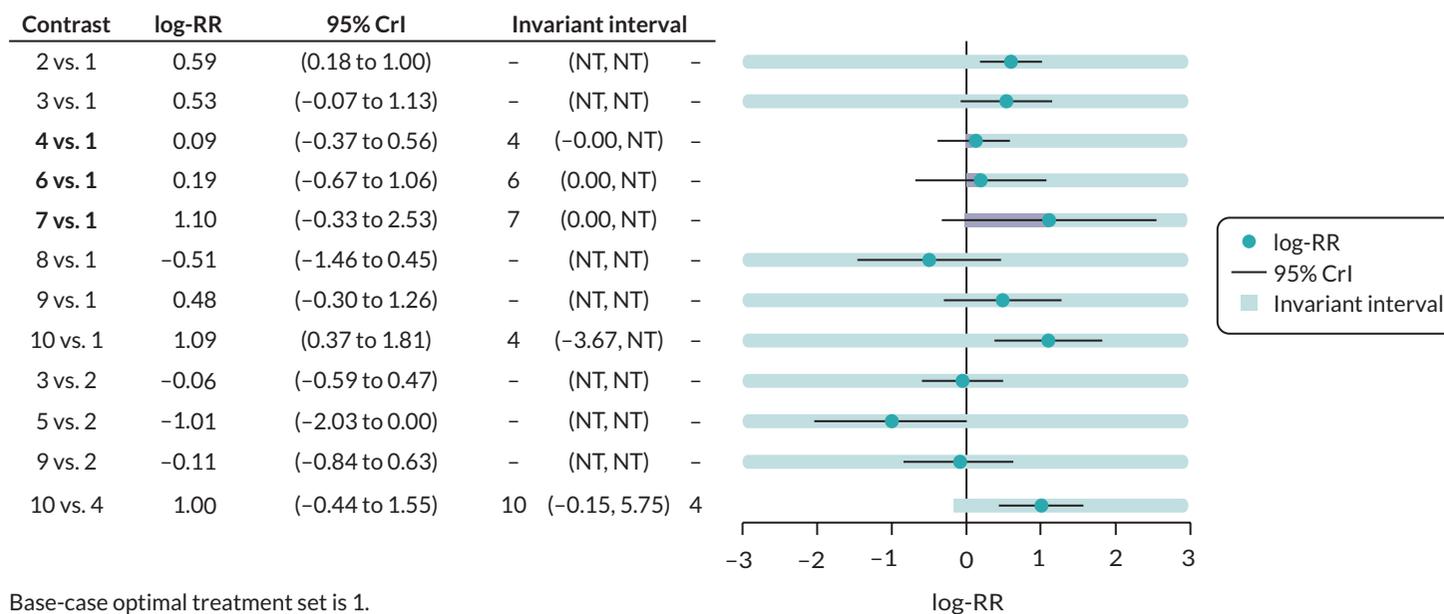


FIGURE 30 Forest plot for results of threshold analysis for local recurrence for the updated NMA.

The light blue shaded bars represent the invariant interval; where the bars are shown in purple, CrIs for the comparison extend beyond the invariant interval.

Treatment codes: 1: RFA, 2: PEI, 3: PAI, 4: MWA, 5: TACE + PEI, 6: RFA + TACE, 7: Laser, 8: RFA + PEI, 9: High-dose PEI, 10: IRE. The optimum treatment for this analysis was RFA + PEI.

Credible intervals for the MWA versus RFA (4 vs. 1), RFA + TACE versus RFA (6 vs. 1), and laser versus RFA (7 vs. 1) comparisons extend beyond the limits of the invariance intervals, suggesting that the recommended treatment is sensitive to the uncertainty in the data, changing the optimum treatment to MWA, RFA + TACE and laser, respectively.

Seven comparisons that included PEI and PAI – PEI versus RFA (2 vs. 1), PAI versus RFA (3 vs. 1), RFA + PEI versus RFA (8 vs. 1), high-dose PEI versus RFA (9 vs. 1), PAI versus PEI (3 vs. 2), TACE + PEI versus PEI (5 vs. 2), high-dose PEI versus PEI (9 vs. 2) – had very large thresholds on the log scale.

The negative thresholds for the MWA versus RFA (4 vs. 1) and RFA + TACE versus RFA (6 vs. 1) comparisons were very small, and changes of 0.09 and 0.19 units in the negative direction change the optimum treatments to MWA and RFA + TACE, respectively.

Thresholds and new optimum treatments, based only on relative effects, are presented in [Report Supplementary Material 5](#).

Chapter 5 Feasibility of economic modelling

This section considers the feasibility of developing a de novo economic model to inform a cost-effectiveness and value of information (VOI) analysis considering ablative and non-surgical therapies for the treatment of small HCC tumours. In considering the feasibility of an appropriate economic evaluation, it is assumed that the developed model will be consistent with the NICE reference case,⁹⁷ adopting a UK perspective and using a cost-utility approach accounting for both the relevant costs and benefits of the assessed technology.

Approach

Assessment of the feasibility of undertaking economic evaluation and VOI analysis was considered by conducting a targeted review exploring previous economic analyses evaluating technologies for the treatment of HCC; see *Review methods* below for details of methods used. Studies identified in the review were then summarised to consider key features and what data are typically required to support these models. Based on these previous evaluations and in consultation with clinical experts, a conceptual model was then developed to consider an appropriate model structure that could be used in any future economic analysis.

The availability of data to inform an economic analysis was considered. This assessment covered the availability of relevant clinical evidence (based principally on the clinical effectiveness review). The availability of evidence concerning quality of life, resource use and costs was also considered; this was informed by evidence identified as part of the clinical effectiveness review, the identified cost-effectiveness studies and established sources of relevant data.

Cost-effectiveness review

Review methods

Targeted literature searches were adapted from the search strategies used to identify RCTs (see [Appendix 1](#)) and included terms for small or early HCC and a broad set of terms aimed at identifying any economic evidence. The following databases were searched in May 2021:

- Ovid MEDLINE(R) ALL: 1946 to 12 May 2021
- Embase: 1974 to 12 May 2021
- NHS Economic Evaluation Database
- Econlit: 1886 to 29 April 2021.

Study design search filters for economic papers were applied to Ovid MEDLINE and Ovid Embase only. The *Canadian Journal of Health Technologies* (CADTH)'s⁹⁸ narrow economic filter was used on MEDLINE and was adapted for use on Embase. No language or geographical restrictions were applied to the searches across any of the databases. A date limit of 2000 onwards was applied to the searches to align with the clinical effectiveness review. Details of the search strategies used are reported in [Report Supplementary Material 1](#).

Study selection was conducted in two stages: (1) titles and abstracts were examined and screened for any study potentially relevant to the cost-effectiveness review; and (2) full texts were then obtained and screened for inclusion. A single reviewer screened all studies.

Studies were included in the review if they assessed the cost-effectiveness of any technology for the treatment of very early/early HCC; note that this is broader than the inclusion criteria for the clinical effectiveness review. A broad range of studies was considered for inclusion in the review, including

economic evaluations conducted alongside trials, modelling studies, and analyses of administrative databases. Only full economic evaluations comparing two or more options and including both costs and consequences (cost-effectiveness, cost-utility or cost-benefit analyses) were included.

Studies meeting the inclusion criteria were summarised, noting key features including the model structure adopted, key assumptions and any data reported that may be relevant to undertaking an economic evaluation of ablative and non-surgical therapies for early HCC. As this was not intended to be a formal review of cost-effectiveness studies, study quality was not assessed.

Results

A flow diagram describing study selection is presented in [Figure 31](#). Searches of the literature for economic evidence identified 496 papers following the removal of duplicates, with 38 identified for full

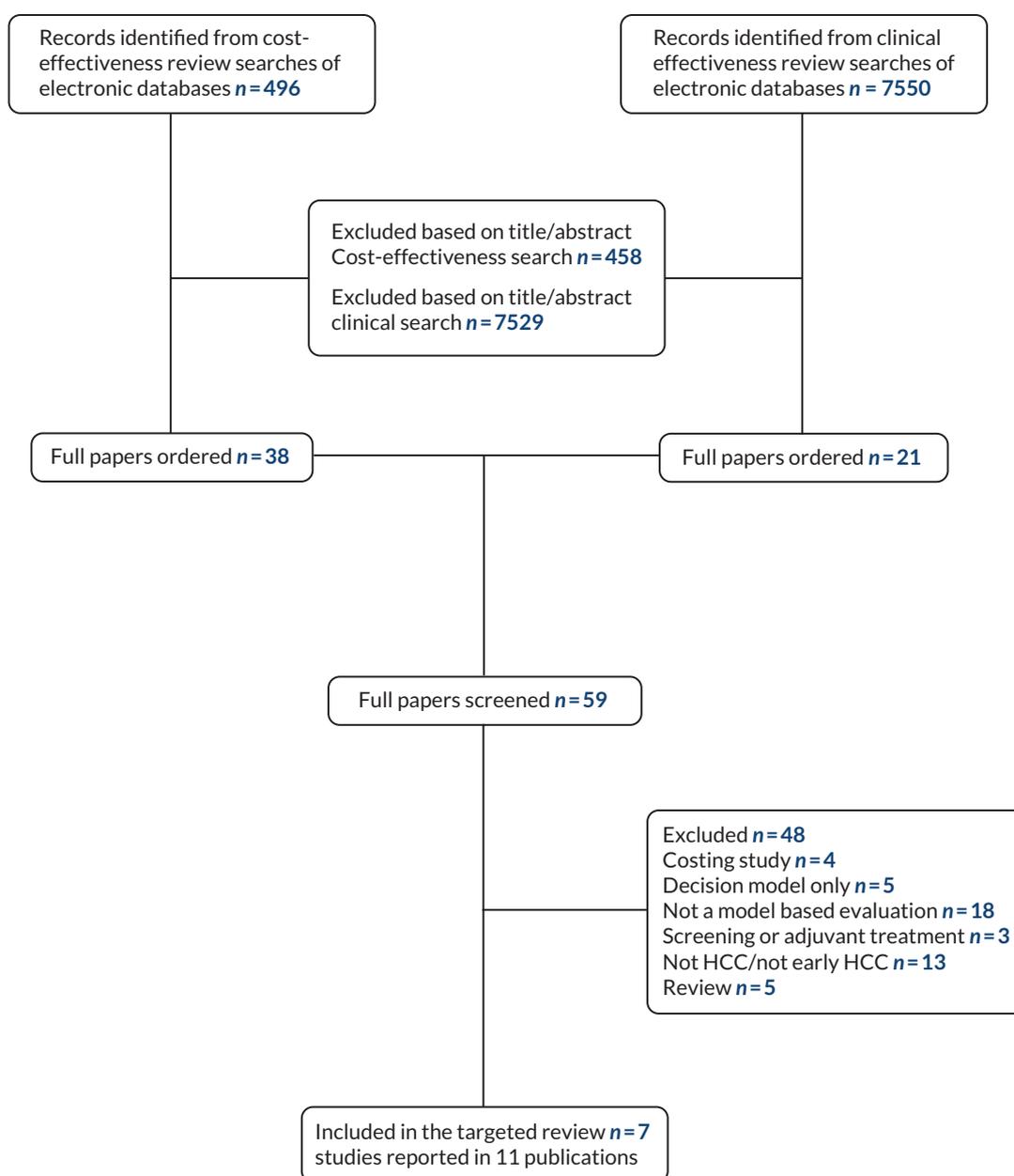


FIGURE 31 Flow diagram of the study selection process (cost-effectiveness review).

text review. A further 21 papers were identified for full text review as part of the clinical effectiveness review, making a total of 59 papers. Following the selection process, seven studies reported in 11 publications were found to meet the eligibility criteria and were included in the review.

An overview of the study characteristics for each included study is presented in [Table 17](#). The majority of studies evaluated two treatment alternatives. Interventions evaluated included liver transplant, resection, RFA, SIRT, and TACE. In UK clinical practice, the use of SIRT, TACE and liver transplant for the treatment of small HCCs is limited; their inclusion in the identified studies reflects the broad inclusion criteria and national differences in clinical practice.

TABLE 17 Data extraction: cost-effectiveness review

Cucchetti (2013)⁹⁹⁻¹⁰¹

Model structure	The modelling approach is not fully clear; described as a Markov model, but potentially adopts a semi-Markov or simulation approach. Model considers survival, recurrence and Child-Pugh status.
Time horizon, perspective and discounting	Time horizon was not stated. Perspective and setting were not stated, though the majority of the costs were drawn from Italian national health system. Costs and benefits were discounted at a rate of 3%.
Population	Patients within the Milan criteria up to three tumours < 3 cm, or one tumour up to 5 cm.
Intervention and comparators	Resection vs. RFA.
Clinical evidence	Parametric extrapolation of survival data (OS and disease-free survival) appears to have been undertaken though the specific approach adopted is unclear. Hazard rates applied to model treatment efficacy were based on the proportion of patients achieving 3-year survival/3-year disease-free survival and were drawn from a meta-analysis of relevant studies. The model also drew on evidence of hospital length of stay which was drawn from the meta-analysis and parameterised in the model.
HRQoL	Health state utilities were based on values reported in the literature, including a review by McLemon <i>et al.</i> ¹¹⁰ Values did not vary by treatment received and were not specific to HCC.
Resources and costs	Cost categories modelled included procedure costs, length of stay, costs of subsequent treatments and patient follow-up costs. Costs applied in the model were obtained from Medicare and Italian national health system sources.

Lai (2014)¹⁰³

Model structure	Markov model with the following health states: small HCC < 3 cm tumour, cancer-free, progressive HCC and death. Additional tunnel states were also used to count the number of ablation procedures, with a maximum of three permitted.
Time horizon, perspective and discounting	Time horizon appeared to be lifetime horizon (until 99% of patients were dead). A Chinese health-care setting was considered, but the perspective was not stated formally. Costs and benefits were discounted at a rate of 3%.
Population	Patients with a solitary, small tumour < 3 cm and Child-Pugh class A or B.
Intervention and comparators	Real-time virtual sonography-guided ablation vs ultrasound-guided ablation.
Clinical evidence	Probabilities for each outcome were drawn from the literature, with the majority of inputs drawn from Cho <i>et al.</i> ¹¹¹ Efficacy was not determined using comparator estimates of effect. Outcomes considered included mortality rates (with separate rates applied to cirrhotic patients, tumour-free patients, progressed HCC), ablation success rate, rate of local recurrence, distant recurrence, probability of seeding tumour (RFA only), liver transplant rate, procedure-related mortality and procedure-related complications.
HRQoL	Health state utilities were based on values reported in the literature, including McLemon <i>et al.</i> ¹¹⁰ Values did not vary by treatment received and were not specific to HCC.
Resources and costs	Cost categories considered included procedure costs, inpatient administration costs associated with RFA, disease management and follow-up care costs, terminal care costs, and AE costs. Values were drawn from the literature and did not consider any UK relevant sources.

continued

TABLE 17 Data extraction: cost-effectiveness review (*continued*)**Lim (2015)¹⁰⁹**

Model structure	Markov cohort model with alternative model structures applied according to treatment received. In the liver resection arm the following health states were modelled: compensated cirrhosis, decompensated cirrhosis, HCC recurrence, dead. In the liver transplant arm the following states were modelled: waiting list compensated cirrhosis, waiting list decompensated cirrhosis, liver transplant contraindicated, post liver transplant, dead.
Time horizon, perspective and discounting	Time horizon was not reported; a payer perspective was adopted though setting was not clear. Costs and benefits discounted at a rate of 3%.
Population	Patients within the Milan criteria up to three tumours < 3 cm, or one tumour up to 5 cm.
Intervention and comparators	Liver resection vs. liver transplant.
Clinical evidence	Evidence was drawn from multiple sources identified in the literature and did not rely on comparative assessment of effectiveness. Outcomes modelled included: decompensation risk, decompensated cirrhosis-related survival, postoperative risks (liver resection and liver transplant), post liver resection recurrence rate, wait list time, dropout risk and survival.
HRQoL	Health state utilities were based on values reported in the literature, though the specific studies used were not reported. Values did not vary by treatment received.
Resources and costs	Cost categories considered included: procedure costs, and disease management and follow-up costs. Costs were drawn from a systematic review of values reported in the literature and the median reported value used. Where data were unavailable, clinical expert opinion was used. Costs used were not directly relevant to the UK.

Naugler (2010)¹⁰⁶

Model structure	Markov model using two distinct structures for each arm. In the watchful waiting arm the following health states were modelled: monitoring without therapy, tumour progression inside Milan criteria, tumour progression outside Milan criteria, liver decompensation, and death. In the immediate treatment arm the following health states were modelled: HCC therapy, tumour progression inside Milan criteria, liver decompensation, and death.
Time horizon, perspective and discounting	Time horizon was 10 years. Perspective and setting were not stated; costs were however, drawn from the US health system. Costs and benefits were discounted at a rate of 3%.
Population	Patients with tumours < 2 cm, not eligible for resection but eligible for transplant with compensated cirrhosis.
Intervention and comparators	Watchful waiting vs. immediate treatment with TACE vs. immediate treatment with RFA.
Clinical evidence	Probabilities for each outcome were drawn from the literature using multiple sources. Efficacy was not determined using comparator estimates of effect. Outcomes modelled in the watchful waiting arm included: tumour progression inside/outside Milan criteria, and survival inside/outside Milan criteria. Outcomes modelled in the immediate treatment arm included: survival within Milan criteria, survival without progression, tumour progression inside Milan criteria. In both arms the model also considered liver decompensation risk, liver transplant rate, and post-transplant survival.
HRQoL	Not considered.
Resources and costs	Cost categories modelled included procedure costs, disease management and patient follow-up costs, drug acquisition costs. Costs applied in the model were obtained from Medicare and were not relevant to a UK setting.

Rostambeigi (2014)^{107,108}

Model structure	The model used a simulation approach. The structure adopted was not clearly reported, but appeared to allow for disease recurrence, mortality, and liver transplant.
Time horizon, perspective and discounting	Time horizon was not stated. Perspective and setting were not stated; costs were however, drawn from the US health system. Discounting of future costs and benefits does not appear to have been applied.
Population	BCLC A.

TABLE 17 Data extraction: cost-effectiveness review (continued)

Intervention and comparators	SIRT vs. TACE.
Clinical evidence	Probabilities for each outcome were drawn from exponential curves and used to estimate survival based on reported survival rates. Other outcomes considered include recurrence and re-treatment of HCC, and transplant rates.
HRQoL	Not considered.
Resources and costs	Cost categories modelled included procedure costs, AEs, and patient follow-up costs. Costs applied in the model were obtained from Medicare reimbursement costs and were not directly relevant to the UK.

Sarasin (2001)¹⁰²

Model structure	A Markov model was developed that accounted for wait time for transplant. Modelled health states included: cirrhosis, HCC, no contraindications to CLT, cured HCC and cirrhosis, contraindications to CLT/palliative care, and death.
Time horizon, perspective and discounting	Time horizon was not stated. A US payer perspective was adopted using 1998 prices. Costs and benefits were discounted at a rate of 3%.
Population	Early HCC – single HCC not exceeding 5 cm in diameter, or up to three tumours up to 3 cm in size, in the absence of vascular or extrahepatic involvement.
Intervention and comparators	CLT vs. LDLT.
Clinical evidence	Parameter inputs were identified via searches of the literature. Outcomes were determined by wait time (2 months for LDLT, 6 months for CLT), probability of developing contraindications, donor mortality, palliative care mortality and post-transplant mortality. Transplant outcomes between CLT and LDLT were assumed to be the same.
HRQoL	Utility values were informed by the literature and did not vary by treatment received.
Resources and costs	Cost categories modelled included chemoembolisation costs incurred while waiting for transplant, transplant-related costs (assumed to be the same for CLT and LDLT), donor assessment (accounting for failures to proceed), and disease management and patient follow-up costs. Costs used were not directly relevant to the UK.

Spolverato (2015)^{104,105}

Model structure	Multistate model with alternative model structures applied according to treatment received. The model considered the following states: undergoing liver resection or radiofrequency treatment (liver resection/RFA only), liver decompensation (liver resection/RFA only), HCC recurrence (liver resection/RFA only), progression of disease within Milan criteria (liver resection/RFA only), progressive disease outside Milan criteria, transplant waiting list, (post) liver transplant, and death.
Time horizon, perspective and discounting	Time horizon was not reported. Italian and US healthcare settings were considered using a payer perspective. Costs and benefits were discounted at a rate of 3%.
Population	Patients within the Milan criteria up to three tumours < 3 cm, or one tumour up to 5 cm.
Intervention and comparators	Liver transplant vs. liver resection or RFA with salvage liver transplantation.
Clinical evidence	Evidence was drawn from multiple sources identified in the literature and did not rely on comparative assessment of effectiveness. Outcomes modelled included: transplant wait time, post-transplant mortality, wait list dropout rate, liver decompensation, disease recurrence.
HRQoL	Health state utilities were based on data reported in Lim <i>et al.</i> ¹⁰⁹ and did not vary by treatment received.
Resources and costs	Cost categories modelled included procedure costs, drug acquisition costs, disease management and patient follow-up costs. Resource data were drawn from two previous reviews of the literature: Cucchetti <i>et al.</i> ⁹⁹⁻¹⁰¹ was used for Italian healthcare costs and Lim <i>et al.</i> ¹⁰⁹ for US costs. Costs used were not directly relevant to the UK.

CLT, cadaveric liver transplantation; LDLT, living donor liver transplantation.

None of the identified studies considered a UK NHS perspective. One study considered an Italian setting only,⁹⁹⁻¹⁰¹ one a US setting only,¹⁰² and one a Chinese setting only.¹⁰³ One further study considered both an Italian and a US setting.^{104,105} In three studies the setting was not formally stated. In two of these studies,¹⁰⁶⁻¹⁰⁸ costs were reported for a US setting, while a third study¹⁰⁹ reported costs for three alternative settings: USA, Singapore and Switzerland. All studies considered a payer perspective, where stated. As no study considered a UK setting, costs utilised are not relevant to the UK perspective. The identified studies are therefore unlikely to represent an informative source of resource data for any future economic evaluation adopting a UK perspective.

The model structures adopted in the identified studies varied significantly, with several alternative underlying approaches adopted. These included Markov models,^{103-106,109} semi-Markov models,⁹⁹⁻¹⁰¹ and simulation approaches.^{107,108} Model structures adopted were typically highly complex, with several using a large number of health states. Importantly, model structures did not conform to the three-state models commonly used in cancer evaluations. Despite a lack of consistency in the approach adopted across models, several features were common to the included studies. These included the modelling of recurrence of disease and the competing risks of declining liver function. Both of these features were uniquely associated with locoregional therapies such as RFA and resection and were not considered relevant to patients receiving a liver transplant. In several models, this meant that the structure adopted differed substantially between treatment arms.^{104-106,109}

Because of the novel model structures adopted, treatment effects were often modelled using several parameters typically drawn from multiple studies. While this approach reflects the complex treatment pathways and allows a broader evidence base to be drawn upon, it comes with significant disadvantages. Namely, in this approach treatment effects are not based on comparative evidence and are highly likely to be subject to confounding biases. Further, while many models considered multiple outcomes, it is clear from model results that survival is the principal driver of benefits. An important consideration for future economic evaluations will therefore be how to best integrate available comparative evidence while also accounting for the divergent treatment pathways. In an ideal scenario this is likely to mean drawing directly on comparative evidence of survival. However, given the potentially curative nature of the evaluated treatments, such comparative evidence may be uninformative due to lack of maturity and developments in care for progressed HCC. It may therefore be necessary to draw on external data sources potentially linked to intermediate outcomes or events like transplant or recurrence of disease to populate an economic model.

Model scope and availability of comparative data

Based on the systematic review of clinical effectiveness evidence and clinical advice, it is anticipated that there is a wide range of relevant comparators. These include established treatments such as resection and MWA, treatments that have more recently become available to UK patients such as SABR, and treatments that are no longer/rarely used in clinical practice (PEI and laser ablation). In principle, all of these therapies could be considered by a future cost-effectiveness analysis. However, clinical advice suggests that many of these newer technologies are rarely used in routine practice (e.g. ECT) owing to a lack of evidence/approval, while older technologies such as PEI and PAI have largely been discontinued due to lack of efficacy and concerns regarding AEs. Further, clinical advice suggests that some technologies such as IRE and SABR would not be used in the whole small-HCC population but instead would be reserved for patients with tumours in locations that are either difficult to treat or patients who are otherwise medically unsuitable for RFA. Any future economic analysis will therefore need to carefully consider the decision problem being addressed and which comparators are likely most relevant to decision-makers. Further, given the absence of evidence for some potentially relevant comparators, including many of the newer technologies, it may be necessary for a future economic analysis to focus only on a subset of all relevant comparators. This may limit the feasibility of implementing an informative economic analysis and is likely to impact on the strength of conclusions that can be drawn.

Model structure and clinical data availability

The model structure typically adopted in economic evaluations of treatments for cancer uses a partition survival model (PSM) based around three health states: (1) pre progression, (2) post progression and (3) death. In a PSM the proportion of patients in each health state is determined directly from the survival curves, typically PFS and OS. Under this approach the proportion of patients in the 'pre-progression' state is determined by the PFS curve while the proportion in the 'post progression' state is determined by the difference between the modelled OS and PFS survival curves. Theoretically this approach could be adopted in the context of early HCC, but it may need adaptation to account for specific features of the indication. For example, as highlighted above, many models account for the competing risk associated with liver decompensation and potential for recurrence but not progressed disease. These complications may undermine the feasibility of a PSM approach, and the adaptations necessary may be easier to accommodate in a state transition model where it is often easier to explicitly acknowledge competing risks.

An alternative to the PSM approach would be to use a state transition model focused on utilising comparative evidence on recurrence and disease-free survival. This approach aligns with much of the previous cost-effectiveness literature and would more readily recognise the surrogate role that recurrence and disease-free survival play in determining OS. Under such an approach, post-recurrence survival would likely be modelled using a common set of assumptions for all treatments. While notionally this is a disadvantage as it assumes a consistent surrogate relationship between recurrence and OS, it would allow external data to be levied; this may provide improved estimates relative to the available trial data, which may be limited due to the short follow-up in many studies. This approach also allows post-recurrence survival to reflect recent developments in the treatment and care of patients with intermediate and advanced-stage HCC. This may be important given the more recent (post 2009) availability of sorafenib and other agents for the treatment of advanced HCC and the fact that the majority of the currently available clinical evidence is not from a UK setting.

Clinical advice on the aims of treatment emphasised the importance of recurrence, and particularly local recurrence, as a marker of treatment success. The importance of local recurrence as a determinant of mortality was also emphasised. It was, however, also emphasised that other factors are also important determinants of survival and may confound any relationship between local recurrence and OS. These included both intrahepatic and extrahepatic recurrence, which may lead to cancer progression regardless of local disease control. Further, clinicians noted the importance of liver function as a competing mortality risk, as well as its significance in determining patient quality of life.

This advice would appear to broadly support the use of a recurrence-focused approach but also emphasises the complexity of very early/early HCC and the need to account for the competing risks of disease progression and liver decompensation. The clinical data available to inform a recurrence-focused approach are, however, limited. Few studies identified in the clinical review reported recurrence, with only 10 of 27 identified studies reporting recurrence outcomes. This may impact on the feasibility of developing a robust economic model based around recurrence of disease, as it means that the totality of the evidence cannot be considered.

More broadly, inherent uncertainties in the clinical evidence, as well as concerns about the quality of included evidence, will have important consequences for any future economic analysis. As presented in *Updated network meta-analyses using RCT and non-RCT evidence*, current clinical evidence is insufficient to make recommendations about the relative effectiveness of the majority of treatments. An economic analysis cannot resolve these uncertainties and will necessarily be limited by them. Importantly, these uncertainties are likely to undermine the ability of any future economic analysis to make recommendations about which treatments are most cost-effective. This may undermine the value of implementing an economic analysis. An economic analysis may, however, still be worthwhile because of its ability to quantify the uncertainty associated with implementation decisions. In doing so, an economic analysis can help provide information about the value of future research; see [Value of information](#) below for further discussion.

Utilities and quality of life

In the literature identified as part of the clinical effectiveness review, no RCTs and only one non-RCT collected quality-of-life data,⁸⁷ and no study reported utility data. Any new economic evaluation will therefore have to identify alternative sources of relevant utility data. The identification of relevant utility data is likely to require detailed searches of the literature. Based on the cost-effectiveness evidence identified in our review, several studies reported utility values that may be relevant to any future analysis.^{99-103,106,109} However, the provenance of some of the values reported is unclear.¹⁰⁹ In other cases, it is also apparent that the values obtained are taken from patients with liver disease rather than specifically from patients with HCC.^{102,103} Further, several of the evaluations identified in the cost-effectiveness review highlighted limitations in the available quality-of-life data.^{102,104,105,109} Identifying relevant utility data is likely to represent a significant challenge and source of uncertainty for any new economic evaluation in early HCC.

Resource use and costs

Resource use and costs should include treatment costs (acquisition, procedures, and monitoring), changes in health service utilisation driven by disease status (i.e. progression-free, progressed disease, and death), and AE management. Costing data from previous economic analyses in early HCC are unlikely to be informative due to differences in perspective; no study was conducted from a UK perspective. Further, few studies reported relevant resource-use estimates associated with specific treatments. Previous economic evaluations are therefore unlikely to provide resource inputs for a new model.

Several of the studies identified in the clinical effectiveness review reported on useful economic outcomes such as length of hospital stay. Assuming these studies are generalisable to a UK setting, these outcomes could be used to support inputs regarding acute care and monitoring following treatment. The majority of resource-use inputs will, however, need to be identified in further research. This may be in the form of a clinician survey to elicit resource utilisation or identification of relevant costing studies. Alternatively, health state management costs may be informed by previous UK economic evaluations in advanced HCC, and adapted to account for the target early HCC population. Costing data for the UK are readily available from several commonly used sources. These include NHS reference costs,¹¹² Personal Social Services Research Unit,¹¹³ and the British National Formulary.¹¹⁴ While further research is necessary, the availability of resource-use and costing data is unlikely to represent a significant barrier to implementing a future economic evaluation.

Value of information

The construction of a de novo economic analysis in which uncertainty is fully parameterised would allow the implementation of a VOI analysis. A VOI analysis permits the value of reducing decision uncertainty to be quantified in monetary terms. The VOI can then be compared with the costs of further studies and used to assess whether additional research should be conducted to reduce decision uncertainty.

In the context of the current evidence, a VOI analysis may be particularly helpful, as there are currently several treatment alternatives for which there is limited evidence on effectiveness. A VOI analysis could help prioritise which of these treatments should be assessed in future trials, accounting for both the degree of clinical uncertainty and the economic case for a specific treatment. This may be of particular relevance in considering treatments that are currently rarely used in NHS practice but may be effective; for example, laser ablation and RFA. Moreover, a VOI analysis may help to provide clearer guidance on where research is not worthwhile despite the presence of clinical uncertainty. For example, VOI may be able to rule out particularly expensive technologies on cost grounds alone despite the potential for clinical benefit.

Chapter 6 Patient and public involvement

Aim

The aim of patient and public involvement was to ensure that the patient's perspective was captured at all stages, from protocol development through to interpreting the results of the project and drawing conclusions and recommendations for further research.

Methods

A patient collaborator was recruited to the project at the proposal writing stage via 'Involvement@York', the patient and public involvement network at the University of York. The patient collaborator attended all advisory group meetings and provided ongoing advice throughout the project. The patient collaborator was also consulted when producing materials in 'plain English', such as materials used when recruiting additional patients to the advisory group and the plain English summary section of the final report. The patient collaborator will be consulted during further dissemination activities.

Four additional patients were identified by our clinical advisors and recruited as members of the advisory group. With help from the patient collaborator, a lay summary of the project was produced describing the project, the role of advisory group members and details of how patients would be compensated for their time. This was circulated to patients who had expressed an interest in being a member of the advisory group. Patients were also provided with a lay summary of the different interventions included in the systematic review.

One member of the project team (RW) was the main contact for all patient advisors and held individual meetings with patients at the protocol development stage. During this initial meeting, patients were given background information to the project and a rudimentary description of the protocol and were asked for their comments, specifically whether any patient-relevant outcomes or aspects of treatment were missing from the protocol. Owing to the COVID-19 pandemic, all advisory group meetings were held via the Zoom™ online videoconferencing platform (Zoom Video Communications, San Jose, CA, USA), rather than in person. Patients were invited to attend the next advisory group meeting and the end-of-project workshop (see *Workshop*). Patients were also asked to comment on the final report.

Results

All four patients were available at the beginning of the project to advise on the protocol. The patient collaborator and three of the patient advisory group members attended the second advisory group meeting held midway through the project to discuss the interim findings, prioritise interventions for further review and prioritise the most relevant patient outcomes. Patients provided helpful information about the outcomes most important to them, such as length of hospital stay and disruption to life (interventions requiring multiple appointments or repeat treatments) and level of pain involved. Non-recurrence of disease was another important outcome to patients. The patient collaborator and two patient advisory group members attended one of the end-of-project workshops. Unfortunately the other two patients were unavailable around the time of the workshops; in view of the reasons for their lack of availability, they were not pursued to attend at a different time. Patients were surprised by the lack of data on patient preference and quality-of-life outcomes in the existing evidence base. The patient collaborator and two patients commented on the final report.

Discussion and conclusions

The patient and public involvement aspect of the project highlighted the outcomes most important to patients, which informed the development of the data extraction form. Their views added context to the review findings and their input was valuable when drawing conclusions and making recommendations for further research. The initial meeting with patients was informative to help the researchers understand the experience of patients, their concerns and preferences.

Reflective/critical perspective

Patient involvement was a valuable part of this project, enabling researchers to understand important aspects of the different treatment options from a patient's perspective. One drawback was that meetings had to be held via the Zoom online videoconferencing platform, owing to the COVID-19 pandemic, which constrained the interactions with patients.

The feedback from patients was positive; they commented that information was presented clearly and that they found the meetings interesting and enjoyed being involved in the project.

Chapter 7 Workshop

Two workshops were held with clinical and patient advisory group members and additional clinicians with an interest in HCC (identified by advisory group members) in order to discuss the project findings and identify key priorities for future research. Due to the COVID-19 pandemic, the workshops were held using the Zoom online videoconferencing platform, on 29 November and 2 December 2021. Prior to the workshops, the attendees were sent a short summary of the findings of the project to date, including a summary of the methods and results of the systematic reviews, NMAs and the assessment of the feasibility of economic modelling.

Members of the project team presented a summary of the findings of the project and responded to clarification questions. There was a general discussion of the interpretation of the project findings, and workshop participants were asked about the key priorities for future research, including interventions, patient groups, and outcomes.

The lack of evidence for many interventions, low quality of the available evidence and uncertainty of the findings was highlighted. The generalisability of the findings of studies from East Asia (where the underlying aetiology of the liver disease differs from that in the West) was discussed, since most of the RCTs assessed RFA, which is more widely used in the East, whereas MWA has become the standard of care in most centres in the West. It was agreed that differences in underlying liver disease are likely to affect the absolute OS of patients, rather than the relative survival when comparing one treatment against another.

The progression in the West from RFA to MWA as the standard of care has been driven by technological advances and ease of use of MWA (which only requires single needle placement, so is both faster and simpler to deliver) rather than data on improved clinical effectiveness. MWA gives a more predictable ablation zone up to 3 cm, whereas the RFA ablation zone is less predictable towards the periphery. However, it was considered that, moving forward, it would not be appropriate to compare the clinical effectiveness of RFA versus MWA, as many interventional radiologists in the UK only know how to use MWA, not RFA, and clinicians believe that MWA is the superior treatment, so it may be difficult to recruit patients to a trial comparing the two treatments. In addition, RFA is only used for tumours up to 2 cm (owing to increased local recurrence after RFA in lesions larger than 2 cm), whereas MWA can be used for larger tumours; therefore, any trial comparing both technologies would have to restrict recruitment to patients with tumours up to 2 cm in order for patients to be eligible for both treatment arms. Lesions close to hepatic vessels are also less amenable to RFA, reducing the eligible patient cohort further.

RFA was used as the baseline treatment in the NMA (for comparison against other treatments) because it was the most widely assessed technology in the RCTs. Historically, surgery was considered to be the gold standard, before RFA became available. However, it would not be appropriate to compare the effectiveness of surgery versus ablation, as the risks of surgery for many patients are too high. Resection is not suitable for cirrhotic patients with marginal liver function or patients with clinically significant portal hypertension. Tumour location is also important; resection would not be suitable for patients with central tumours, particularly in patients with cirrhosis, as the risks of resection are much higher than those of ablation. At the second workshop, the comparison of MWA versus resection was discussed further, as some centres are still quite 'surgery heavy' and may want to see more trial evidence on MWA versus resection, although most centres are moving towards MWA owing to the complications of resection making it less acceptable than ablation.

Specific effectiveness outcomes and the association between liver decompensation (liver failure) and mortality were discussed. Registry data suggest that around half of patients who undergo ablation will die following liver decompensation, and half will die without liver decompensation; therefore, the risk

between recurrence and mortality is important, but there is substantial competing risk according to the severity of underlying disease. At the second workshop it was highlighted that some HCC treatments have a risk of causing liver decompensation, although patients with early HCC have good Child–Pugh scoring and good performance status.

It is difficult to demonstrate treatment benefit in a trial when there are competing risks of both liver disease progression to decompensation in addition to the risks of recurrent or new HCC. Recurrence can be local (near the site of the previously ablated lesion) or distant (a new lesion elsewhere within the liver); therefore, treatment of the original tumour may not impact on OS. Rates of recurrent and new HCC are very high; up to half of patients will have a new metachronous cancer within 3 years of treatment of the index lesion, which is a further driver of poor outcomes in this patient group. Rates of metachronous disease would be expected to be similar between different treatment arms in a trial, unless one of the interventions treats the whole liver. This is why transplantation is theoretically the best treatment for early-stage HCC, because it replaces the liver that has malignant potential with a new one, so there is no longer the risk of metachronous disease or decompensation. However, liver transplant is not normally the primary intervention for the population of patients with early-stage HCC.

Quality of life was only reported in one included study, a non-randomised study undertaken in China. It is important to assess quality-of-life outcomes and patient acceptability in any future trial; there is a lack of evidence on these important outcomes in the existing literature.

The problem of patient recruitment was discussed, as there are not many patients with early-stage (≤ 3 cm) HCC in the UK. 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. Therefore, an international multicentre RCT may be more appropriate than a UK-based trial.

At the first workshop, clinicians said that SABR and proton beam therapy are interventions of interest and that a trial of SABR or proton beam therapy versus MWA would be useful, although use of proton beam therapy is limited by geographical availability. Local control rates with both treatments are very high; therefore, undertaking a trial that was sufficiently powered to show a survival benefit would be difficult, since neither deals directly with recurrence (metachronous or extrahepatic disease) and neither has an impact on rates of decompensation. Local recurrence would have to be the primary outcome in such a trial, with OS and PFS as secondary outcomes. At the second workshop it was also agreed that local recurrence and overall recurrence are both important outcomes.

It is internationally recognised that there needs to be more trial-based evidence for SABR in the treatment of patients with early-stage HCC. The availability of such evidence is limited by the fact that ablation techniques such as MWA and RFA are usually employed first for patients with early HCC and SABR reserved for recurrent, refractory or more advanced disease. SABR can usually only be delivered once because of the radiation dose, whereas ablation can be repeated; therefore, there is also the question of when it should be used – should it be saved until later in the treatment pathway? There was discussion around assessing different treatment sequences. Although treatment sequencing is an important question, the difficulty is the heterogeneity of recurrence, which has implications for the next treatment choice; therefore, it may not be possible to predetermine the second line in the sequence. Both MWA and SABR can be used for patients with tumours ≤ 3 cm, and both interventions can be used to treat more than one lesion at once; therefore, trial eligibility criteria would have to reflect this. There would also need to be eligibility criteria limitations based on liver function, as patients with advanced/moderately advanced liver disease are not suitable for SABR but could possibly be suitable for ablation; patients recruited to a trial would have to be eligible for both treatments.

At the second workshop, clinicians considered that a trial of SABR versus MWA may be less appropriate; MWA is a good treatment for small tumours, while SABR is usually reserved for tumours that do

not respond or are unsuitable for ablation or are in a difficult location. Therefore, SABR and other radiotherapy techniques would not replace MWA. In addition, MWA can be repeated, while SABR can usually only be used once. This positioning of SABR reflects current NHS England commissioning guidance which suggests SABR and MWA for different patient populations; for patients with very early/early-stage HCC, ablation is the first choice, while if the lesion cannot be clearly visualised for ablation or is in a location that cannot be reached with a needle, then TACE would be offered. If TACE is contraindicated (e.g. for cardiac reasons or if the patient has had TACE previously and failed), then SABR would be offered. The clinicians also noted there is a study in North America comparing SABR versus proton beam therapy; proton beam therapy may be the preferred modality for patients depending on disease location.

At the first workshop, clinicians said that IRE can be used for lesions that are very central; therefore, a trial of IRE versus MWA for the subgroup of patients with central lesions may be useful, although SABR could also be used. At the second workshop it was agreed that IRE is sometimes used for more challenging tumours, but owing to the evidence base being very limited for IRE, SABR is the preferred option. In addition, IRE is quite costly; therefore, MWA would be used when suitable; they would not be comparable in a trial.

ECT is very similar to IRE but with the addition of bleomycin. It is beginning to feature in Europe, so may be of interest.

Cryoablation was not considered to be of interest as it is a high-risk treatment. It has not been widely adopted in the West. At the second workshop, it was stated that more evidence is being published on cryoablation, especially for lesions that are difficult to treat with MWA, such as those that are near the dome of the liver or close to the heart, where freezing therapy is slightly less damaging than heat treatment; thus it is mostly used for those lesions that are difficult to treat because of nearby vital structures. However, if IRE is available, that would be used rather than cryoablation, so cryoablation has a lower priority.

Laser has also not been widely adopted in the West. It involves multiple needle placement, whereas MWA only requires single needle placement so is both faster and simpler to deliver. However, there are no clinical effectiveness data comparing it with MWA, so the comparative effectiveness is unknown. However, ease of use is an important consideration in treatment choice; any intervention with a substantial learning curve barrier is going to be less easily accepted from a clinical perspective. HIFU has also been around for several years but has not been widely adopted.

Histotripsy is currently being evaluated as an investigational product; therefore, it should not be assessed further until efficacy has been demonstrated. However, it appears to be very promising and may be of interest further down the line.

At the second workshop, it was considered that the questions to answer in early HCC are more in the setting of challenging locations, less fit patients and in the setting of incomplete response to primary therapy, rather than a comparison with the current preferred first treatment option. There is probably some variation between multidisciplinary teams on whether they would offer TACE and whether they have SABR and/or IRE available. It may be difficult to define the population and ensure that a trial was acceptable to multidisciplinary teams that might have slight variations in practice and also looking at what technologies are available locally to a patient.

Chapter 8 Discussion

Summary of findings

The aim of this research was to evaluate and compare the effectiveness of ablative and non-surgical therapies for patients with small (up to 3 cm) HCC tumours. The key objectives were: to systematically identify all RCTs of ablative and non-surgical therapies for HCC; to evaluate their quality and applicability to UK populations; to determine the comparative effectiveness of therapies using NMA techniques; to supplement the RCT evidence with non-randomised prospective comparative studies of specific therapies where the evidence base was insufficient; to identify priority areas where additional high-quality evidence is required; and to assess whether future economic analysis based on the findings would be feasible and worthwhile.

Thirty-seven RCTs (one ongoing, 36 completed) were included in the systematic review. Several included patients with tumours larger than 3 cm, but reported separate results for the subgroup of patients with tumours up to 3 cm, although often the data reported for the subgroup were limited to response and/or AE outcomes. The RCT evidence was limited; most studies were small and at a high RoB (12 RCTs) or had some bias concerns (14 RCTs). The vast majority of RCTs were conducted in China or Japan, which has implications for the generalisability of results to the UK population, owing to differences in HCC aetiology and the different treatment options for the underlying liver disease. The most frequently assessed ablative therapy was RFA, which is widely used in Asia. However, in the UK and Europe MWA has been more widely adopted because of advances in microwave technology; MWA gives a more predictable ablation zone and is easier and faster to use, requiring single needle placement. Many interventional radiologists in the UK do not have experience of using RFA.

The results of many of the included RCTs were heterogeneous, particularly for the comparison of RFA versus surgical resection, with some RCTs favouring surgical resection and others favouring RFA or reporting similar OS and disease-free survival rates between treatment groups. However, AE rates were higher after resection. There was no evidence to suggest a difference between treatment with RFA and resection in the NMA.

Data comparing RFA with MWA, laser ablation or proton beam therapy were limited, with few RCTs and very small sample sizes. RCTs assessing RFA in combination with other treatments were also limited by small sample sizes. The uncertainty associated with the available data is demonstrated in the NMA results, where CIs were generally wide and most crossed the line of no effect. The estimated treatment effectiveness ranking was also very uncertain, with very wide CIs for most interventions.

The only firm conclusion that can be drawn from the available RCT data is that RFA appears to be better than PEI in terms of OS, PFS and recurrence. However, AEs appear to be more frequent after RFA than PEI, although this outcome could not be evaluated in a NMA. PAI appears to have similar effectiveness to PEI and had marginally worse PFS than RFA in the NMA, although data for this comparison were more limited.

One trial assessed RFA in combination with iodine-125, which appeared to be superior to RFA in terms of OS and overall recurrence; however, clinical advisors stated that this is only used in selected centres in China, and very few centres outside of China have used this combination.

No RCT evidence was identified for several of the interventions of interest: HIFU, cryoablation, IRE, ECT, histotripsy, SABR and wider radiotherapy techniques. As highlighted at the project workshop, histotripsy is currently being evaluated as an investigational product; therefore, it is unlikely that randomised evidence will be available within the next few years. Cryoablation, IRE, ECT and SABR are generally

reserved for the subgroup of patients with lesions that are more challenging to treat because of their location. SABR is also reserved in the treatment pathway for patients with recurrent, refractory or more advanced disease, or patients with comorbidities that make them unsuitable for ablative therapies. This makes it more difficult to undertake a randomised trial, as recruited patients would have to be eligible for both treatment arms. In addition, some of these technologies are less widely available and have a higher cost than ablative technologies such as RFA and MWA.

The threshold analysis suggested that additional evidence could plausibly change the NMA result for comparisons including RFA, MWA or laser ablation, as well as RFA in combination with TACE, systemic chemotherapy or iodine-125. Therefore, a systematic review of non-randomised prospective comparative studies was undertaken to identify evidence on RFA, MWA, laser ablation, HIFU, cryoablation, IRE, ECT, histotripsy, SABR and wider radiotherapy techniques, compared with each other or with surgical resection.

The systematic review of non-randomised evidence included 14 studies, although only two studies did not have a high RoB. Several studies allocated patients to treatment groups based on tumour characteristics (such as tumour location), meaning that there were differences in baseline characteristics between treatment groups that could be prognostic. This has implications for the interpretation of the non-randomised evidence; in addition, included patients may not have been eligible for both of the treatments assessed. Again, the vast majority of studies were conducted in China or Japan, with implications for the generalisability of results to the UK HCC patient population. In view of the significant limitations of the non-randomised studies, the studies with a high RoB were not included in the updated NMAs, leaving only the two studies that had a low RoB or some bias concerns. Additional non-randomised comparative data from Leeds Teaching Hospitals NHS Trust were made available by one of the clinical advisors, prior to publication; these data were also included in the updated NMAs.

The results of the updated NMAs including the non-randomised evidence were largely consistent with those of the NMAs of RCTs. As with the NMAs of randomised evidence, the findings were highly uncertain. However, the results suggested that MWA appears to be better than PEI and PAI in terms of OS and PFS. Resection appears to be better than PEI in terms of OS, and better than PEI and PAI in terms of PFS. In addition, IRE appears to be worse than RFA and RFA + PEI in terms of local recurrence.

The feasibility of developing an economic analysis to inform decision-makers on the cost-effectiveness of alternative treatments for small HCCs was assessed. This included a targeted literature review, which was undertaken to identify previous economic evaluations in very early/early HCC. The key features of the identified studies were summarised and used to inform the development of a conceptual model and to consider the data needed to develop a robust economic analysis. The review identified that previous economic evaluations have used recurrence events and liver function to predict long-term outcomes. This approach is likely to be the most appropriate way to model early HCC given the current evidence. Limitations in the available clinical data are, however, likely to impact on the feasibility of developing a robust economic analysis and limit any conclusions that could be drawn. Specifically, uncertainties in the clinical effectiveness will pervade any future economic analysis.

Given these uncertainties, a VOI analysis may be helpful and could help prioritise which of these treatments should be assessed in future trials, accounting for both the degree of clinical uncertainty and the economic case for a specific treatment. This may be of particular relevance in considering effective treatments that are currently rarely used in NHS practice.

There are considerable limitations to the existing evidence base on ablative and non-surgical therapies for early HCC. Two workshops were held to discuss the project findings and identify key priorities for future research; three patients and six clinicians provided expert advice. In view of the wide adoption of MWA as the standard of care within the UK and Europe, it was agreed that MWA would be the most appropriate comparator in any future trials. Clinicians considered that ablative technologies that are

more complex and take longer to deliver than MWA (e.g. laser and RFA, which require multiple needle placement) are unlikely to displace MWA as the preferred ablative therapy, despite a lack of clinical effectiveness evidence demonstrating better outcomes.

Specific interventions considered to be of particular interest to the HCC community were SABR and proton beam therapy, although these radiotherapy-based treatments can usually only be delivered once, whereas ablation can be repeated. In addition, there would need to be limitations to trial eligibility criteria, as patients with advanced/moderately advanced liver disease are not suitable for SABR because of the radiotherapy dose delivered to the surrounding liver. SABR and other radiotherapy techniques are unlikely to replace MWA as the first treatment choice; these techniques are generally reserved for a subgroup of patients depending on their suitability for ablation, tumour location and other patient and disease characteristics. A trial of IRE versus MWA for the subgroup of patients with central lesions may be useful, although again IRE would be unlikely to replace MWA in patients suitable for ablation. A trial of ECT versus MWA was also considered to be of interest. For early HCC, further research may be most relevant in the setting of challenging locations, less fit patients and incomplete response to primary therapy, rather than a comparison with the current preferred first treatment option (MWA).

Histotripsy was identified as an investigational product that may be promising in the future; however, it is at an early stage of regulatory approval, so should not be assessed until efficacy has been demonstrated.

Because of the low number of patients in the UK with early-stage HCC who would be eligible for all treatments within a trial, particularly for those interventions reserved for the subgroup of patients with more challenging tumours, it is likely to be more feasible to undertake an international multicentre RCT than a UK-based trial, in terms of recruiting sufficient patients to demonstrate a significant difference in outcomes. However, patients' disease characteristics, such as aetiology of liver disease and prior treatments received, would need to be similar to those of HCC patients in the UK to ensure that trial results were generalisable to the UK HCC population. Unfortunately, there were insufficient data on specific patient subgroups (i.e. tumour size and number, severity of cirrhosis and underlying liver disease) to enable subgroup analysis to be undertaken within the review. Therefore, it is unclear whether these characteristics are effect modifiers.

Local recurrence, overall recurrence, OS, PFS and HRQoL are important outcomes that should be assessed in any future trials. The definition of specific outcomes, such as recurrence and PFS, should be consistent in future trials to allow results to be compared and synthesised in the future.

The 2022 update of the BCLC strategy for prognosis prediction and treatment recommendation states that further prospective studies are needed to define the role of SABR for very early HCC.⁷

Strengths and limitations

The key strengths of this assessment are the comprehensive searches for relevant RCT evidence, the systematic data extraction and assessment of the quality and applicability of the included studies, and the inclusion of relevant data in NMAs of four important clinical effectiveness outcomes in an attempt to draw indirect comparisons of the therapies and rank them from best to worst in terms of the relevant outcomes.

The systematic review of RCTs was supplemented with a targeted review of non-randomised evidence in an attempt to fill gaps in the RCT evidence base and strengthen the evidence where data on specific comparisons were considered to be weak. Attention was focused on those interventions with current clinical relevance and those comparisons sensitive to potential changes in the evidence, as determined using novel threshold analysis techniques.

DISCUSSION

The project benefited from the expertise of several patient and clinical advisors, with meetings held at key stages of the project. However, the absence of 'in person' meetings, owing to the COVID-19 pandemic, constrained the interactions with patients. In addition, two of the patient advisory group members were unfortunately unavailable for the workshops at the end of the project.

The assessment was limited by the weaknesses in the clinical evidence base. There was no evidence on several of the interventions of interest, and the evidence was extremely weak (in terms of size and quality) for most of the other therapies, limiting our ability to draw any firm conclusions. Because of the significant gaps in the evidence base, the recommendations for prioritising specific therapies and comparisons for future research were primarily made based on expert advice received during the end-of-project workshop.

Chapter 9 Conclusions

Implications for practice

The evidence on ablative and non-surgical therapies for early and very early HCC is very limited. The only firm conclusions that can be drawn from the available data are that PEI and PAI are inferior to RFA, and that they also appear to be inferior to MWA and resection, for certain survival outcomes. There is insufficient evidence to draw any conclusions on quality-of-life outcomes.

The uptake of specific ablative therapies in the UK appears to be based more on technological advancements and ease/speed of use (and NHS England commissioning policies) than on high-quality evidence demonstrating superior clinical effectiveness of one therapy over another.

Recommendations for research

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, it is likely to be difficult to recruit sufficient numbers of patients to demonstrate a significant survival benefit, particularly in the presence of a competing risk of recurrence from the underlying liver disease.

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.

It is difficult to make firm recommendations for research based on our findings. The current evidence suggests a trial of MWA versus RFA versus resection could address uncertainty about the standard of care; however, clinicians consider this unlikely to be helpful as RFA is no longer widely used in NHS practice.

Clinical experts suggest that SABR is a promising intervention and could be compared with MWA; this may have international relevance, allowing for wider patient recruitment through multinational trials. However, SABR can usually only be used once because it is limited by the radiotherapy dose received by the surrounding liver, so further research is needed to identify where it should sit in the treatment pathway.

There were insufficient data on specific patient subgroups (i.e. relating to tumour size and number, severity of cirrhosis and underlying liver disease) to enable subgroup analysis to be undertaken. Therefore, further research to assess whether certain disease characteristics may modify treatment effect could be beneficial.

Feasibility studies could address these 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.

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Publications

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Data-sharing statement

The majority of data are available in the appendices to the report; any additional information can be obtained from the corresponding author.

Ethics statement

This systematic review did not require ethical approval.

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Appendix 1 Search strategies

The MEDLINE search strategies can be found in [Appendix 1.1–1.4](#), along with a list of further databases and resources searched. All other search strategies can be found in [Report Supplementary Material 1](#).

The terms used in all search strategies build upon those used in the searches to inform a previous systematic review on SIRT therapies for hepatocellular carcinoma:

Walton M, Wade R, Claxton L, Sharif-Hurst S, Harden M, Patel J, *et al.* Selective internal radiation therapies for unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma: systematic review, network meta-analysis and economic evaluation. *Health Technol Assess* 2020;24(48)

Appendix 1.1 Search strategies for identification of randomised controlled trials

The following databases were searched:

- MEDLINE ALL (Ovid)
- Embase (Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Science Citation Index (Web of Science)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (CRD databases)
- International Health Technology Assessment database
- Epistemonikos
- International Prospective Register of Systematic Reviews (PROSPERO)
- ClinicalTrials.gov
- European Union Clinical Trials Register.

The MEDLINE search strategy can be found below. See [Report Supplementary Material 1](#) for all other search strategies.

MEDLINE ALL

(includes: epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid <http://ovidsp.ovid.com/>

Date range: 1946 to 1 February 2021

Date searched: 3 February 2021

Records retrieved: 2303

The MEDLINE strategy below includes a search filter to limit retrieval to RCTs using the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format.

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). *Cochrane*

Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from: www.training.cochrane.org/handbook.

- 1 Carcinoma, Hepatocellular/ (86,979)
- 2 Liver Neoplasms/ (151,355)
- 3 ((liver or hepatocellular or hepato-cellular or hepatic\$) adj3 (carcinoma\$ or cancer\$ or neoplas\$ or tumour\$ or tumor\$ or malign\$)).ti,ab. (150,762)
- 4 (hepatocellularcarcinoma\$ or hepatocarcinoma\$ or hepato-carcinoma\$).ti,ab. (4183)
- 5 hepatoma\$.ti,ab. (28,611)
- 6 HCC.ti,ab. (58,929)
- 7 or/1-6 (234,592)
- 8 Neoplasm Staging/ (177,611)
- 9 (small\$ or early or earlystage?).ti,ab. (3,163,695)
- 10 (((BCLC or Barcelona-Clinic Liver Cancer) adj3 ("0" or A or A1 or A2 or A3 or A4)) or BCLC0-A).ti,ab. (578)
- 11 ("1" or "2" or "3" or one or two or three) adj (cm\$ or centimet\$).ti,ab. (77,157)
- 12 (1cm\$ or 2cm\$ or 3cm\$).ti,ab. (4783)
- 13 ((carcinoma\$ or tumor\$ or tumour\$ or lesion\$ or nodule\$) adj6 (size\$ or diameter\$)).ti,ab. (124,495)
- 14 (eHCC or sHCC).ti,ab. (251)
- 15 or/8-13 (3,424,647)
- 16 14 or (7 and 15) (50,618)
- 17 Radiofrequency Ablation/ (1071)
- 18 Catheter Ablation/ (33,067)
- 19 Radiofrequency Therapy/ (1098)
- 20 ((radiofrequenc\$ or radio frequenc\$) adj3 ablat\$).ti,ab. (20,597)
- 21 RFA.ti,ab. (6924)
- 22 RF ablation.ti,ab. (2496)
- 23 RTA.ti,ab. (2494)
- 24 RFTA.ti,ab. (62)

- 25 or/17-24 (45,285)
- 26 16 and 25 (3125)
- 27 Microwaves/ (17,445)
- 28 (microwave\$ or micro wave\$).ti,ab. (38,436)
- 29 (MWA or MCT or PMCT or PMWA).ti,ab. (7692)
- 30 or/27-29 (47,890)
- 31 16 and 30 (715)
- 32 Laser Therapy/ (38,202)
- 33 (laser\$ adj2 ablat\$).ti,ab. (10,008)
- 34 LTA.ti,ab. (3499)
- 35 or/32-34 (48,883)
- 36 16 and 35 (142)
- 37 High-Intensity Focused Ultrasound Ablation/ (1728)
- 38 Ultrasonic Therapy/ (9714)
- 39 High intensity focus?ed ultrasound.ti,ab. (3137)
- 40 HIFU.ti,ab. (2449)
- 41 or/37-40 (12,933)
- 42 16 and 41 (132)
- 43 Cryosurgery/ (13,169)
- 44 Cryotherapy/ (5214)
- 45 (cryoablat\$ or cryo-ablat\$ or cryotherap\$ or cryo-therap\$ or cryosurg\$ or cryo-surg\$).ti,ab. (14,455)
- 46 or/43-45 (23,464)
- 47 16 and 46 (317)
- 48 Ethanol/ (88,324)
- 49 ((alcohol or ethanol) adj2 (inject\$ or ablat\$)).ti,ab. (5254)
- 50 (PEI or PEIT).ti,ab. (8408)
- 51 or/48-50 (98,037)

APPENDIX 1

52 16 and 51 (975)

53 Acetic Acid/ (10,269)

54 Acetates/ (39,925)

55 (acetic acid adj2 (inject\$ or ablat\$)).ti,ab. (408)

56 PAI.ti,ab. (14,810)

57 PAAI.ti,ab. (19)

58 or/53-57 (62,615)

59 16 and 58 (132)

60 Electroporation/ (8033)

61 electroporation.ti,ab. (10,705)

62 IRE.ti,ab. (2151)

63 or/60-62 (15,275)

64 16 and 63 (122)

65 ((stereotactic or stereotaxic) adj3 ablat\$).ti,ab. (1271)

66 ((stereotactic or stereotaxic) adj3 (radiotherap\$ or radiation)).ti,ab. (9612)

67 (SABR or SABRT).ti,ab. (803)

68 SBRT.ti,ab. (4238)

69 SABER.ti,ab. (356)

70 or/65-69 (10,729)

71 16 and 70 (428)

72 Ablation Techniques/ (2918)

73 (ablat\$ adj2 (therap\$ or intervention\$ or treatment\$ or technique\$ or method\$ or procedure\$)).ti,ab. (16,748)

74 (ablat\$ adj2 (chemical\$ or thermal\$)).ti,ab. (4065)

75 (ablat\$ adj2 (tumour\$ or tumor\$)).ti,ab. (4083)

76 or/72-75 (24,549)

77 16 and 76 (1788)

- 78 Chemoembolization, Therapeutic/ (5983)
- 79 (chemo-emboli\$ or chemoemboli\$).ti,ab. (8271)
- 80 TACE.ti,ab. (5534)
- 81 cTACE.ti,ab. (144)
- 82 (DEBTACE or DEB-TACE).ti,ab. (243)
- 83 (eluting adj2 bead\$).ti,ab. (624)
- 84 DC bead\$.ti,ab. (108)
- 85 or/78-84 (11,130)
- 86 16 and 85 (3538)
- 87 Embolization, Therapeutic/ (32,829)
- 88 (embolization\$ or embolisation\$ or embolize\$ or embolise\$ or embolizing\$ or embolising\$ or embolotherap\$).ti,ab. (52,479)
- 89 TAE.ti,ab. (2435)
- 90 or/87-89 (63,331)
- 91 16 and 90 (2015)
- 92 ((locoregional or loco-regional) adj2 (therap\$ or intervention\$ or treatment\$ or technique\$ or method\$ or procedure\$)).ti,ab. (3346)
- 93 16 and 92 (531)
- 94 (Therasphere\$ or Thera-sphere\$).ti,ab. (79)
- 95 (SIR-Sphere\$ or SIRSphere\$).ti,ab. (119)
- 96 (QuiremSphere\$ or Quirem-Sphere\$).ti,ab. (4)
- 97 or/94-96 (167)
- 98 16 and 97 (44)
- 99 Microspheres/ (28,670)
- 100 (microsphere\$ or sphere\$).ti,ab. (76,678)
- 101 (microbead\$ or bead\$).ti,ab. (56,354)
- 102 or/99-101 (139,820)
- 103 Yttrium Radioisotopes/ (3105)

- 104 Yttrium/ (3157)
- 105 Yttrium Isotopes/ (709)
- 106 (Yttrium\$ or 90Yttrium\$ or Y90 or Y-90 or 90Y or 90-Y).ti,ab. (9775)
- 107 Holmium/ (904)
- 108 (Holmium\$ or 166Holmium\$ or Ho-166 or Ho166 or 166Ho or 166-Ho).ti,ab. (3496)
- 109 Radiopharmaceuticals/ (51,067)
- 110 or/103-109 (66,136)
- 111 102 and 110 (1871)
- 112 ((radioactiv\$ or radio-activ\$ or radionuclide\$ or radio-nuclide\$ or radioisotope\$ or radio-isotope\$ or radiolabel\$ or radio-label\$ or radiopharmaceutic\$ or radio-pharmaceutic\$) adj2 (sphere\$ or microsphere\$ or bead\$ or microbead\$)).ti,ab. (4168)
- 113 (radiomicrosphere\$ or radio-microsphere\$).ti,ab. (33)
- 114 or/111-113 (5932)
- 115 16 and 114 (315)
- 116 Brachytherapy/ (19,954)
- 117 (brachytherap\$ or brachy-therap\$ or microbrachytherap\$).ti,ab. (18,064)
- 118 or/116-117 (25,595)
- 119 118 and (110 or 112 or 113) (1048)
- 120 16 and 119 (85)
- 121 (radioemboli\$ or radio-emboli\$ or radioembolotherap\$ or radio-embolotherap\$).ti,ab. (1791)
- 122 TARE.ti,ab. (276)
- 123 (internal\$ adj3 (radiation\$ or radiotherap\$ or radio therap\$ or radionuclide\$ or radio-nuclide\$ or radioisotope\$ or radio-isotope\$)).ti,ab. (2446)
- 124 ((intra-arterial\$ or intraarterial\$) adj3 (radiation\$ or radiotherap\$ or radio therap\$ or radionuclide\$ or radio-nuclide\$ or radioisotope\$ or radio-isotope\$)).ti,ab. (284)
- 125 ((intra-arterial\$ or intraarterial\$) adj2 (brachytherap\$ or brachy-therap\$)).ti,ab. (20)
- 126 SIRT.ti,ab. (1519)
- 127 (SIR adj2 (therap\$ or treatment\$)).ti,ab. (88)
- 128 (radiation adj2 (segmentectom\$ or lobectom\$)).ti,ab. (53)

129 or/121-128 (5699)

130 16 and 129 (617)

131 26 or 31 or 36 or 42 or 47 or 52 or 59 or 64 or 71 or 77 (5352)

132 86 or 91 or 93 or 98 or 115 or 120 or 130 (5241)

133 randomized controlled trial.pt. (521,951)

134 controlled clinical trial.pt. (94,049)

135 randomized.ab. (510,387)

136 placebo.ab. (215,580)

137 drug therapy.fs. (2,274,478)

138 randomly.ab. (351,559)

139 trial.ab. (541,682)

140 groups.ab. (2,157,357)

141 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 (4,916,502)

142 exp animals/ not humans.sh. (4,782,806)

143 141 not 142 (4,274,490)

144 131 and 143 (1485)

145 132 and 143 (1633)

146 144 or 145 (2615)

147 limit 146 to yr="2000 -Current" (2303)

Key:

/ = subject heading (MeSH heading)

sh = subject heading (MeSH heading)

exp = exploded subject heading (MeSH heading)

\$ = truncation

? = optional wild card character – stands for zero or one characters

ti,ab = terms in title or abstract fields

adj3 = terms within three words of each other (any order)

pt = publication type

fs = floating subheading

Search strategies for identification of randomised controlled trials of wider radiotherapy techniques (March 2021)

MEDLINE ALL

(includes: epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid <http://ovidsp.ovid.com/>

Date range: 1946 to 16 March 2021

Date searched: 17 March 2021

Records retrieved: 399

The MEDLINE strategy below includes a search filter to limit retrieval to RCTs using the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format.

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.2 (updated February 2021). Cochrane, 2021. Available from: www.training.cochrane.org/handbook.

1 Carcinoma, Hepatocellular/ (87,724)

2 Liver Neoplasms/ (152,378)

3 ((liver or hepatocellular or hepato-cellular or hepatic\$) adj3 (carcinoma\$ or cancer\$ or neoplas\$ or tumour\$ or tumor\$ or malign\$)).ti,ab. (151,424)

4 (hepatocellularcarcinoma\$ or hepatocarcinoma\$ or hepato-carcinoma\$).ti,ab. (4202)

5 hepatoma\$.ti,ab. (28,603)

6 HCC.ti,ab. (59,303)

7 or/1-6 (235,478)

8 Neoplasm Staging/ (178,539)

9 (small\$ or early or earlystage?).ti,ab. (3,174,425)

10 (((BCLC or Barcelona-Clinic Liver Cancer) adj3 ("0" or A or A1 or A2 or A3 or A4)) or BCLC0-A).ti,ab. (588)

11 ("1" or "2" or "3" or one or two or three) adj (cm\$ or centimet\$).ti,ab. (77,490)

- 12 (1cm\$ or 2cm\$ or 3cm\$).ti,ab. (4785)
- 13 ((carcinoma\$ or tumor\$ or tumour\$ or lesion\$ or nodule\$) adj6 (size\$ or diameter\$)).ti,ab. (125,055)
- 14 (eHCC or sHCC).ti,ab. (254)
- 15 or/8-13 (3,436,575)
- 16 14 or (7 and 15) (50,862)
- 17 Electrochemotherapy/ (673)
- 18 (electrochemotherap* or electro-chemotherap* or electro chemotherap* or electroporabili?ation).ti,ab. (1115)
- 19 (electric* adj2 stimulat* adj2 (therap* or chemotherap* or chemo-therap* or chemo therap* or treat*)).ti,ab. (1260)
- 20 or/17-19 (2670)
- 21 histotripsy.ti,ab. (209)
- 22 Radiotherapy/ or Radiotherapy, Conformal/ or Radiotherapy, Intensity-Modulated/ or Radiotherapy, High-Energy/ or Radiotherapy, Image-Guided/ (72,234)
- 23 (radiotherap* or radiation-therap* or radiation therap*).ti,ab. (237,815)
- 24 ((intensity-modulat* or intensity modulat* or volumetric-modulat* or volumetric modulat*) adj4 (arc therap* or arc-therap*)).ti,ab. (2469)
- 25 (helical* adj4 tomotherap*).ti,ab. (1214)
- 26 or/22-25 (267,755)
- 27 Proton Therapy/ (3960)
- 28 (proton* adj4 therap*).ti,ab. (7126)
- 29 or/27-28 (8349)
- 30 20 or 21 or 26 or 29 (275,176)
- 31 16 and 30 (1887)
- 32 randomized controlled trial.pt. (525,223)
- 33 controlled clinical trial.pt. (94,097)
- 34 randomized.ab. (512,974)
- 35 placebo.ab. (216,151)
- 36 drug therapy.fs. (2,290,533)

37 randomly.ab. (353,254)

38 trial.ab. (543,763)

39 groups.ab. (2,167,571)

40 or/32-39 (4,942,795)

41 31 and 40 (496)

42 exp animals/ not humans.sh. (4,800,681)

43 41 not 42 (478)

44 limit 43 to yr="2000 -Current" (399)

Key:

/ = subject heading (MeSH heading)

sh = subject heading (MeSH heading)

exp = exploded subject heading (MeSH heading)

\$ = truncation

? = optional wild card character – stands for zero or one characters

ti,ab = terms in title or abstract fields

adj3 = terms within three words of each other (any order)

pt = publication type

fs = floating subheading

Appendix 1.2 Search strategies for identification of non-randomised studies where randomised controlled trial evidence was not available

The following databases were searched:

- MEDLINE ALL (Ovid)
- Embase (Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Science Citation Index (Web of Science).

The MEDLINE search strategy can be found below. See [Report Supplementary Material 1](#) for all other search strategies.

MEDLINE ALLw

(includes: epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid <http://ovidsp.ovid.com/>

Date range: 1946 to 27 July 2021

Date searched: 28 July 2021

Records retrieved: 1139

1 Carcinoma, Hepatocellular/ (90,761)

2 Liver Neoplasms/ (156,595)

3 ((liver or hepatocellular or hepato-cellular or hepatic\$) adj3 (carcinoma\$ or cancer\$ or neoplas\$ or tumour\$ or tumor\$ or malign\$)).ti,ab. (156,050)

4 (hepatocellularcarcinoma\$ or hepatocarcinoma\$ or hepato-carcinoma\$).ti,ab. (4256)

5 hepatoma\$.ti,ab. (28,811)

6 HCC.ti,ab. (61,752)

7 or/1-6 (241,089)

8 Neoplasm Staging/ (182,051)

9 (small\$ or early or earlystage?).ti,ab. (3,247,367)

10 (((BCLC or Barcelona-Clinic Liver Cancer) adj3 ("0" or A or A1 or A2 or A3 or A4)) or BCLCO-A).ti,ab. (617)

11 ("1" or "2" or "3" or one or two or three) adj (cm\$ or centimet\$)).ti,ab. (79,017)

12 (1cm\$ or 2cm\$ or 3cm\$).ti,ab. (4905)

13 ((carcinoma\$ or tumor\$ or tumour\$ or lesion\$ or nodule\$) adj6 (size\$ or diameter\$)).ti,ab. (128,094)

14 (eHCC or sHCC).ti,ab. (265)

15 or/8-13 (3,515,054)

16 14 or (7 and 15) (52,166)

17 High-Intensity Focused Ultrasound Ablation/ (1845)

18 Ultrasonic Therapy/ (9862)

19 High intensity focus?ed ultrasound.ti,ab. (3223)

20 HIFU.ti,ab. (2524)

21 or/17-20 (13,202)

22 16 and 21 (133)

APPENDIX 1

23 Cryosurgery/ (13,402)

24 Cryotherapy/ (5359)

25 (cryoablat\$ or cryo-ablat\$ or cryotherap\$ or cryo-therap\$ or cryosurg\$ or cryo-surg\$).ti,ab. (14,771)

26 or/23-25 (23,935)

27 16 and 26 (323)

28 Electroporation/ (8248)

29 electroporation.ti,ab. (10,923)

30 IRE.ti,ab. (2244)

31 or/28-30 (15,583)

32 16 and 31 (133)

33 ((stereotactic or stereotaxic) adj3 ablat\$).ti,ab. (1364)

34 ((stereotactic or stereotaxic) adj3 (radiotherap\$ or radiation)).ti,ab. (10,149)

35 (SABR or SABRT).ti,ab. (859)

36 SBRT.ti,ab. (4543)

37 SABER.ti,ab. (421)

38 or/33-37 (11,398)

39 16 and 38 (456)

40 Electrochemotherapy/ (698)

41 (electrochemotherap* or electro-chemotherap* or electro chemotherap* or electropermeabili?ation).ti,ab. (1153)

42 (electric* adj2 stimulat* adj2 (therap* or chemotherap* or chemo-therap* or chemo therap* or treat*)).ti,ab. (1304)

43 40 or 41 or 42 (2757)

44 16 and 43 (25)

45 histotripsy.ti,ab. (230)

46 16 and 45 (7)

47 Radiotherapy, Conformal/ or Radiotherapy, Intensity-Modulated/ or Radiotherapy, High-Energy/ or Radiotherapy, Image-Guided/ (30,927)

48 ((radiotherap* or radiation-therap* or radiation therap*) adj3 (conformal or intensity-modulat* or intensity modulat* or high-energy or high energy)).ti,ab. (14,403)

49 ((intensity-modulat* or intensity modulat* or volumetric-modulat* or volumetric modulat*) adj4 (arc therap* or arc-therap*)).ti,ab. (2595)

50 (helical* adj4 tomotherap*).ti,ab. (1237)

51 47 or 48 or 49 or 50 (36,559)

52 16 and 51 (274)

53 Proton Therapy/ (4266)

54 (proton* adj4 therap*).ti,ab. (7420)

55 53 or 54 (8702)

56 16 and 55 (106)

57 22 or 27 or 32 or 39 or 44 or 46 or 52 or 56 (1292)

58 exp animals/ not humans.sh. (4,866,074)

59 57 not 58 (1226)

60 limit 59 to yr="2000-Current" (1139)

Key:

/ = subject heading (MeSH heading)

sh = subject heading (MeSH heading)

exp = exploded subject heading (MeSH heading)

\$ = truncation

* = truncation

? = optional wild card character – stands for zero or one characters

ti,ab = terms in title or abstract fields

adj3 = terms within three words of each other (any order)

Appendix 1.3 Search strategies for identification of non-randomised studies where additional evidence could plausibly change the network meta-analysis result, as identified by the threshold analysis

The following databases were searched:

- MEDLINE ALL (Ovid)
- Embase (Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Science Citation Index (Web of Science)

The MEDLINE search strategy can be found below. See [Report Supplementary Material 1](#) for all other search strategies.

MEDLINE ALL

(includes: epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid <http://ovidsp.ovid.com/>

Date range: 1946 to 23 August 2021

Date searched: 24 August 2021

Records retrieved: 2539

1 Carcinoma, Hepatocellular/ (91,350)

2 Liver Neoplasms/ (157,448)

3 ((liver or hepatocellular or hepato-cellular or hepatic\$) adj3 (carcinoma\$ or cancer\$ or neoplas\$ or tumour\$ or tumor\$ or malign\$)).ti,ab. (156,958)

4 (hepatocellularcarcinoma\$ or hepatocarcinoma\$ or hepato-carcinoma\$).ti,ab. (4266)

5 hepatoma\$.ti,ab. (28,844)

6 HCC.ti,ab. (62,236)

7 or/1-6 (242,196)

8 Neoplasm Staging/ (182,692)

9 (small\$ or early or earlystage?).ti,ab. (3,261,749)

10 (((BCLC or Barcelona-Clinic Liver Cancer) adj3 ("0" or A or A1 or A2 or A3 or A4)) or BCLC0-A).ti,ab. (628)

11 ("1" or "2" or "3" or one or two or three) adj (cm\$ or centimet\$).ti,ab. (79,327)

12 (1cm\$ or 2cm\$ or 3cm\$).ti,ab. (4920)

13 ((carcinoma\$ or tumor\$ or tumour\$ or lesion\$ or nodule\$) adj6 (size\$ or diameter\$)).ti,ab. (128,670)

- 14 (eHCC or sHCC).ti,ab. (268)
- 15 or/8-13 (3,530,492)
- 16 14 or (7 and 15) (52,397)
- 17 Laser Therapy/ (38,954)
- 18 (laser\$ adj2 ablat\$).ti,ab. (10,374)
- 19 LTA.ti,ab. (3598)
- 20 or/17-19 (49,955)
- 21 Radiofrequency Ablation/ (1620)
- 22 Catheter Ablation/ (34,863)
- 23 Radiofrequency Therapy/ (1141)
- 24 ((radiofrequenc\$ or radio frequenc\$) adj3 ablat\$).ti,ab. (21,317)
- 25 RFA.ti,ab. (7252)
- 26 RF ablation.ti,ab. (2534)
- 27 RTA.ti,ab. (2555)
- 28 RFTA.ti,ab. (63)
- 29 or/21-28 (47,522)
- 30 Microwaves/ (18,128)
- 31 (microwave\$ or micro wave\$).ti,ab. (39,869)
- 32 (MWA or MCT or PMCT or PMWA).ti,ab. (8015)
- 33 or/30-32 (49,569)
- 34 Carcinoma, Hepatocellular/su (13,662)
- 35 Liver Neoplasms/su (27,831)
- 36 Hepatectomy/ (31,584)
- 37 Surgical Procedures, Operative/ (56,264)
- 38 ((surgical\$ or surger\$ or operat\$ or resect\$) adj6 (carcinoma\$ or tumor\$ or tumour\$ or lesion\$ or nodule\$ or neoplasm\$ or liver\$ or lobe\$)).ti,ab. (257,196)
- 39 (hepatectom\$ or hemi-hepatectom\$ or hemihepatectom\$ or lobectom\$ or microlobectom\$ or microlobectom\$ or segmentectom\$ or trisegmentectom\$).ti,ab. (46,091)

40 ((carcinoma\$ or tumor\$ or tumour\$ or lesion\$ or nodule\$ or neoplasm\$ or liver\$ or lobe\$) adj4 (excis\$ or remov\$ or dissect\$)).ti,ab. (71,760)

41 or/34-40 (396,793)

42 20 and (29 or 33 or 41) (3589)

43 29 and (20 or 33 or 41) (8135)

44 33 and (20 or 29 or 41) (2905)

45 41 and (20 or 29 or 33) (9295)

46 16 and (42 or 43 or 44 or 45) (2696)

47 exp animals/ not humans/ (4,877,412)

48 46 not 47 (2619)

49 limit 48 to yr="2000-Current" (2539)

Key:

/ = indexing term (Medical Subject Heading: MeSH)

/su = indexing term with subheading for surgery

exp = exploded indexing term (MeSH)

\$ = truncation

ti,ab = terms in either title or abstract fields

adj3 = terms within three words of each other (any order).

Appendix 1.4 Search strategies for identification of economic studies

The following databases were searched:

- MEDLINE ALL (Ovid)
- Embase (Ovid)
- EconLit (Ovid)
- NHS Economic Evaluations Database (CRD databases).

The MEDLINE search strategy can be found below. See [Report Supplementary Material 1](#) for all other search strategies.

Ovid MEDLINE(R) ALL

(includes epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid <http://ovidsp.ovid.com/>

Date range searched: 1946 to 12 May 2021

Date searched: 13 May 2021

Records retrieved: 181

The MEDLINE strategy below (lines 17–24) includes a narrow search filter to limit retrieval to economic studies. The filter was designed by the *Canadian Journal of Health Technologies* (CADTH).

Strings attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016. [cited 2021 05 13]. Available from: <https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#narrow>

- 1 Carcinoma, Hepatocellular/ (88,831)
- 2 Liver Neoplasms/ (153,869)
- 3 ((liver or hepatocellular or hepato-cellular or hepatic\$) adj3 (carcinoma\$ or cancer\$ or neoplas\$ or tumour\$ or tumor\$ or malign\$)).ti,ab. (153,407)
- 4 (hepatocellularcarcinoma\$ or hepatocarcinoma\$ or hepato-carcinoma\$).ti,ab. (4221)
- 5 hepatoma\$.ti,ab. (28,694)
- 6 HCC.ti,ab. (60,357)
- 7 or/1-6 (237,841)
- 8 Neoplasm Staging/ (179,919)
- 9 (small\$ or early or earlystage?).ti,ab. (3,206,080)
- 10 (((BCLC or Barcelona-Clinic Liver Cancer) adj3 ("0" or A or A1 or A2 or A3 or A4)) or BCLCO-A).ti,ab. (604)
- 11 (("1" or "2" or "3" or one or two or three) adj (cm\$ or centimet\$)).ti,ab. (78,139)
- 12 (1cm\$ or 2cm\$ or 3cm\$).ti,ab. (4828)
- 13 ((carcinoma\$ or tumor\$ or tumour\$ or lesion\$ or nodule\$) adj6 (size\$ or diameter\$)).ti,ab. (126,376)
- 14 (eHCC or sHCC).ti,ab. (257)
- 15 or/8-13 (3,470,534)
- 16 14 or (7 and 15) (51,398)
- 17 *economics/ (10,739)
- 18 exp *"costs and cost analysis"/ (74,182)
- 19 (economic adj2 model*).mp. (13,712)

20 (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kf,kw. (35,068)

21 (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw. (76,616)

22 (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kf,kw. (32,546)

23 (cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov).ab. (61,298)

24 or/17-23 (187,991)

25 16 and 24 (199)

26 exp animals/ not humans.sh. (4,823,832)

27 25 not 26 (199)

28 limit 27 to yr="2000-Current" (181)

Key:

/ or.sh. = indexing term (Medical Subject Heading: MeSH)

exp = exploded indexing term (MeSH)

\$ or * = truncation

ti,ab = terms in either title or abstract fields

kw,kf = terms in keyword or keyfield field

adj3 = terms within three words of each other (any order).

mp = multipurpose field

? = replaces or adds up to one additional character

Appendix 2 Studies excluded at full paper stage with rationale (randomised controlled trial searches)

Study	Reason for exclusion
An, 2021 ¹¹⁵	Not a RCT
Chang, 2018 ¹¹⁶	No relevant intervention/comparison
Cho, 2014 ¹¹⁷	Not a RCT
Chong, 2017a ¹¹⁸	Not early HCC patients (≤ 3 cm tumour)
Chong, 2017b ¹¹⁹	Not early HCC patients (≤ 3 cm tumour)
Chong, 2018 ¹²⁰	Duplicate report
Chong, 2020 ¹²¹	Not early HCC patients (≤ 3 cm tumour)
Crocetti, 2018 ¹²²	Not a RCT
Di Costanzo, 2011a ¹²³	Not early HCC patients (≤ 3 cm tumour)
Di Costanzo, 2011b ¹²⁴	Not early HCC patients (≤ 3 cm tumour)
Di Costanzo, 2011c ¹²⁵	Not early HCC patients (≤ 3 cm tumour)
Di Costanzo, 2013 ¹²⁶	Not early HCC patients (≤ 3 cm tumour)
Di Costanzo, 2015 ¹²⁷	Not early HCC patients (≤ 3 cm tumour)
Duan, 2011 ¹²⁸	Not early HCC patients (≤ 3 cm tumour)
DuBay, 2011 ¹²⁹	Not a RCT
Fan, 2019 ¹³⁰	Not a RCT
Fang, 2005 ¹³¹	Not a RCT
Ferrer Puchol, 2011 ¹³²	Not a RCT
Filippiadis, 2021 ¹³³	Not early HCC patients (≤ 3 cm tumour)
Fong, 2016 ¹³⁴	Not early HCC patients (≤ 3 cm tumour)
Frangakis, 2010 ¹³⁵	Not a RCT
Fukushima, 2015 ¹³⁶	No relevant intervention/comparison
Gerunda, 2000 ¹³⁷	Not early HCC patients (≤ 3 cm tumour)
Giorgio, 2010a ¹³⁸	Duplicate report
Giorgio, 2010b ¹³⁹	Duplicate report
Guo, 2005 ¹⁴⁰	Not early HCC patients (≤ 3 cm tumour)
Guo, 2013 ¹⁴¹	Not a RCT
Ha, 2016 ¹⁴²	Not a RCT
Hayes, 2008 ¹⁴³	Not a RCT
He, 2018 ¹⁴⁴	Not early HCC patients (≤ 3 cm tumour)
Hong, 2005 ¹⁴⁵	Not a RCT

continued

Study	Reason for exclusion
Hsiao, 2020 ¹⁴⁶	Not a RCT
Hsu, 2012 ¹⁴⁷	Not a RCT
Huang, 2009 ¹⁴⁸	Not early HCC patients (\leq 3 cm tumour)
Huang, 2020 ¹⁴⁹	Not a RCT
Hung, 2011 ¹⁵⁰	Not a RCT
Huo, 2003 ⁸²	Not a RCT
Hyun, 2016 ¹⁵¹	Not a RCT
Iida, 2014 ¹⁵²	Not a RCT
Ikeda, 2001 ¹⁵³	Not a RCT
Imai, 2013 ¹⁵⁴	Not a RCT
Jiang, 2015 ¹⁵⁵	Not a RCT
Jiang, 2017a ¹⁵⁶	Not a RCT
Jiang, 2017b ¹⁵⁷	Not early HCC patients (\leq 3 cm tumour)
Kaibori, 2012a ¹⁵⁸	Not early HCC patients (\leq 3 cm tumour)
Kaibori, 2012b ¹⁵⁹	Not early HCC patients (\leq 3 cm tumour)
Kayali, 2013 ¹⁶⁰	Not early HCC patients (\leq 3 cm tumour)
Kim, 2019 ¹⁶¹	Not a RCT
Kim, 2021 ¹⁶²	Duplicate report
Kitamoto, 2003 ¹⁶³	Not a RCT
Kiyoshi, 2010 ¹⁶⁴	Duplicate report
Kobayashi, 2007 ¹⁶⁵	No relevant intervention/comparison
Koda, 2000 ¹⁶⁶	Duplicate report
Koh, 2015 ¹⁶⁷	Not early HCC patients (\leq 3 cm tumour)
Kong, 2014 ¹⁶⁸	Not a RCT
Lai, 2016 ¹⁶⁹	Not a RCT
Lambert, 2020 ¹⁷⁰	Not early HCC patients (\leq 3 cm tumour)
Lee, 2009 ¹⁷¹	Not a RCT
Lee, 2018a ¹⁷²	Not early HCC patients (\leq 3 cm tumour)
Lee, 2018b ¹⁷³	Not a RCT
Li, 2007 ¹⁷⁴	Not early HCC patients (\leq 3 cm tumour)
Li, 2011 ¹⁷⁵	Not early HCC patients (\leq 3 cm tumour)
Li, 2012 ¹⁷⁶	Not early HCC patients (\leq 3 cm tumour)
Liao, 2017 ¹⁷⁷	No relevant intervention/comparison
Lin, 2005 ¹⁷⁸	Duplicate report
Lin, 2007a ¹⁷⁹	Not a RCT
Lin, 2007b ¹⁸⁰	Not a RCT
Liu, 2012 ¹⁸¹	Not early HCC patients (\leq 3 cm tumour)

Study	Reason for exclusion
Liu, 2015 ¹⁸²	Not early HCC patients (\leq 3 cm tumour)
Liu, 2016 ¹⁸³	Not early HCC patients (\leq 3 cm tumour)
Liu, 2019 ¹⁸⁴	No relevant intervention/comparison
Liu, 2020 ¹⁸⁵	Not a RCT
Lu, 2006 ¹⁸⁶	Not early HCC patients (\leq 3 cm tumour)
Lu, 2008 ¹⁸⁷	Not early HCC patients (\leq 3 cm tumour)
Luo, 2005 ¹⁸⁸	Not a RCT
Ma, 2019 ¹⁸⁹	Not early HCC patients (\leq 3 cm tumour)
Maeda, 2003 ¹⁹⁰	Not early HCC patients (\leq 3 cm tumour)
Masuda, 2007 ¹⁹¹	Not a RCT
Mbalisike, 2015 ¹⁹²	Not early HCC patients (\leq 3-cm tumour)
Meniconi, 2015 ¹⁹³	Not a RCT
Meyer, 2013 ¹⁹⁴	Not early HCC patients (\leq 3 cm tumour)
Mohamed, 2018 ¹⁹⁵	Not early HCC patients (\leq 3 cm tumour)
Mornex, 2007a ¹⁹⁶	Not a RCT
Mornex, 2007b ¹⁹⁷	Duplicate report
Murakami, 2007 ¹⁹⁸	Not a RCT
Ng, 2017 ⁷³	Duplicate report
Ni, 2007 ¹⁹⁹	Not early HCC patients (\leq 3 cm tumour)
NIHR Horizon Scanning Centre ²⁰⁰	Not a RCT
Nouso, 2016 ²⁰¹	No relevant intervention/comparison
Ohmoto, 2006 ²⁰²	Not a RCT
Ohmoto, 2009 ²⁰³	Not a RCT
Olschewski, 2002 ²⁰⁴	Duplicate report
Paik, 2016 ²⁰⁵	Not a RCT
Panaro, 2014 ²⁰⁶	Not a RCT
Park, 2020 ²⁰⁷	No relevant intervention/comparison
Peng, 2008 ²⁰⁸	Not a RCT
Petrowsky, 2008 ²⁰⁹	Not a RCT
Pompili, 2013 ²¹⁰	Not a RCT
Riaz, 2009 ²¹¹	Not a RCT
Roche, 2002 ²¹²	Not a RCT
Ryu, 2017 ²¹³	Not a RCT
Santambrogio, 2009 ²¹⁴	Not a RCT
Shen, 2018 ²¹⁵	Not early HCC patients (\leq 3 cm tumour)
Sherman, 2006 ²¹⁶	Not a RCT

continued

Study	Reason for exclusion
Shi, 2014 ²¹⁷	Not a RCT
Shibata, 2006 ²¹⁸	No relevant intervention/comparison
Sun, 2020 ²¹⁹	Not a RCT
Tashiro, 2011 ²²⁰	Not a RCT
Toyoda, 2008 ²²¹	Not a RCT
Tsai, 2008 ²²²	Not a RCT
Vivarelli, 2004 ²²³	Not a RCT
Wang, 2014 ²²⁴	Duplicate report
Wang, 2015 ²²⁵	No relevant outcome assessed
Wu, 2016 ²²⁶	Not a RCT
Xu, 2012 ²²⁷	Not early HCC patients (\leq 3 cm tumour)
Xu, 2013 ²²⁸	Duplicate report
Xu, 2015a ²²⁹	Not a RCT
Xu, 2015b ²³⁰	Not early HCC patients (\leq 3 cm tumour)
Yamamoto, 2001 ²³¹	Not a RCT
Yamasaki, 2011 ²³²	Not early HCC patients (\leq 3 cm tumour)
Yin, 2014 ²³³	Not early HCC patients (\leq 3 cm tumour)
Yin, 2015 ²³⁴	Duplicate report
Yin, 2019 ²³⁵	Not a RCT
Yu, 2016 ²³⁶	Duplicate report
Yuan, 2017 ²³⁷	Not early HCC patients (\leq 3 cm tumour)
Yuen, 2003 ²³⁸	Not early HCC patients (\leq 3 cm tumour)
Yun, 2011 ²³⁹	Not a RCT
Zeng, 2018 ²⁴⁰	Not early HCC patients (\leq 3 cm tumour)
Zhang, 2013 ²⁴¹	Not a RCT
Zhang, 2015 ²⁴²	Not a RCT
Zhang, 2016 ²⁴³	Not a RCT
Zhao, 2011 ²⁴⁴	Not early HCC patients (\leq 3 cm tumour)
Zhi, 2006 ²⁴⁵	Not a RCT
Zhou, 2009 ²⁴⁶	Not early HCC patients (\leq 3 cm tumour)
Zhou, 2014 ²⁴⁷	Not a RCT
Zhou, 2019 ²⁴⁸	Not early HCC patients (\leq 3 cm tumour)
Zhu, 2007 ²⁴⁹	Not early HCC patients (\leq 3 cm tumour)
Zhu, 2019 ²⁵⁰	Not early HCC patients (\leq 3 cm tumour)

Appendix 3 Risk of bias assessment results (randomised controlled trials)

Trial	ROB arising from the randomisation process	ROB due to deviations from the intended intervention	ROB due to missing outcome data	ROB in measurement of the outcome	ROB in selection of the reported result	Overall judgement of ROB
Abdelaziz, 2014 – Complete response ⁶⁴	High	Low	Low	Low	Low	High
Aikata, 2006 – OS (abstract) ⁴³	Some concerns	High	High	Low	Low	High
Aikata, 2006 – PFS (abstract) ⁴³	Some concerns	High	High	Low	Some concerns	High
Azab, 2011 – Complete response ⁶⁵	Some concerns	Low	Low	Low	Low	Some concerns
Bian, 2014 – Recurrence ⁷⁸	Some concerns	Low	Low	Low	Low	Some concerns
Brunello, 2008 – OS ⁴⁴	Low	Low	Low	Low	Low	Low
Chen, 2005 – OS ⁶⁷	Some concerns	Low	Low	Low	Low	Some concerns
Chen, 2005 – OS ⁶⁶	Some concerns	Low	High	Low	Low	High
Chen, 2006 – OS ⁶⁸	Low	High	Low	Low	Low	High
Chen, 2006 – PFS ⁶⁸	Low	High	Low	Low	Some concerns	High
Chen, 2014 – OS ⁴⁵	Low	Low	Low	Low	Low	Low
Chen, 2014 – Recurrence ⁴⁵	Low	Low	Low	Low	Low	Low
Fang, 2014 – OS ⁴⁶	Some concerns	Low	Low	Low	Low	Some concerns
Fang, 2014 – Disease-free survival ⁴⁶	Some concerns	Low	Low	Low	Some concerns	Some concerns
Fang, 2014 – Recurrence ⁴⁶	Some concerns	Low	Low	Low	Low	Some concerns
Ferrari, 2007 – OS ⁷⁷	Some concerns	Low	Low	Low	Low	Some concerns
Gan, 2004 – Recurrence ⁴⁷	Some concerns	Low	High	Low	Low	High
Giorgio, 2011 – OS ⁴⁸	Low	High	High	Low	Low	High
Giorgio, 2011 – Recurrence ⁴⁸	Low	High	High	Low	Low	High

continued

Trial	ROB arising from the randomisation process	ROB due to deviations from the intended intervention	ROB due to missing outcome data	ROB in measurement of the outcome	ROB in selection of the reported result	Overall judgement of ROB
Huang, 2005 – OS ⁴⁹	High	High	High	Low	Low	High
Huang, 2005 – PFS ⁴⁹	High	High	High	Low	Low	High
Huang, 2005 – Recurrence ⁴⁹	High	High	High	Low	Some concerns	High
Huang, 2010 – OS ⁶⁹	Low	Low	High	Low	Low	High
Huo, 2003 – OS ⁷⁰	High	Low	High	Low	Low	High
Izumi, 2019 – PFS (abstract) ⁵⁰	Some concerns	High	High	Low	Some concerns	High
Kim, 2020 – OS ⁵¹	Some concerns	Low	Low	Low	Low	Some concerns
Kim, 2020 – PFS ⁵¹	Some concerns	Low	Low	Low	Low	Some concerns
Koda, 2001 – OS ⁵²	Low	Low	Low	Low	Low	Low
Koda, 2001 – Recurrence ⁵²	Low	Low	Low	Low	Low	Low
Lencioni, 2003 – OS ⁷¹	Low	Low	Low	Low	Low	Low
Lencioni, 2003 – PFS ⁷¹	Low	Low	Low	Low	Low	Low
Lencioni, 2003 – Recurrence ⁷¹	Low	Low	Low	Low	Low	Low
Lin, 2004 – OS ⁵⁹	Low	Low	Low	Low	Low	Low
Lin, 2004 – PFS ⁵⁹	Low	Low	Low	Low	Low	Low
Lin, 2004 – Recurrence ⁵⁹	Low	Low	Low	Low	Low	Low
Lin, 2005 – OS ⁵³	Some concerns	Low	Low	Low	Low	Some concerns
Lin, 2005 – PFS ⁵³	Some concerns	Low	Low	Low	Low	Some concerns
Liu, 2016 – OS ⁷²	Some concerns	Low	Low	Low	Low	Some concerns
Mizuki, 2010 – OS ⁶⁰	Low	Some concerns	Some concerns	Low	Low	Some concerns
Mizuki, 2010 – PFS ⁶⁰	Low	Some concerns	Some concerns	Low	Low	Some concerns
Ng, 2017 – OS ⁷⁹	Low	Low	Low	Low	Low	Low
Ng, 2017 – PFS ⁷⁹	Low	Low	Low	Low	Low	Low
Orlacchio, 2014 – OS ⁶¹	Some concerns	Low	Some concerns	Low	Low	Some concerns
Peng, 2012 – OS ⁷⁴	Low	Low	Low	Low	Low	Low

Trial	ROB arising from the randomisation process	ROB due to deviations from the intended intervention	ROB due to missing outcome data	ROB in measurement of the outcome	ROB in selection of the reported result	Overall judgement of ROB
Peng, 2012 – Recurrence-free survival ⁷⁴	Low	Low	Low	Low	Low	Low
Shibata, 2002 – Recurrence ⁶²	Low	Low	Some concerns	Low	Low	Some concerns
Shibata, 2009 – OS ⁵⁴	High	Low	Low	Low	Low	High
Shibata, 2009 – PFS ⁵⁴	High	Low	Low	Low	Low	High
Shiina, 2005 – OS ⁵⁵	Some concerns	Low	Low	Low	Low	Some concerns
Vietti Violi, 2018 – OS ⁶³	Low	Some concerns	Low	Low	Low	Some concerns
Vietti Violi, 2018 – Progression ⁶³	Low	Some concerns	Low	Low	Low	Some concerns
Vietti Violi, 2018 – TTP ⁶³	Low	Some concerns	Low	Low	Low	Some concerns
Xia, 2020 – OS ⁷⁵	Low	Low	Low	Low	Low	Low
Xia, 2020 – Recurrence-free survival ⁷⁵	Low	Low	Low	Low	Low	Low
Yan, 2016 – OS ⁵⁶	High	Some concerns	Low	Low	Low	High
Yan, 2016 – PFS ⁵⁶	High	Some concerns	Low	Low	Low	High
Zhang, 2007 – OS ⁷⁶	Low	Low	Low	Low	Low	Low
Zou, 2017 – Response ⁵⁷	Some concerns	Low	Low	Low	Low	Some concerns
Total	High: 9 Some concerns: 20 Low: 29	High: 10 Some concerns: 7 Low: 41	High: 12 Some concerns: 4 Low: 42	Low: 58	Some concerns: 5 Low: 53	High: 19 Some concerns: 21 Low: 18

Appendix 4 Characteristics and results of randomised controlled trials included in the review

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
RFA vs. MWA					
Abdelaziz, 2014 ⁶⁴ Egypt	111 patients (with 128 tumours) ≤ 5 cm; subgroup of 87 tumours ≤ 3 cm	RFA (n = 32 tumours ≤ 3 cm)	MWA (n = 55 tumours ≤ 3 cm)	<p>Response: RFA: Complete ablation: 30/32 (93.8%) tumours; partial ablation: 2/32 (6.2%) tumours. MWA: Complete ablation: 54/55 (98.2%) tumours; partial ablation: 1/55 (1.8%) tumours.</p> <p>Adverse events: There were no major complications or deaths in either group. No other results reported for ≤ 3 cm tumour subgroup.</p>	High
Shibata, 2002 ⁶² Japan	72 patients (with 94 tumours) < 4 cm; subgroup of 88 tumours ≤ 3 cm	RFA (n = 36 patients, 3 of whom had tumours 3–4cm)	MWA (n = 36 patients, 3 of whom had tumours 3–4 cm)	<p>Response: RFA: 46/48 (96%) nodules showed complete response and 2 (4%) had residual lesions or incomplete response. MWA: 41/46 (89%) nodules showed complete response and 5 (11%) showed incomplete response.</p> <p>Adverse events: RFA: one major complication (3%) (segmental hepatic infarction). MWA: four major complications (11%) (liver abscess, cholangitis, subcutaneous abscess with skin burn and subcapsular hematoma). No other results reported, other than Kaplan–Meier curve.</p>	Some concerns
Vietti Violi, 2018 ⁶³ Switzerland and France	152 patients with tumours ≤ 4 cm (mean tumour size 1.8 cm, <8% patients had tumours > 3 cm)	MWA (n = 76 patients, 6 of whom had tumours 3–4 cm)	RFA (n = 76 patients, 5 of whom had tumours 3–4 cm)	<p>OS: MWA: 2 years: 86%. RFA: 2 years: 84%.</p> <p>Recurrence: MWA: 2 years: 6% (local tumour progression). RFA: 2 years: 12% (local tumour progression). Comparison between groups: RR 1.62, 95% CI 0.66 to 3.94.</p> <p>TTP: MWA: Median 12 months (95% CI 5 to 28). RFA: Median 16 months (95% CI 4 to 24). Comparison between groups: HR 0.72, 95% CI 0.44 to 1.18.</p> <p>Response: MWA: 95% achieved complete response after one treatment; 5% achieved complete response after two treatments. RFA: 96% achieved complete response after one treatment; 4% achieved complete response after two treatments.</p> <p>Adverse events: MWA: 2 (2%) grade IV AEs; 5 (5%) grade I–II AEs. RFA: 3 (3%) grade III AEs; 12 (11.5%) grade I–II AEs. No treatment-related deaths in either group.</p>	Some concerns

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
RFA vs. PEI					
Azab, 2011 ⁶⁵ Egypt	90 patients (with 98 tumours) ≤ 5 cm; subgroup of 48 tumours ≤ 3 cm	PEI + RFA (n = 16 tumours ≤ 3 cm)	RFA alone (n = 16 tumours ≤ 3 cm) PEI alone (n = 16 tumours ≤ 3 cm)	<p>Response: PEI + RFA: 15/16 (93.8%) nodules had complete ablation and 1/16 (6.2%) had partial ablation after one session; 16/16 (100%) nodules had complete ablation after two sessions. RFA alone: 12/16 (75%) nodules had complete ablation and 4/16 (25%) had partial ablation after one session; 14/16 (87.5%) nodules had complete ablation and 2/16 (12.5%) had partial ablation after two sessions. PEI alone: 0% nodules had complete ablation after two sessions; 13/16 (81.25%) nodules had complete ablation and 3/16 (18.75%) had partial ablation after all sessions.</p> <p>Adverse events: There were no mortalities related to any of the techniques. No other results reported for ≤ 3cm tumour subgroup.</p>	Some concerns
Brunello, 2008 ⁴⁴ Italy	139 patients with tumours ≤ 3 cm	RFA (n = 70 patients)	PEI (n = 69 patients)	<p>OS: RFA: Number of events (death): 26. PEI: Number of events (death): 28. Comparison between groups: HR 0.82, 95% CI 0.48 to 1.41. Adjusted HR 0.88, 95% CI 0.50 to 1.53.</p> <p>Distant intrahepatic recurrence: RFA: Number of events: 32. PEI: Number of events: 35.</p> <p>Response: RFA: 1-year response: 46/70 (65.7%). Early complete response (30-50 days): 67/70 (95.7%). PEI: 1-year response: 25/69 (36.2%). Early complete response (30-50 days, patients with 1-year follow-up only): 42/64 (65.6%).</p> <p>Adverse events: RFA: Treatment-emergent AEs: 10 (14.3%) patients; major complications: 2 patients. PEI: Treatment-emergent AEs: 12 (17.4%) patients; major complications: 2 patients.</p> <p>Economic outcomes: Mean direct medical costs were €4097 for PEI and €6540 for RFA. ICER for using RFA instead of PEI was €8286 (95% CI €2742 to €20,917).</p>	Low
					continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Giorgio, 2011 ⁴⁸ Italy	285 patients with tumours ≤ 3 cm	RFA (n = 142 patients)	PEI (n = 143 patients)	<p>OS: RFA: 1 year: 95%; 2 years: 90%; 3 years: 83%; 4 years: 73%; 5 years: 70%. PEI: 1 year: 95%; 2 years: 83%; 3 years: 78%; 4 years: 70%; 5 years: 68%. Comparison between groups: HR 0.81, 95% CI 0.46 to 1.39.</p> <p>Local recurrence: RFA: 1 year: 4.1%; 2 years: 5.7%; 3 years: 7.8%; 4 years: 8.9%; 5 years: 11.7%. PEI: 1 year: 5.2%; 2 years: 6.7%; 3 years: 9.4%; 4 years: 11.5%; 5 years: 12.8%.</p> <p>Adverse events: RFA: Major complication: 0.9%. PEI: Major complication: 1.9%. No deaths related to the procedure in either group and no cases of seeding.</p> <p>Economic outcomes: In Italy the medical costs of both procedures were the same so cost calculated only on basis of technical material. The overall cost for PEI needles plus ethanol was €1359 plus VAT, the cost of the generator plus the RFA electrode needles was €171,000 plus VAT, with a statistically significant difference (p < 0.001).</p>	High
Lencioni, 2003 ⁷¹ Authors from Italy and Germany	104 patients with tumours ≤ 5 cm (large proportion had tumours ≤ 3 cm)	PEI (n = 50 patients with mean tumour size 2.8 cm; 84% had tumours ≤ 3 cm)	RFA (n = 54 patients with mean tumour size 2.8 cm; 88% had tumours ≤ 3 cm)	<p>OS: PEI: 1 year: 96%; 2 years: 88%. RFA: 1 year: 100%; 2 years: 98%. PEI: Number of events (death): 5. RFA: Number of events (death): 1.</p> <p>Event-free survival: PEI: 1 year: 77%; 2 years: 43%. RFA: 1 year: 86%; 2 years: 64%.</p> <p>Local recurrence: PEI: Number of events: 13. RFA: Number of events: 3.</p> <p>Response: PEI: 60/73 (82%) tumours had complete response after one cycle; 69/73 (94.5%) tumours had complete response after two cycles. RFA: 63/69 (91%) tumours had complete response after one session; 68/69 (98.6%) tumours had complete response after two sessions.</p> <p>Adverse events: PEI: No procedure-related death, haemorrhage, infection, needle-track seeding or hepatic failure. Mild to moderate pain requiring analgesics: 13; fever: 5; chemical thrombosis of a portal venous branch: 1. RFA: No procedure-related death, haemorrhage, infection, needle-track seeding or hepatic failure. Mild to moderate pain requiring analgesics: 15; fever: 10; pleural effusions: 4 lesions; asymptomatic arteriovenous shunts: 3.</p>	Low

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Lin, 2004 ⁵⁹ Authors from Taiwan	157 patients with tumours ≤ 4 cm; subgroup of 114 patients with tumours ≤ 3 cm	RFA (n = 37 patients with tumours ≤ 3 cm)	Low-dose PEI (n = 38 patients with tumours ≤ 3 cm) High-dose PEI (n = 39 patients with tumours ≤ 3 cm)	<p>OS: RFA in patients with tumours 1–2 cm: 1 year: 96%; 2 years: 84%; 3 years: 78%. RFA in patients with tumours 2.1–3 cm: 1 year: 89%; 2 years: 78%; 3 years: 73%. Low-dose PEI in patients with tumours 1–2 cm: 1 year: 94%; 2 years: 78%; 3 years: 70%. Low-dose PEI in patients with tumours 2.1–3 cm: 1 year: 84%; 2 years: 70%; 3 years: 62%. High-dose PEI in patients with tumours 1–2 cm: 1 year: 93%; 2 years: 80%; 3 years: 72%. High-dose PEI in patients with tumours 2.1–3 cm: 1 year: 83%; 2 years: 71%; 3 years: 64%.</p> <p>Cancer-free survival: RFA in patients with tumours 1–2 cm: 1 year: 84%; 2 years: 64%; 3 years: 49%. RFA in patients with tumours 2.1–3 cm: 1 year: 76%; 2 years: 53%; 3 years: 40%. Low-dose PEI in patients with tumours 1–2 cm: 1 year: 73%; 2 years: 57%; 3 years: 41%. Low-dose PEI in patients with tumours 2.1–3 cm: 1 year: 68%; 2 years: 57%; 3 years: 30%. High-dose PEI in patients with tumours 1–2 cm: 1 year: 71%; 2 years: 61%; 3 years: 43%. High-dose PEI in patients with tumours 2.1–3 cm: 1 year: 63%; 2 years: 51%; 3 years: 32%.</p> <p>Local tumour progression: RFA in patients with tumours 1–2 cm: 1 year: 4%; 2 years: 9%; 3 years: 9%. RFA in patients with tumours 2.1–3 cm: 1 year: 11%; 2 years: 18%; 3 years: 18%. Low-dose PEI in patients with tumours 1–2 cm: 1 year: 8%; 2 years: 13%; 3 years: 13%. Low-dose PEI in patients with tumours 2.1–3 cm: 1 year: 18%; 2 years: 37%; 3 years: 37%. High-dose PEI in patients with tumours 1–2 cm: 1 year: 7%; 2 years: 12%; 3 years: 12%. High-dose PEI in patients with tumours 2.1–3 cm: 1 year: 21%; 2 years: 33%; 3 years: 33%.</p> <p>Adverse events: RFA: One patient (1.9%) had transient pleural effusion, although not reported whether their tumour was < 3cm or not. No other severe adverse effect was observed. Low-dose PEI: No severe adverse effect was observed. High-dose PEI: No severe adverse effect was observed.</p> <p>Economic outcomes: RFA: Mean hospital stay: 4.4 days (range 3–15). Low-dose PEI: Mean hospital stay: 1.6 days (range 2–3). High-dose PEI: Mean hospital stay: 2.1 days (range 2–4).</p>	Low
					continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Lin, 2005 ⁵³ Taiwan	187 patients with tumours ≤ 3 cm	RFA (n = 62 patients)	PEI (n = 62 patients) PAI (n = 63 patients)	<p>OS: RFA: 1 year: 93%; 2 years: 81%; 3 years: 74%. PEI: 1 year: 88%; 2 years: 66%; 3 years: 51%. PAI: 1 year: 90%; 2 years: 67%; 3 years: 53%. RFA: Number of events (death): 10 (16.1%). PEI: Number of events (death): 17 (27.4%). PAI: Number of events (death): 15 (23.8%).</p> <p>Cancer-free survival: RFA: 1 year: 74%; 2 years: 60%; 3 years: 43%. PEI: 1 year: 70%; 2 years: 41%; 3 years: 21%. PAI: 1 year: 71%; 2 years: 43%; 3 years: 23%.</p> <p>Recurrence: RFA: 1 year: 10%; 2 years: 14%; 3 years: 14%. PEI: 1 year: 16%; 2 years: 34%; 3 years: 34%. PAI: 1 year: 14%; 2 years: 31%; 3 years: 31%. RFA: Number of local recurrence events: 8/60 (13.3%). PEI: Number of local recurrence events: 19/55 (34.5%). PAI: Number of local recurrence events: 17/58 (29.3%).</p> <p>Complete response: RFA: 96.1% (75/78 tumours). PEI: 88.1% (67/76 tumours). PAI: 92.4% (73/79 tumours).</p> <p>Adverse events: RFA: 4.8% (3/62 patients) had serious AEs (2 patients with haemothorax and 1 with gastric bleeding and perforation). PEI: No serious AEs. PAI: No serious AEs.</p> <p>Economic outcomes: RFA: Mean hospitalisation: 4.2 days (range 3–18). PEI: Mean hospitalisation: 1.7 days (range 2–3). PAI: Mean hospitalisation: 2.2 days (range 2–5).</p>	Some concerns

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Shiina, 2005 ⁵⁵ Japan	232 patients with tumours ≤ 3 cm	RFA (n = 118 patients)	PEI (n = 114 patients)	<p>OS: RFA: 4 years: 74% (95% CI 65% to 84%). PEI: 4 years: 57% (95% CI 45% to 71%). RFA: Number of events (death): 25 (21.2%). PEI: Number of events (death): 40 (35.1%). Comparison between groups: RR 0.54, 95% CI 0.33 to 0.89.</p> <p>Recurrence: RFA: Number of events: 78 (66.1%) (new lesion: 74; local tumour progression: 2; extrahepatic recurrence: 2). PEI: Number of events: 90 (78.9%) (new lesion: 73; local tumour progression: 13; extrahepatic recurrence: 4). Comparison between groups: RR 0.57, 95% CI 0.41 to 0.80. Local tumour progression: RR 0.12, 95% CI 0.03 to 0.55.</p> <p>Adverse events: RFA: AEs grade ≥ 3: 6 (5.1%) (1 transient jaundice, 1 skin burn, 1 hepatic infarction and 3 seeding of malignant cells). PEI: AEs grade ≥ 3: 3 (2.6%) (1 liver abscess and 2 neoplastic seeding).</p> <p>Economic outcomes: RFA: Length of hospitalisation: 10.8 ± 5.5 days. PEI: Length of hospitalisation: 26.1 ± 9.9 days.</p>	Some concerns
					continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
RFA vs. PAI					
Lin, 2005 ⁵³ Taiwan	187 patients with tumours ≤3cm	RFA (n = 62 patients)	PEI (n = 62 patients) PAI (n = 63 patients)	<p>OS: RFA: 1 year: 93%; 2 years: 81%; 3 years: 74%. PEI: 1 year: 88%; 2 years: 66%; 3 years: 51%. PAI: 1 year: 90%; 2 years: 67%; 3 years: 53%. RFA: Number of events (death): 10 (16.1%). PEI: Number of events (death): 17 (27.4%). PAI: Number of events (death): 15 (23.8%).</p> <p>Cancer-free survival: RFA: 1 year: 74%; 2 years: 60%; 3 years: 43%. PEI: 1 year: 70%; 2 years: 41%; 3 years: 21%. PAI: 1 year: 71%; 2 years: 43%; 3 years: 23%.</p> <p>Recurrence: RFA: 1 year: 10%; 2 years: 14%; 3 years: 14%. PEI: 1 year: 16%; 2 years: 34%; 3 years: 34%. PAI: 1 year: 14%; 2 years: 31%; 3 years: 31%. RFA: Number of local recurrence events: 8/60 (13.3%). PEI: Number of local recurrence events: 19/55 (34.5%). PAI: Number of local recurrence events: 17/58 (29.3%).</p> <p>Complete response: RFA: 96.1% (75/78 tumours). PEI: 88.1% (67/76 tumours). PAI: 92.4% (73/79 tumours).</p> <p>Adverse events: RFA: 4.8% (3/62 patients) had serious AEs (2 patients with haemothorax and 1 with gastric bleeding and perforation). PEI: No serious AEs. PAI: No serious AEs.</p> <p>Economic outcomes: RFA: Mean hospitalisation: 4.2 days (range 3–18). PEI: Mean hospitalisation: 1.7 days (range 2–3). PAI: Mean hospitalisation: 2.2 days (range 2–5).</p>	Some concerns
RFA vs. laser ablation					
Ferrari, 2007 ⁷⁷ Authors from Italy	81 patients with tumours ≤ 4 cm; subgroup of 28 patients with tumours ≤ 2.5 cm	Laser ablation (n = 12 patients with tumours ≤ 2.5 cm)	RFA (n = 16 patients with tumours ≤ 2.5 cm)	<p>Adverse events: No deaths or major or minor complications occurred during the procedures in either group and no cases of neoplastic seeding observed. No other results reported for ≤ 2.5 cm subgroup, other than Kaplan–Meier curve.</p>	Some concerns

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Orlacchio, 2014 ⁶¹ Italy	30 patients with tumours ≤ 4 cm (mean tumour size 2.4 cm)	Laser ablation (n = 15 patients with mean tumour size 2.34 cm)	RFA (n = 15 patients with mean tumour size 2.41 cm)	<p>OS: Laser ablation: Number of events (death): 0 RFA: Number of events (death): 0</p> <p>PFS: Laser ablation: 3 months: 85%; 6 months: 62%; 1 year: 54%. RFA: 3 months: 92%; 6 months: 86%; 1 year: 86%.</p> <p>Recurrence: Laser ablation: Number of events (local disease progression): 6 (40%). RFA: Number of events (local disease progression): 2 (13.3%).</p> <p>Complete response: Laser ablation: 66.7% nodules (10/15) after first procedure; 3/5 patients after a second procedure (87% in total). RFA: 86.7% nodules (13/15) after first procedure; 1/2 patients after a second procedure (93% in total).</p> <p>Adverse events: Laser ablation: 2 (13.3%) (1 vasovagal reaction and 1 postablation syndrome). RFA: 14 (93.3%) (2 vasovagal reactions and 12 postablation syndrome). No major complications in either arm.</p>	Some concerns
Zou, 2017 ⁵⁷ China	74 patients with tumours ≤ 3 cm	Laser ablation (n = 35 patients)	RFA (n = 39 patients)	<p>Response: Laser ablation: 31 (88.6%) had a complete response; 4 (11.4%) had a partial response. RFA: 36 (92.3%) had a complete response; 3 (7.7%) had a partial response.</p> <p>Patient satisfaction: Self-made satisfaction questionnaire including intraoperative discomfort, postoperative therapy effects, adverse reactions and physical recovery. Maximum score of 100, 81–100 = great satisfaction, 61–80 = general satisfaction, < 60 = dissatisfaction. Laser ablation: great satisfaction: 30 (85.7%), general satisfaction: 3 (8.6%), dissatisfaction: 2 (5.7%). RFA: great satisfaction: 25 (64.1%), general satisfaction: 2 (5.1%), dissatisfaction: 12 (30.8%).</p> <p>Adverse events: Laser ablation: Fever: 4 (11.4%); nausea: 17 (48.6%); vomiting: 10 (28.6%); diarrhoea: 1 (2.9%); abdominal pain: 26 (74.3%); skin rash: 1 (2.9%). RFA: Fever: 5 (12.8%); nausea: 19 (48.7%); vomiting: 12 (30.8%); diarrhoea: 1 (2.6%); abdominal pain: 29 (74.4%); skin rash: 3 (7.7%).</p>	Some concerns

continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
RFA vs. resection					
Chen, 2005 (reported in Chinese) ⁶⁷ China	132 patients with tumours ≤ 5 cm; subgroup of 55 patients with tumours ≤ 3 cm	Resection (<i>n</i> = 31 patients with tumours ≤ 3 cm)	RFA (<i>n</i> = 24 patients with tumours ≤ 3 cm)	No results reported for ≤ 3 cm subgroup, other than Kaplan–Meier curve.	Some concerns
Fang, 2014 ⁴⁶ China	120 patients with tumours ≤ 3 cm	RFA (<i>n</i> = 60 patients)	Hepatectomy (<i>n</i> = 60 patients)	<p>OS: RFA: 1 year: 97.5%; 2 years: 91.2%; 3 years: 82.5%. Hepatectomy: 1 year: 93.7%; 2 years: 86.2%; 3 years: 77.5%.</p> <p>Disease-free survival: RFA: 1 year: 91.6%; 2 years: 87.4%; 3 years: 55.4%. Hepatectomy: 1 year: 90.4%; 2 years: 85.2%; 3 years: 41.3%.</p> <p>Recurrence: RFA: Number of events: 22. Hepatectomy: Number of events: 21.</p> <p>Response: RFA: Complete tumour treatment: 57/60 (95.0%). Hepatectomy: Complete tumour treatment: 58/60 (96.7%).</p> <p>Adverse events: RFA: Postoperative complications: 2. Major complications: 1. Hospital mortality: 0. Serious pain requiring analgesic (not included in postoperative complications): 3. Hepatectomy: Postoperative complications: 17. Major complications: 14. Hospital mortality: 0. Serious pain requiring analgesic (not included in postoperative complications): 43.</p> <p>Economic outcomes: RFA: ICU stay: 0. Hospital days (mean): 4.3 (SD 1.5). Hepatectomy: ICU stay: 6 (10%). Hospital days (mean): 11.8 (SD 3.1).</p>	Some concerns
Feng, 2012 ⁵⁸ China	168 patients with tumours < 4 cm; subgroup of 56 patients with tumours ≤ 2 cm	RFA (<i>n</i> = 31 patients with tumours ≤ 2 cm)	Surgical resection (<i>n</i> = 25 patients with tumours ≤ 2 cm)	No results reported for ≤ 2 cm subgroup.	N/A

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Huang, 2010 ⁶⁹ China	230 patients with tumours ≤ 5 cm; subgroup of 159 patients with tumours ≤ 3 cm	RFA (n = 88 patients with tumours ≤ 3 cm)	Resection (n = 71 patients with tumours ≤ 3 cm)	<p>OS: RFA in patients with solitary tumours ≤ 3 cm (n = 57): 1 year: 91.2%; 2 years: 84.2%; 3 years: 77.2%; 4 years: 71.9%; 5 years: 61.4%. RFA in patients with multifocal tumours ≤ 3 cm (n = 31): 1 year: 77.4%; 2 years: 64.5%; 3 years: 58.1%; 4 years: 58.1%; 5 years: 45.2%. Resection in patients with solitary tumours ≤ 3 cm (n = 45): 1 year: 100%; 2 years: 97.8%; 3 years: 95.6%; 4 years: 86.7%; 5 years: 82.2%. Resection in patients with multifocal tumours ≤ 3 cm (n = 26): 1 year: 92.3%; 2 years: 88.5%; 3 years: 80.8%; 4 years: 73.1%; 5 years: 69.2%.</p> <p>Adverse events: No deaths within same hospital admission. No other results reported for ≤ 3 cm subgroup, other than separate Kaplan–Meier curves for solitary tumours ≤ 3 cm and multifocal tumours ≤ 3 cm.</p>	High
Izumi, 2019 ⁵⁰ (conference abstract) Japan	308 patients with tumours ≤ 3 cm	RFA (n = 148 analysed)	Surgery (n = 145 analysed)	<p>Recurrence-free survival: RFA: 3 years: 47.7%. Surgery: 3 years: 49.8%. Comparison between groups: HR 0.96.</p> <p>Adverse events: No perioperative mortality in either group.</p>	High
Ng, 2017 ⁷³ China	218 patients with tumours ≤ 5 cm; subgroup of 55 patients with tumours ≤ 2 cm	Resection (n = 29 patients with tumours ≤ 2 cm)	RFA (n = 26 patients with tumours ≤ 2 cm)	<p>OS: Resection: 1 year: 100%; 3 years: 93%; 5 years: 76%. RFA: 1 year: 100%; 3 years: 89%; 5 years: 69%.</p> <p>Disease-free survival: Resection: 1 year: 83%; 3 years: 66%; 5 years: 52%. RFA: 1 year: 77%; 3 years: 62%; 5 years: 46%.</p> <p>Economic outcomes: Resection: Median hospital stay: 7 days. RFA: Median hospital stay: 4 days.</p>	Low
Xia, 2020 ⁷⁵ China	240 patients with recurrent HCC tumours ≤ 5 cm; subgroup of 159 patients with tumours ≤ 3 cm	RFA (78 patients with tumours ≤ 3 cm)	Repeat hepatectomy (81 patients with tumours ≤ 3 cm)	<p>OS: Comparison between group: In HR 0.05, 95% CI -0.4 to 0.5. HR 1.05, 95% CI 0.67 to 1.65 (calculated by CRD).</p> <p>Repeat-recurrence-free survival: Comparison between group: In HR 0.07, 95% CI -0.34 to 0.47. HR 1.07, 95% CI 0.71 to 1.6 (calculated by CRD).</p>	Low
Zhu, 2021 (protocol) ⁸⁰ China	Ongoing RCT	RFA	Laparoscopic hepatectomy	N/A	N/A

continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
RFA vs. proton beam radiotherapy					
Kim, 2021 ¹⁶² South Korea	144 patients with recurrent/residual tumours < 3 cm	Proton beam radiotherapy (n = 72 patients)	RFA (n = 72 patients)	<p>OS: Proton beam radiotherapy: 2 years: 91.7%; 3 years: 80.8%; 4 years: 75.4%. RFA: 2 years: 90.3%; 3 years: 86.0%; 4 years: 77.0%. Comparison between groups: HR (2 years) 1.07, 95% CI 0.58 to 1.98.</p> <p>PFS: Proton beam radiotherapy: Median 13.4 months (90% CI 7.69 to 16.76 months). RFA: Median 13.7 months (90% CI 9.86 to 18.89 months). Proton beam radiotherapy: 2 years: 31.9%; 3 years: 26.3%; 4 years: 18.7%. RFA: 2 years: 31.9%; 3 years: 17.9%; 4 years: 12.6%. HR (2 years) 0.99, 95% CI 0.70 to 1.41. Proton beam radiotherapy: Number of events (progression): 56 RFA: Number of events (progression): 62</p> <p>Adverse events: Proton beam radiotherapy: AEs grade ≥ 3: 0. RFA: AEs grade ≥ III: 9 (16%). No treatment-related late hepatic failure and death without evidence of disease progression and/or subsequent treatment.</p>	Some concerns
RFA vs. RFA + TACE					
Aikata, 2006 (conference abstract) ⁴³ Authors from Japan	44 patients with tumours < 3 cm	RFA + TACE (n = 21 patients)	RFA alone (n = 23 patients)	<p>OS: RFA + TACE: 1 year: 95.2%; 2 years: 95.2%; 3 years: 84%. RFA alone: 1 year: 100%; 2 years: 82.6%; 3 years: 73.9%.</p> <p>Local tumour progression: RFA + TACE: 1 year: 9.5%; 2 years: 9.5%; 3 years: 9.5%. RFA alone: 1 year: 4.3%; 2 years: 8.7%; 3 years: 8.7%.</p> <p>Adverse events: There were no major complications in either group.</p>	High
Peng, 2012 ⁷⁴ China	139 patients with recurrent HCC tumours ≤ 5 cm; subgroup of 87 patients with tumours ≤ 3 cm	RFA + TACE (n = 41 patients with tumours ≤ 3 cm)	RFA alone (n = 46 patients with tumours ≤ 3 cm)	<p>OS: RFA + TACE: 1 year: 98%; 3 years: 70%; 5 years: 50%. RFA alone: 1 year: 83%; 3 years: 60%; 5 years: 50%.</p> <p>Recurrence-free survival: RFA + TACE: 1 year: 90%; 3 years: 48%; 5 years: 48%. RFA alone: 1 year: 86%; 3 years: 26%; 5 years: 26%.</p>	Low

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Shibata, 2009 ⁵⁴ Japan	89 patients with tumours ≤ 3 cm	RFA + TACE (n = 46 patients)	RFA alone (n = 43 patients)	<p>OS: RFA + TACE: 1 year: 100%; 2 years: 100%; 3 years: 84.8%; 4 years: 72.7%. RFA alone: 1 year: 100%; 2 years: 88.8%; 3 years: 84.5%; 4 years: 74%. RFA + TACE: Number of events (death): 5 (10.9%). RFA alone: Number of events (death): 6 (13.9%).</p> <p>Event-free survival: RFA + TACE: 1 year: 71.3%; 2 years: 59.9%; 3 years: 48.8%; 4 years: 36.6%. RFA alone: 1 year: 74.3%; 2 years: 52.4%; 3 years: 29.7%; 4 years: 29.7%.</p> <p>Local PFS RFA + TACE: 1 year: 84.6%; 2 years: 81.1%; 3 years: 69.7%; 4 years: 55.8%. RFA alone: 1 year: 88.4%; 2 years: 74.1%; 3 years: 74.1%; 4 years: 61.7%.</p> <p>Local tumour progression: RFA + TACE: 1 year: 14.4%; 2 years: 17.6%; 3 years: 17.6%; 4 years: 17.6%. RFA alone: 1 year: 11.4%; 2 years: 14.4%; 3 years: 14.4%; 4 years: 14.4%. RFA + TACE: Number of recurrence events: 8 (17.4%). RFA alone: Number of recurrence events: 6 (13.9%).</p> <p>Complete response: RFA + TACE: 100%. RFA alone: 100%.</p> <p>Adverse events: RFA + TACE: 1 major complication (2%) (segmental hepatic infarction). RFA alone: 1 major complication (2%) (pseudoaneurysm of the anterosuperior branch of the right hepatic artery).</p>	High
RFA vs. RFA + PEI					
Azab, 2011 ⁶⁵ Egypt	90 patients (with 98 tumours) ≤ 5 cm; subgroup of 48 tumours ≤ 3 cm	PEI + RFA (n = 16 tumours ≤ 3 cm)	RFA alone (n = 16 tumours ≤ 3 cm) PEI alone (n = 16 tumours ≤ 3 cm)	<p>Response: PEI + RFA: 15/16 (93.8%) nodules had complete ablation and 1/16 (6.2%) had partial ablation after one session; 16/16 (100%) nodules had complete ablation after two sessions. RFA alone: 12/16 (75%) nodules had complete ablation and 4/16 (25%) had partial ablation after one session; 14/16 (87.5%) nodules had complete ablation and 2/16 (12.5%) had partial ablation after two sessions. PEI alone: 0% nodules had complete ablation after two sessions; 13/16 (81.25%) nodules had complete ablation and 3/16 (18.75%) had partial ablation after all sessions.</p> <p>Adverse events: There were no mortalities related to any of the techniques. No other results reported for ≤ 3 cm tumour subgroup.</p>	Some concerns
					continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Chen, 2005 (reported in Chinese) ⁶⁶ China	86 patients with tumours ≤ 5 cm; subgroup of 47 patients with tumours ≤ 3 cm	RFA + PEI (n = 24 patients with tumours ≤ 3 cm)	RFA alone (n = 23 patients with tumours ≤ 3 cm)	<p>OS: RFA + PEI: 1 year: 86.8%; 2 years: 79.0%. RFA alone: 1 year: 81.2%; 2 years: 64.9%.</p> <p>Recurrence: RFA + PEI: 1 year: 4.3%; 2 years: 20.9%. RFA alone: 1 year: 16.8%; 2 years: 34.1%.</p> <p>Adverse events: There were no serious AEs in either group.</p>	High
Zhang, 2007 ⁷⁶ China	133 patients with tumours ≤ 7 cm; subgroup of 60 patients with tumours ≤ 3 cm	RFA + PEI (29 patients with tumours ≤ 3 cm)	RFA alone (31 patients with tumours ≤ 3 cm)	<p>OS: RFA + PEI: 1 year: 96.5%; 2 years: 92.9%; 3 years: 83.6%; 4 years: 77.4%; 5 years: 55.3%. RFA alone: 1 year: 93.5%; 2 years: 80.7%; 3 years: 76.6%; 4 years: 70.2%; 5 years: 50.2%.</p> <p>Response: RFA + PEI: 52/66 (78.8%) had complete tumour ablation after one treatment, 14 (21.2%) had complete tumour ablation after a second treatment. RFA alone: 48/67 (71.6%) had complete tumour ablation after one treatment, 18 (26.9%) had complete tumour ablation after a second treatment and 1 patient (1.5%) had viable tumour cells after two treatment sessions. Tumour diameter was a significant prognostic factor for overall recurrence, intrahepatic recurrence and local recurrence.</p>	Low
RFA vs. RFA + iodine-131 metuximab					
Bian, 2014 ⁷⁸ China	127 patients with BCLC stage 0–B; subgroup of 78 patients with tumours < 3 cm	RFA + iodine-131 metuximab (n = 38 patients with tumours < 3 cm)	RFA alone (n = 40 patients with tumours < 3 cm)	<p>Recurrence: Comparison between groups: HR 0.46, 95% CI 0.21 to 1.01.</p> <p>Adverse events: There were no serious AEs or treatment-related deaths in either group. No other results reported for < 3 cm tumour subgroup.</p>	Some concerns

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
RFA vs. RFA + iodine-125					
Chen, 2014 ⁴⁵ China	136 patients with tumours ≤ 3 cm	RFA + iodine-125 (n = 68 patients)	RFA alone (n = 68 patients)	<p>OS: RFA + iodine-125: Mean 95.8 months. RFA alone: Mean 70.8 months. RFA + iodine-125: 1 year: 100%; 2 years: 95.6%; 3 years: 86.7%; 4 years: 73.5%; 5 years: 66.1%. RFA alone: 1 year: 95.6%; 2 years: 85.2%; 3 years: 75.0%; 4 years: 58.8%; 5 years: 47.0%. RFA + iodine-125: Number of events (death): 23. RFA alone: Number of events (death): 36. Comparison between groups: HR 0.502, 95% CI 0.313 to 0.806.</p> <p>Recurrence: RFA + iodine-125: 1 year: 4.5%; 2 years: 11.8%; 3 years: 22.1%; 4 years: 32.4%; 5 years: 39.8%. RFA alone: 1 year: 14.8%; 2 years: 25.0%; 3 years: 35.3%; 4 years: 47.1%; 5 years: 57.4%. RFA + iodine-125: Number of events: 27. RFA alone: Number of events: 39. Comparison between groups: HR 0.508, 95% CI 0.317 to 0.815. RFA + iodine-125: Mean time to recurrence: 93 months. RFA alone: Mean time to recurrence: 66.8 months.</p> <p>Response: RFA + iodine-125: Complete ablation after one treatment: 56/68; complete response after two treatments: 12/68. RFA alone: Complete ablation after one treatment: 49/68; complete response after two treatments: 19/68.</p> <p>Adverse events: RFA + iodine-125: AEs grade ≥ 3: 15 events (not patient numbers) RFA alone: AEs grade ≥ 3: 11 events (not patient numbers) No procedure-related mortalities and no iodine-125 seed migration from the liver to the heart or other organs.</p>	Low
RFA vs. RFA + chemotherapy					
Gan, 2004 (reported in Chinese) ⁴⁷ China	38 patients with tumours ≤ 3 cm	RFA alone (n = 18 patients)	RFA+ chemotherapy (n = 20 patients)	<p>Recurrence: RFA alone: 1 year: 50% (6/12 analysed). RFA + chemotherapy: 1 year: 27% (4/15 analysed). RFA: Number of events: 6 (1 original location recurrence + 5 other location recurrence). RFA + chemotherapy: Number of events: 4 (4 other location recurrence).</p> <p>Adverse events: There were no serious AEs in either group.</p>	High
					continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
RFA + TACE vs. resection					
Liu, 2016 ⁷² China	200 patients with tumours ≤ 5 cm; subgroup of 135 patients with tumours ≤ 3 cm	Partial hepatectomy (n = 66 patients with tumours ≤ 3 cm)	TACE + RFA (n = 69 patients with tumours ≤ 3 cm)	No results reported for ≤ 3 cm subgroup, other than Kaplan–Meier curve. Adverse events: No 30- or 90-day mortality in either group.	Some concerns
PEI vs. PAI					
Lin, 2005 ⁵³ Taiwan	187 patients with tumours ≤ 3 cm	RFA (n = 62 patients)	PEI (n = 62 patients) PAI (n = 63 patients)	OS: RFA: 1 year: 93%; 2 years: 81%; 3 years: 74%. PEI: 1 year: 88%; 2 years: 66%; 3 years: 51%. PAI: 1 year: 90%; 2 years: 67%; 3 years: 53%. RFA: Number of events (death): 10 (16.1%). PEI: Number of events (death): 17 (27.4%). PAI: Number of events (death): 15 (23.8%). Cancer-free survival: RFA: 1 year: 74%; 2 years: 60%; 3 years: 43%. PEI: 1 year: 70%; 2 years: 41%; 3 years: 21%. PAI: 1 year: 71%; 2 years: 43%; 3 years: 23%. Recurrence: RFA: 1 year: 10%; 2 years: 14%; 3 years: 14%. PEI: 1 year: 16%; 2 years: 34%; 3 years: 34%. PAI: 1 year: 14%; 2 years: 31%; 3 years: 31%. RFA: Number of local recurrence events: 8/60 (13.3%). PEI: Number of local recurrence events: 19/55 (34.5%). PAI: Number of local recurrence events: 17/58 (29.3%). Complete response: RFA: 96.1% (75/78 tumours). PEI: 88.1% (67/76 tumours). PAI: 92.4% (73/79 tumours). Adverse events: RFA: 4.8% (3/62 patients) had serious AEs (2 patients with haemothorax and 1 with gastric bleeding and perforation). PEI: No serious AEs. PAI: No serious AEs. Economic outcomes: RFA: Mean hospitalisation: 4.2 days (range 3–18). PEI: Mean hospitalisation: 1.7 days (range 2–3). PAI: Mean hospitalisation: 2.2 days (range 2–5).	Some concerns

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
PEI vs. resection					
Huang, 2005 ⁴⁹ Taiwan	82 patients with tumours ≤ 3 cm	PEI (n = 40 patients)	Resection (n = 42 patients)	<p>OS: PEI: 1 year: 100%; 2 years: 100%; 3 years: 96.7%; 4 years: 92.1%; 5 years: 46.0%. Resection: 1 year: 97.4%; 2 years: 91.3%; 3 years: 88.1%; 4 years: 88.1%; 5 years: 81.8%.</p> <p>PFS: PEI: 1 year: 76.1%; 2 years: 64.5%; 3 years: 49.1%; 4 years: 44.6%; 5 years: 44.6%. Resection: 1 year: 89.5%; 2 years: 71.3%; 3 years: 60.9%; 4 years: 56.2%; 5 years: 48.2%.</p> <p>Recurrence: PEI: Number of events: 18. Resection: Number of events: 15.</p> <p>Adverse events: PEI: 3 patients had adverse effects (1 decreased blood pressure, 2 wound pain). Resection: No significant complications.</p>	High
PEI vs. RFA + PEI					
Azab, 2011 ⁶⁵ Egypt	90 patients (with 98 tumours) ≤ 5 cm; subgroup of 48 tumours ≤ 3 cm	PEI + RFA (n = 16 tumours ≤ 3 cm)	RFA alone (n = 16 tumours ≤ 3 cm) PEI alone (n = 16 tumours ≤ 3 cm)	<p>Response: PEI + RFA: 15/16 (93.8%) nodules had complete ablation and 1/16 (6.2%) had partial ablation after one session; 16/16 (100%) nodules had complete ablation after two sessions. RFA alone: 12/16 (75%) nodules had complete ablation and 4/16 (25%) had partial ablation after one session; 14/16 (87.5%) nodules had complete ablation and 2/16 (12.5%) had partial ablation after two sessions. PEI alone: 0% nodules had complete ablation after two sessions; 13/16 (81.25%) nodules had complete ablation and 3/16 (18.75%) had partial ablation after all sessions.</p> <p>Adverse events: There were no mortalities related to any of the techniques. No other results reported for ≤ 3 cm tumour subgroup.</p>	Some concerns
					continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
PEI vs. PEI + TACE					
Koda, 2001 ⁵² Japan	52 patients with tumours < 3 cm	TACE + PEI (n = 26 patients)	PEI alone (n = 26 patients)	<p>OS: TACE + PEI: 1 year: 100%; 2 years: 94.4%; 3 years: 80.8%; 5 years: 40.4%. PEI alone: 1 year: 91.3%; 2 years: 81.6%; 3 years: 65.9%; 5 years: 37.7%. TACE + PEI: Number of events: 4. PEI alone: Number of events: 8.</p> <p>Recurrence: TACE + PEI local residual disease: 1 year: 3.7%; 2 years: 19.3%; 3 years: 19.3%, 5 years: 19.3%. TACE + PEI new nodular recurrence: 1 year: 8.7%; 2 years: 41.9%; 3 years: 50.2%; 5 years: 50.2%. PEI alone local residual disease: 1 year: 34.2%; 2 years: 39.3%; 3 years: 39.3%, 5 years: 39.3%. PEI alone new nodular recurrence: 1 year: 26.9%; 2 years: 60.1%; 3 years: 80.1%; 5 years: 100%. TACE + PEI local residual disease: Number of events: 4 nodules (of 31). PEI alone local residual disease: Number of events: 11 nodules (of 34). TACE + PEI new nodular recurrence: Number of events: 9. PEI alone new nodular recurrence: Number of events: 17.</p> <p>Adverse events: TACE + PEI: Major complications: 2. PEI alone: Major complications: 0. TACE + PEI: After TACE: continuous abdominal pain: 6; severe abdominal pain: 6; fever: 19; high-grade fever: 10; liver dysfunction: 3; leukocytosis: 11; C-reactive protein: 22. After PEI: continuous abdominal pain: 16; severe abdominal pain: 7; fever: 20; high-grade fever: 10; liver dysfunction: 3; leukocytosis: 4; C-reactive protein: 20. PEI alone: continuous abdominal pain: 11; severe abdominal pain: 5; fever: 22; high-grade fever: 5; liver dysfunction: 3; leukocytosis: 5; C-reactive protein: 15.</p>	Low
Mizuki, 2010 ⁶⁰ Japan	30 patients with tumours ≤ 4 cm (large proportion had tumours ≤ 3 cm)	PEI alone (n = 14 patients with average tumour size 2.64 cm)	TACE + PEI (n = 16 patients with average tumour size 2.65 cm)	<p>OS: PEI alone: Mean 57.2 months, 95% CI 37.2 to 77.2 months. TACE + PEI: Mean 42.4 months, 95% CI 29.2 to 55.6 months. PEI alone: Number of events (death): 6/14 (44%). TACE + PEI: Number of events (death): 8/13 (61.5%).</p> <p>Cancer-free survival: PEI alone: Mean 16.7 months, 95% CI 7.3 to 26.0 months. TACE + PEI: Mean 22.9 months, 95% CI 12.4 to 33.4 months.</p> <p>Recurrence: PEI alone: Number of events: 10 (71.4%). TACE + PEI: Number of events: 11 (84.6%).</p> <p>Adverse events: In all 30 cases, serious adverse effects or complications were not related to treatment with TACE and/or PEI.</p>	Some concerns

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
PAI vs. PAI + TACE					
Huo, 2003 ⁷⁰ Taiwan	108 patients with tumours ≤ 5 cm; subgroup of 55 patients with tumours ≤ 3 cm	Sequential TACE and PAI (n = 24 patients with tumours ≤ 3 cm)	PAI alone (n = 31 patients with tumours ≤ 3 cm)	<p>OS: Sequential TACE and PAI: 1 year: 100%; 3 years: 73%. PAI alone: 1 year: 100%; 3 years: 49%.</p> <p>Cancer-free survival: There were no significant differences in cancer-free survival between the two groups of patients with tumour sizes ≤ 3 cm (p = 0.217).</p> <p>Adverse events: Sequential TACE and PAI: Transient fever, abdominal pain and elevation of liver enzymes were present in the majority of patients (in whole sample) after TACE. No serious complications that necessitated intensive care. PAI alone: Side effects relatively mild. Most patients (in whole sample) experienced transient mild to moderate local pain during or after acetic acid injection, which could be controlled with additional analgesics. No serious complications that necessitated intensive care.</p>	High
Percutaneous local ablative therapy vs. resection					
Chen, 2006 ⁶⁸ China	180 patients with tumours ≤ 5 cm; subgroup of 79 patients with tumours ≤ 3 cm	Percutaneous local ablative therapy (initial RFA followed by RFA/PEI if residual tumour, and TACE if residual tumour remained) (n = 37 patients with tumours ≤ 3 cm)	Partial hepatectomy (n = 42 patients with tumours ≤ 3 cm)	<p>No results reported for ≤ 3 cm subgroup, other than Kaplan–Meier curve. No significant difference in overall and disease-free survival between the two treatment groups in the ≤ 3 cm subgroup.</p>	High
					continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
MWA + sorafenib vs. resection					
Yan, 2016 ⁵⁶ China	120 patients with tumours ≤ 3 cm	Resection (n = 60 patients)	MWA+ sorafenib (n = 60 patients)	<p>OS: Resection: Mean 51.2 ± 1.5 months. MWA + sorafenib: Mean 64.6 ± 2.4 months. Resection: 1 year: 90.7%; 3 years: 71.5%; 5 years: 56.7%. MWA + sorafenib: 1 year: 91.1%; 3 years: 72.8%; 5 years: 57.5%.</p> <p>Tumour-free survival: Resection: 1 year: 87.8%; 3 years: 44.3%; 5 years: 33.2%. MWA + sorafenib: 1 year: 86.2%; 3 years: 48.3%; 5 years: 34.6%.</p> <p>Recurrence: Resection: 5 years: 18.3%. MWA + sorafenib: 5 years: 38.3%. Resection: Number of events: 11 (2 local recurrence, 9 distant recurrence). MWA + sorafenib: Number of events: 23 (7 local recurrence, 16 distant recurrence).</p> <p>Adverse events: Resection: Pain: 38 (63.3%); fever: 29 (48.3%); abdominal bleeding: 7 (11%); infection: 18 (30%). MWA + sorafenib: Pain: 14 (23.3%); fever: 15 (25%); abdominal bleeding: 2 (3.3%); infection: 1 (1.7%).</p>	High
ICER, incremental cost-effectiveness ratio.					

Appendix 5 Studies excluded at full paper stage with rationale (non-randomised controlled trial searches)

Study	Reason for exclusion
Abdelaziz, 2014 ⁶⁴	Duplicate report
Aikata, 2018 ²⁵¹	Not a prospective comparative study
Al-Judaibi, 2018 ²⁵²	Not a prospective comparative study
Anand, 2012 ²⁵³	Not early HCC patients (≤ 3 cm tumour)
Barabino, 2018 ²⁵⁴	Not a prospective comparative study
Bassanello, 2003 ²⁵⁵	Not early HCC patients (≤ 3 cm tumour)
Beyer, 2018 ²⁵⁶	Not early HCC patients (≤ 3 cm tumour)
Bhutiani, 2016 ²⁵⁷	Not early HCC patients (≤ 3 cm tumour)
Borzio, 2007 ²⁵⁸	No relevant intervention/comparison
Bouda, 2020 ²⁵⁹	Not a prospective comparative study
Bu, 2015 ²⁶⁰	Not a prospective comparative study
Bujold, 2011 ²⁶¹	Not early HCC patients (≤ 3 cm tumour)
Casaccia, 2017 ²⁶²	Not early HCC patients (≤ 3 cm tumour)
Chagnon, 2007 ²⁶³	Not a prospective comparative study
Chen, 2007 ²⁶⁴	No relevant intervention/comparison
Chen, 2019 ²⁶⁵	Not early HCC patients (≤ 3 cm tumour)
Cheung, 2012 ²⁶⁶	Not a prospective comparative study
Cheung, 2013 ²⁶⁷	Not early HCC patients (≤ 3 cm tumour)
Cho, 2015 ²⁶⁸	Not a prospective comparative study
Chong, 2020 ²⁶⁹	Not a prospective comparative study
Cillo, 2014 ²⁷⁰	Not a prospective comparative study
Costa, 2015 ²⁷¹	Not a prospective comparative study
De Geus, 2018 ²⁷²	Not a prospective comparative study
Denecke, 2015 ²⁷³	Not early HCC patients (≤ 3 cm tumour)
Di Costanzo, 2015 ¹²⁷	Not early HCC patients (≤ 3 cm tumour)
Di Sandro, 2019 ²⁷⁴	Not a prospective comparative study
Ding, 2021 ²⁷⁵	Not a prospective comparative study
Ei, 2013 ²⁷⁶	Duplicate report
Eloubeidi, 2000 ²⁷⁷	Not a prospective comparative study
Ferrari, 2007 ⁷⁷	Duplicate report
Freeman, 2021 ²⁷⁸	Not a prospective comparative study

continued

Study	Reason for exclusion
Gannon, 2009 ²⁷⁹	Not early HCC patients (≤ 3 cm tumour)
Garavoglia, 2013 ²⁸⁰	No relevant intervention/comparison
Ghweil, 2019 ²⁸¹	Not early HCC patients (≤ 3 cm tumour)
Guibal, 2013 ²⁸²	Not early HCC patients (≤ 3 cm tumour)
Guo, 2005 ¹⁴⁰	Duplicate report
Guo, 2010 ²⁸³	Not a prospective comparative study
Guo, 2013 ¹⁴¹	Not a prospective comparative study
Hara, 2018 ²⁸⁴	Not a prospective comparative study
Hara, 2019 ²⁸⁵	Not a prospective comparative study
Hasegawa, 2013 ²⁸⁶	Not a prospective comparative study
He, 2018 ²⁸⁷	Not a prospective comparative study
Helmberger, 2007 ²⁸⁸	No relevant intervention/comparison
Hiraoka, 2008 ²⁸⁹	Not a prospective comparative study
Hiraoka, 2017 ²⁹⁰	Not a prospective comparative study
Ho, 2012 ²⁹¹	Not early HCC patients (≤ 3 cm tumour)
Hong, 2005 ¹⁴⁵	Not early HCC patients (≤ 3 cm tumour)
Hsiao, 2020 ¹⁴⁶	Not a prospective comparative study
Hsu, 2013 ²⁹²	Not a prospective comparative study
Huang, 2012 ²⁹³	Not early HCC patients (≤ 3 cm tumour)
Hung, 2011 ¹⁵⁰	Not a prospective comparative study
Iida, 2014 ¹⁵²	Not a prospective comparative study
Ikeda, 2005 ²⁹⁴	Not a prospective comparative study
Ikeda, 2007 ²⁹⁵	Not a prospective comparative study
Imai, 2012 ²⁹⁶	Duplicate report
Imai, 2013	Not a prospective comparative study
Ismailova, 2017	Not early HCC patients (≤ 3 cm tumour)
Ito, 2015 ²⁹⁷	Duplicate report
Ito, 2016 ²⁹⁸	Not a prospective comparative study
Jiang, 2015	Not a prospective comparative study
Jianyong, 2017 ²⁹⁹	Not a prospective comparative study
Juloori, 2020 ³⁰⁰	Not early HCC patients (≤ 3 cm tumour)
Kang, 2014 ³⁰¹	Not a prospective comparative study
Kanwal, 2012 ³⁰²	Not early HCC patients (≤ 3 cm tumour)
Katsoulakis, 2014 ³⁰³	Not early HCC patients (≤ 3 cm tumour)
Kawamura, 2019 ³⁰⁴	Not a prospective comparative study
Kawaoka, 2019 ³⁰⁵	Not a prospective comparative study
Kennedy, 2004 ³⁰⁶	Not early HCC patients (≤ 3 cm tumour)
Kim, 2014a ³⁰⁷	Not early HCC patients (≤ 3 cm tumour)

Study	Reason for exclusion
Kim, 2014b ³⁰⁸	Not a prospective comparative study
Kim, 2016 ³⁰⁹	Not early HCC patients (≤ 3 cm tumour)
Kim, 2018 ³¹⁰	Not early HCC patients (≤ 3 cm tumour)
Kim, 2019 ³¹¹	Not early HCC patients (≤ 3 cm tumour)
Kim, 2021 ¹⁶²	Duplicate report
Kimura, 2018a ³¹²	Not early HCC patients (≤ 3 cm tumour)
Kimura, 2018b ³¹³	Duplicate report
Ko, 2020 ³¹⁴	Not a prospective comparative study
Komatsu, 2011 ³¹⁵	Not early HCC patients (≤ 3 cm tumour)
Komatsu, 2019 ³¹⁶	Not early HCC patients (≤ 3 cm tumour)
Kooby, 2010 ³¹⁷	Not early HCC patients (≤ 3 cm tumour)
Kuang, 2011 ³¹⁸	Not a prospective comparative study
Kudithipudi, 2017 ³¹⁹	Not early HCC patients (≤ 3 cm tumour)
Kuo, 2010 ³²⁰	Not a prospective comparative study
Kuo, 2021 ³²¹	Not a prospective comparative study
Kuromatsu, 2009 ³²²	Not a prospective comparative study
Kwon, 2012 ³²³	No relevant intervention/comparison
Lai, 2016 ¹⁶⁹	Not a prospective comparative study
Lapinski, 2021 ³²⁴	Not early HCC patients (≤ 3 cm tumour)
Lee, 2012 ³²⁵	Not a prospective comparative study
Lee, 2014 ³²⁶	Not a prospective comparative study
Lee, 2018 ³²⁷	Not a prospective comparative study
Lee, 2019 ³²⁸	Duplicate report
Lee, 2021 ³²⁹	Not a prospective comparative study
Lei, 2014 ³³⁰	Not a prospective comparative study
Li, 2015 ³³¹	Not early HCC patients (≤ 3 cm tumour)
Li, 2016 ³³²	Not a prospective comparative study
Li, 2019 ³³³	Not early HCC patients (≤ 3 cm tumour)
Lin, 2007 ¹⁷⁹	Not a prospective comparative study
Liu, 2016 ³³⁴	Not a prospective comparative study
Liu, 2017 ³³⁵	Not a prospective comparative study
Liu, 2018a ³³⁶	Not a prospective comparative study
Liu, 2018b ³³⁷	Not a prospective comparative study
Liu, 2019 ³³⁸	Not a prospective comparative study
Loo, 2020 ³³⁹	Not early HCC patients (≤ 3 cm tumour)
Lu, 2010 ³⁴⁰	Not a prospective comparative study
Maezawa, 2005 ³⁴¹	Not early HCC patients (≤ 3 cm tumour)

continued

Study	Reason for exclusion
Mariani, 2017 ³⁴²	Not a prospective comparative study
Martin, 2016 ³⁴³	Not a prospective comparative study
Merle, 2005 ³⁴⁴	Not early HCC patients (≤ 3 cm tumour)
Ming, 2012 ³⁴⁵	Not a prospective comparative study
Mizumoto, 2011 ³⁴⁶	Not early HCC patients (≤ 3 cm tumour)
Mo, 2003 ³⁴⁷	Not early HCC patients (≤ 3 cm tumour)
Mohnike, 2019 ³⁴⁸	Not early HCC patients (≤ 3 cm tumour)
Molinari, 2009 ³⁴⁹	Duplicate report
Molinari, 2014 ³⁵⁰	Not a prospective comparative study
Mornex, 2005 ³⁵¹	Not early HCC patients (≤ 3 cm tumour)
Mornex, 2007 ¹⁹⁷	Not a prospective comparative study
Murakami, 2007 ¹⁹⁸	Not a prospective comparative study
Nahon, 2021 ³⁵²	Not early HCC patients (≤ 3 cm tumour)
Nanashima, 2004 ³⁵³	Not a prospective comparative study
Nanashima, 2010 ³⁵⁴	Not a prospective comparative study
Nathan, 2013 ³⁵⁵	Not a prospective comparative study
Ogiso, 2021 ³⁵⁶	Not a prospective comparative study
Oh, 2019 ³⁵⁷	Not a prospective comparative study
Oh, 2020 ³⁵⁸	Not a prospective comparative study
Ohmoto, 2006 ³⁵⁹	Not a prospective comparative study
Paik, 2016 ²⁰⁵	Not a prospective comparative study
Pan, 2020 ³⁶⁰	Not a prospective comparative study
Park, 2007 ³⁶¹	Not a prospective comparative study
Park, 2018 ³⁶²	Not early HCC patients (≤ 3 cm tumour)
Park, 2020 ³⁶³	Duplicate report
Peng, 2011 ³⁶⁴	Not a prospective comparative study
Peng, 2012 ³⁶⁵	Duplicate report
Peng, 2013 ³⁶⁶	Not a prospective comparative study
Peng, 2014 ³⁶⁷	Not a prospective comparative study
Pompili, 2013 ²¹⁰	Not a prospective comparative study
Praktiknjo, 2018 ³⁶⁸	Not early HCC patients (≤ 3 cm tumour)
Pryor, 2019 ³⁶⁹	Not early HCC patients (≤ 3 cm tumour)
Rong, 2020 ³⁷⁰	Not early HCC patients (≤ 3 cm tumour)
Ruzzenente, 2012 ³⁷¹	Not a prospective comparative study
Ryu, 2018 ³⁷²	Not a prospective comparative study
Ryu, 2019 ³⁷³	Not a prospective comparative study
Sako, 2003 ³⁷⁴	Not a prospective comparative study
Santambrogio, 2009a ²¹⁴	Not early HCC patients (≤ 3 cm tumour)

Study	Reason for exclusion
Santambrogio, 2009b ³⁷⁵	Not a prospective comparative study
Santambrogio, 2017 ³⁷⁶	Not a prospective comparative study
Santambrogio, 2018 ³⁷⁷	Not a prospective comparative study
Santambrogio, 2021 ³⁷⁸	Not a prospective comparative study
Schaible, 2020 ³⁷⁹	Not early HCC patients (≤ 3 cm tumour)
Sheng, 2015 ³⁸⁰	Not a prospective comparative study
Shi, 2014 ²¹⁷	Not a prospective comparative study
Shibata, 2001 ³⁸¹	Duplicate report
Shiozawa, 2015 ³⁸²	Not early HCC patients (≤ 3 cm tumour)
Simo, 2011 ³⁸³	Not a prospective comparative study
Song, 2019 ³⁸⁴	Not a prospective comparative study
Spangenberg, 2008 ³⁸⁵	Not a prospective comparative study
Stuart, 2018 ³⁸⁶	Not a prospective comparative study
Su, 2020 ³⁸⁷	Not early HCC patients (≤ 3 cm tumour)
Suh, 2013 ³⁸⁸	Not a prospective comparative study
Sun, 2020 ²¹⁹	Not a prospective comparative study
Sutter, 2018 ³⁸⁹	Not early HCC patients (≤ 3 cm tumour)
Takamatsu, 2014 ³⁹⁰	Not early HCC patients (≤ 3 cm tumour)
Takami, 2009 ³⁹¹	Not early HCC patients (≤ 3 cm tumour)
Takami, 2010 ³⁹²	Not a prospective comparative study
Takayama, 2010 ³⁹³	Not a prospective comparative study
Takayasu, 2018a ³⁹⁴	Not a prospective comparative study
Takayasu, 2018b ³⁹⁴	Duplicate report
Takeda, 2008 ³⁹⁵	Not early HCC patients (≤ 3 cm tumour)
Takeda, 2016 ³⁹⁶	Not early HCC patients (≤ 3 cm tumour)
Tanaka, 2015 ³⁹⁷	Not a prospective comparative study
Tanguturi, 2015 ³⁹⁸	Not early HCC patients (≤ 3 cm tumour)
Tashiro, 2011 ²²⁰	Not a prospective comparative study
Tatineni, 2019 ³⁹⁹	Not early HCC patients (≤ 3 cm tumour)
Teramoto, 2005 ⁴⁰⁰	Not a prospective comparative study
Toro, 2012 ⁴⁰¹	Not early HCC patients (≤ 3 cm tumour)
Toyoda, 2008 ²²¹	Not a prospective comparative study
Trotschel, 2016 ⁴⁰²	Not a prospective comparative study
Ueno, 2020 ⁴⁰³	Not a prospective comparative study
Utsunomiya, 2014 ⁴⁰⁴	Not a prospective comparative study
Vietti Violi, 2017a ⁴⁰⁵	Duplicate report
Vietti Violi, 2017b ⁴⁰⁶	Duplicate report

continued

Study	Reason for exclusion
Vitale, 2012 ⁴⁰⁷	Not early HCC patients (≤ 3 cm tumour)
Vitali, 2016 ⁴⁰⁸	Not a prospective comparative study
Vivarelli, 2004 ²²³	Not a prospective comparative study
Wang, 2007 ⁴⁰⁹	Not early HCC patients (≤ 3 cm tumour)
Wang, 2012 ⁴¹⁰	Not a prospective comparative study
Wang, 2015a ⁴¹¹	Not early HCC patients (≤ 3 cm tumour)
Wang, 2015b ⁴¹²	Not a prospective comparative study
Wang, 2019 ⁴¹³	Not a prospective comparative study
Wang, 2020 ⁴¹⁴	Not early HCC patients (≤ 3 cm tumour)
Wei, 2020 ⁴¹⁵	Not early HCC patients (≤ 3 cm tumour)
Wigg, 2017 ⁴¹⁶	Not early HCC patients (≤ 3 cm tumour)
Wiggermann, 2012 ⁴¹⁷	Not a prospective comparative study
Wong, 2021 ⁴¹⁸	Not early HCC patients (≤ 3 cm tumour)
Wu, 2020 ⁴¹⁹	Not early HCC patients (≤ 3 cm tumour)
Xie, 2019 ⁴²⁰	Not early HCC patients (≤ 3 cm tumour)
Xu, 2009 ⁴²¹	Not early HCC patients (≤ 3 cm tumour)
Xu, 2014 ⁴²²	Not early HCC patients (≤ 3 cm tumour)
Xu, 2015 ⁴²³	Not a prospective comparative study
Yamao, 2018 ⁴²⁴	Not a prospective comparative study
Yamashita, 2017 ⁴²⁵	Not a prospective comparative study
Yamashita, 2019 ⁴²⁶	Not a prospective comparative study
Yamazaki, 2009 ⁴²⁷	Not a prospective comparative study
Yang, 2010 ⁴²⁸	Not early HCC patients (≤ 3 cm tumour)
Ye, 2008 ⁴²⁹	No relevant intervention/comparison
Yi, 2014 ⁴³⁰	No relevant intervention/comparison
Yohji, 2012 ⁴³¹	Not a prospective comparative study
Yoon, 2018 ⁴³²	Not early HCC patients (≤ 3 cm tumour)
Yu, 2014 ⁴³³	Not early HCC patients (≤ 3 cm tumour)
Yun, 2009 ⁴³⁴	Duplicate report
Yun, 2011 ²³⁹	Not a prospective comparative study
Zhang, 2008 ⁴³⁵	No relevant intervention/comparison
Zhang, 2013 ²⁴¹	Not a prospective comparative study
Zhang, 2016 ²⁴³	Not a prospective comparative study
Zheng, 2020 ⁴³⁶	Not a prospective comparative study
Zhou, 2014 ²⁴⁷	Not a prospective comparative study
Zhu, 2007 ²⁴⁹	Not early HCC patients (≤ 3 cm tumour)
Zhu, 2021 ⁸⁰	Duplicate report

Appendix 6 Characteristics and results of non-randomised studies included in the review

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
RFA vs. MWA					
Barabino, 2016 ⁹³ (conference abstract) Italy	154 patients with HCC unsuitable for percutaneous treatments or hepatic resection	Laparoscopic RFA [n = 94 patients with average tumour size 1.92 (±0.5) cm]	Laparoscopic MWA [n = 60 patients with average tumour size 2.15 (±0.53) cm]	<p>OS: Laparoscopic RFA: 5 years: 50%. Laparoscopic MWA: 5 years: 37%.</p> <p>Disease-free survival: Laparoscopic RFA: 5 years: 19%. Laparoscopic MWA: 5 years: 12%. Laparoscopic RFA: Local tumour progression rate: 21.2%. Laparoscopic MWA: Local tumour progression rate: 8.3%.</p> <p>Response: Laparoscopic RFA: Complete ablation: 95%. Laparoscopic MWA: Complete ablation: 95%.</p> <p>Adverse events: Laparoscopic RFA: 1% major complications. Laparoscopic MWA: 2% major complications. No deaths related to the procedure in either group.</p>	High
Qian, 2012 ⁸⁹ China	42 patients with < 3 cm tumours	MWA (n = 22 patients)	RFA (n = 20 patients)	<p>PFS: MWA: 4/22 (18.2%) had local tumour progression, 1/22 (4.5%) had a new intrahepatic tumour. RFA: 3/20 (15%) had local tumour progression, 4/20 (20%) had a new intrahepatic tumour.</p> <p>Response: MWA: Complete ablation: 21/22 (95.5%) after the first ablation, 100% after the second ablation. RFA: Complete ablation: 19/20 (95%) after the first ablation, 100% after the second ablation.</p> <p>Adverse events: No skin burns, tumour seeding or treatment-related death in either group.</p>	Low
RFA vs. resection					
Choi, 2004 ⁸⁴ (conference abstract) Korea	164 patients with ≤ 3 cm tumours	RFA (n = 62 patients)	Hepatic resection (n = 102 patients)	<p>OS: RFA: 1 year: 100%; 3 years: 73.9%. Resection: 1 year: 97.1%; 3 years: 83.0%.</p> <p>Recurrence-free survival: RFA: 1 year: 74.1%; 3 years: 40.2%. Resection: 1 year: 75.9%; 3 years: 54.7%. RFA: Local recurrence rate: 11.3%; Remote recurrence rate: 53.7%. Resection: Local recurrence rate: 2.0%; Remote recurrence rate: 45.3%.</p>	High

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Du, 2012 ⁹² China	116 patients with tumours ≤ 5 cm; subgroup of 60 patients with tumours ≤ 3 cm	RFA (n = 31 patients with tumours ≤ 3 cm)	Surgical resection (n = 29 patients with tumours ≤ 3 cm)	Relapse: RFA: 1 year: 12.9%. Resection: 1 year: 13.8%. RFA: Number of events: 4. Resection: Number of events: 4. No other results reported for ≤ 3cm tumour subgroup.	High
Elgendi, 2014 ⁸⁵ (conference abstract) Egypt	51 patients with < 3 cm tumours in locations not amenable for percutaneous route	Intraoperative RFA (n = 24 patients)	Surgical resection (n = 27 patients)	OS: Intraoperative RFA: 1 year: 92%; 3 years: 74%. Resection: 1 year: 93%; 3 years: 81%. Recurrence: No tumours showed local recurrence after median 37 months follow-up in either group. Response: Intraoperative RFA: Complete ablation: 100%. Resection: Complete resection: 100%. Adverse events: Complication rate was comparable between treatment groups.	High
Elgendi, 2015 ⁹¹ (conference abstract) Egypt	92 patients with < 2 cm tumours in locations not amenable for percutaneous route	Intraoperative RFA (n = 44 patients)	Surgical resection (n = 48 patients)	OS: Intraoperative RFA: 1 year: 91%; 3 years: 76%. Resection: 1 year: 92%; 3 years: 83%. Recurrence: No tumours showed local recurrence after median 46 months follow-up in either group. Response: Intraoperative RFA: Complete ablation: 100%. Resection: Complete resection: 100%. Adverse events: Complication rate was comparable between treatment groups.	High

continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Harada, 2016 ⁹⁶ Japan	121 patients with < 5 cm tumours and portal hypertension (large proportion had tumours ≤ 3 cm)	RFA (n = 40 patients)	Surgical resection [n = 81 patients, a few had tumours > 3 cm; mean 2.1 cm (range 0.7–5 cm)]	<p>OS: RFA: 1 year: 97.2%; 3 years: 84.1%; 5 years: 50.6%. Resection: 1 year: 93.4%; 3 years: 84.5%; 5 years: 37.1%. HR (RFA vs. resection) 0.86, 95% CI 0.58 to 1.74.</p> <p>Recurrence-free survival: RFA: 1 year: 36.1%; 3 years: 22.2%; 5 years: 4.8%. Resection: 1 year: 74.1%; 3 years: 48.8%; 5 years: 42.9%. RFA: Number of events: 34/40 (85%); 27 intrahepatic distant recurrences and 7 local recurrences. Resection: Number of events: 34/81 (42%); 33 intrahepatic distant recurrences and one local recurrence. HR (RFA vs. resection) 2.74, 95% CI 1.70 to 4.43.</p> <p>Adverse events: RFA: 5 (12.5%) Resection: 38 (46.9%) RFA: Clavien–Dindo ≥ grade III AEs: 1 (2.5%). Resection: Clavien–Dindo ≥ grade III AEs: 13 (16.1%). One in-hospital death occurred in the resection group, secondary to sepsis.</p> <p>Economic outcomes: RFA: Median postoperative hospital stay: 8 days (range 2–29). Resection: Median postoperative hospital stay: 15 days (range 7–80).</p>	High
Huang, 2014 ⁸⁷ China	346 patients with ≤ 3 cm tumours	RFA (n = 121 patients)	Surgical resection (n = 225 patients)	<p>Health-related quality of life: FACT-Hep: Patients treated with RFA had significantly better HRQoL total scores after 3, 6, 12, 24 and 36 months than those who had resection (further details reported in supplementary tables/figures).</p> <p>Adverse events: RFA: 6 Clavien–Dindo grade III (2 pleural effusion requiring tapping, 2 pneumothorax or haemorrhage), 1 liver abscess, 1 intra-abdominal haemorrhage). No grade I, II, IV or V AEs. Resection: 10 Clavien–Dindo grade I, 3 Clavien–Dindo grade II, 59 Clavien–Dindo grade III (9 delayed gastric emptying, 14 pleural effusion requiring tapping, 10 biliary leakage, 5 intra-abdominal abscess, 15 moderate/severe ascites, 6 intra-abdominal haemorrhage), 3 grade IV (2 liver failure, 1 renal insufficiency), 0 grade V AEs. No hospital death in either group.</p> <p>Economic outcomes: RFA: Average duration of procedure: 44 minutes. Resection: Average duration of procedure: 166.5 minutes. RFA: Average length of hospital stay: 7.1 days. Resection: Average length of hospital stay: 14.5 days. Blood transfusion rates were higher in the resection group. No other results reported, other than Kaplan–Meier curves.</p>	Unclear

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Peng, 2010 ⁸⁸ (conference abstract) China	195 patients with ≤ 3 cm tumours	RFA (n = 79) as first choice, otherwise surgical resection (n = 24) (total n = 103 patients)	Surgical resection (n = 75) as first choice, otherwise RFA (n = 17) (total n = 92 patients)	OS: RFA: 1 year: 95.9%; 3 years: 75.8%; 4 years: 70.7%. Resection: 1 year: 90.1%; 3 years: 63.7%; 4 years: 55.5%. Adverse events: RFA: No cases of treatment-related mortality. Resection: Two cases of treatment-related mortality.	High
Tateishi, 2020 (conference abstract) ⁹⁰ Japan	740 patients with ≤ 3 cm tumours	RFA (n = 369 patients)	Surgery (n = 371 patients)	Recurrence: RFA: 3 years: 61.7%. Surgery: 3 years: 66.0%. RFA: Number of events: 218. Surgery: Number of events: 192. Adjusted HR using inversed probability of treatment weighting 0.89, 95% CI 0.72 to 1.1.	High
MWA vs. resection					
Horigome, 2000 ⁸⁶ Japan	105 patients with ≤ 3 cm tumours	Hepatic resection (n = 43 patients)	MWA (n = 29 patients) PEI (n = 33 patients)	Recurrence: Resection: Number of events: 31 (72%); 13 had intrahepatic metastases, 18 had multicentric occurrence. MWA: Number of events: 11 (38%); 7 had intrahepatic metastases, 4 had multicentric occurrence. PEI: Number of events: 22 (67%); 16 had intrahepatic metastases, 6 had multicentric occurrence.	High
HIFU vs. RFA					
Cheung, 2013 ⁸³ China	106 patients (with 119 tumours) with < 3 cm tumours (primary or first recurrence)	HIFU (n = 47 patients, 52 tumours)	RFA (n = 59 patients, 67 tumours)	OS: HIFU: 1 year: 97.4%, 3 years: 81.2%. RFA: 1 year: 94.6%, 3 years: 79.8%. Disease-free survival: HIFU: 1 year: 63.6%, 3 years: 25.9%. RFA: 1 year: 62.4%, 3 years: 34.1%. Response: HIFU: Complete response: 87.2%. RFA: Complete response: 94.9%. Adverse events: HIFU: 10 (21.3%); 2 pneumothorax, 1 third degree skin burn, 7 relatively minor complications. RFA: 5 (8.5%); 2 pleural effusion requiring tapping, 1 liver abscess, 1 oesophageal variceal bleeding, 1 mild wound infection. HIFU: Clavien–Dindo ≥ grade III AEs: 3. RFA: Clavien–Dindo ≥ grade III AEs: 4. Economic outcomes: HIFU: Median hospital stay: 4 days (range 2–18). RFA: Median hospital stay: 6 days (range 1–31).	High

continued

Study name and location	Participant information	Intervention	Comparator	Main results	ROB
Cryoablation vs. RFA or MWA					
Ei, 2015 ⁹⁵ Japan	119 patients with < 5 cm tumours (large proportion had tumours ≤ 3 cm)	Cryoablation (<i>n</i> = 55 patients with median tumour size 2.5 cm; maximum 4 cm)	RFA (<i>n</i> = 27) or microwave (<i>n</i> = 37) (Total <i>n</i> = 64 patients with median tumour size 1.9 cm; maximum 4.5 cm)	<p>OS: Cryoablation: 2 years: 88% in ≤ 2 cm subgroup; 86% in > 2 cm subgroup. RFA/MWA: 2 years: 95% in ≤ 2 cm subgroup; 85% in > 2 cm subgroup.</p> <p>Local recurrence-free survival: Cryoablation: 2 years: 80%. RFA/MWA: 2 years: 68%.</p> <p>Local recurrence: Cryoablation: 2 years: 19% in ≤ 2 cm subgroup; 21% in > 2 cm subgroup. RFA/MWA: 2 years: 23% in ≤ 2 cm subgroup; 56% in > 2 cm subgroup.</p> <p>Initial recurrence at other sites of the liver: Cryoablation: 2 years: 38%. RFA/MWA: 2 years: 34%.</p> <p>Distant metastases (bone/lung): Cryoablation: 2 years: 2 patients.</p> <p>Adverse events: Cryoablation: 6; 3 Clavien–Dindo grade III (2 pleural effusion, 1 intraabdominal bleeding), 3 grade I/II. RFA/MWA: 7; 3 Clavien–Dindo grade III (haemothorax, wound infection, pneumonia), 4 grade I/II. No in-hospital mortality in either group.</p> <p>Economic outcomes: Cryoablation: Median operative time: 180 minutes. RFA/MWA: Median operative time: 132 minutes. Length of hospital stay: median 8 days (IQR 6–11 days) in both groups.</p>	High
IRE vs. RFA					
Sugimoto, 2019 ⁹⁴ Japan	21 patients (with 24 tumours)	IRE [<i>n</i> = 10 patients (13 tumours) with median tumour size 2.03 (SD 0.44) cm]	RFA [<i>n</i> = 11 patients (11 tumours) with median tumour size 1.73 (SD 0.67) cm]	<p>Recurrence: IRE: 1 patient had local tumour progression at 6 months. RFA: 0 patients had local tumour progression at 6 months. No other results reported, other than systemic immune responses.</p>	High
IQR, interquartile range.					

EME
HSDR
HTA
PGfAR
PHR

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