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REVIEW ARTICLE

# Treatment strategies for early stage hepatocellular carcinoma: a systematic review and network meta-analysis of randomised clinical trials

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## Abstract

**Background:** Several treatment strategies for early stage hepatocellular cancers (HCC) have been evaluated in randomised controlled trials (RCTs). This network meta-analysis (NMA) aimed to explore the relative effectiveness of these different approaches on their impact on overall (OS) and recurrence-free survival (RFS).

**Methods:** A systematic review was conducted to identify RCT's reported up to 23rd January 2020. Indirect comparisons of all regimens were simultaneously compared using random-effects NMA.

**Results:** Twenty-eight RCT's, involving 3,618 patients, reporting 13 different treatment strategies for early stage HCC were identified. Median follow-up, reported in 22 studies, ranged from 12–93 months. In this NMA, RFA in combination with iodine-125 was ranked first for both RFS (HR: 0.50, 95% CI: 0.19–1.31) and OS (HR: 0.41, 95% CI: 0.19–0.94). In subgroup with solitary HCC, lack of studies reporting RFS precluded reliable analysis. However, RFA in combination with iodine-125 was associated with markedly better OS (HR: 0.21, 95% CI: 0.05–0.93).

**Conclusion:** This NMA identified RFA in combination with iodine-125 as a treatment delivering better RFS and OS, in patients with early stage HCC, especially for those with solitary HCC. This technique warrants further evaluation in both Asia and Western regions.

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## Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and is the second leading cause of death for cancer worldwide, with 5-year survival is less than 12% without treatment.[1] With improved imaging techniques, patients are more frequently being diagnosed with early-stage (A) HCC (single HCC $\leq$5 cm; or up to 3 nodules, $\leq$3 cm).[2,3] Currently, the most commonly used treatment strategies for early-stage HCC are liver transplantation, hepatic resection and local ablative or liver directed techniques.[4–6] High cost and donor shortages limit the availability of liver transplantation and only 15–20% of HCCs are resectable at diagnosis.[4]

With the development of medical engineering and interventional technology local ablative therapeutics, such as radiofrequency ablation (RFA),[7] microwave ablation (MWA),[8] percutaneous ethanol injection (PEI),[9] laser ablation,[10] high-intensity focused ultrasound (HIFU),[11] cryoablation[12] and selective internal radiation therapy using yttrium-90[13] can benefit patients with early-stage HCC. These treatment modalities offer alternatives for patients who may not be fit enough for hepatic

resection or can be used as a bridge to liver transplantation, as recommended by both European and American guidelines.[14,15] Other adjuvant therapies, such as concomitant agents (e.g. iodine-131), combination therapies with transcatheter arterial chemoembolization (TACE), or other local ablative techniques such as irreversible electroporation (IRE) have also been extensively applied. The mechanisms of these interventions mainly induce cell death, by thermal coagulation, rapid freezing, cell dehydration, or chemotherapy, but the precise mechanisms and benefits of the individual techniques are still debated.[12,16]

According to latest studies and the National Comprehensive Cancer Network (NCCN) guidelines, treatment strategies including hepatic resection, TACE, RFA and PEI are effective and recommended for early-stage HCC.[17] However best practice has not been universally accepted, with a lack consistency between centres and regions, where – in addition to tumour stage - differences in availability of treatments, but also in patient demographics (age, underlying disease etiology, presence of cirrhosis) may affect treatment decisions and outcomes. A number of studies have also demonstrated molecular tumour characteristics that may predispose to early recurrence or resistance to chemotherapy. While there is no worldwide consensus on best practice, there is clearly a need for additional evidence or combination assessments to guide best evidence-based practice. Meta-analyses can facilitate meaningful comparisons between studies. Although previous network meta-analyses (NMA) have been conducted to support the best choice of treatment for early-stage HCC, some of these are outdated,[18] some have not been very comprehensive, while some not focused specifically on clearly defined early stage HCC.[19,20]

This NMA aimed to compare different treatment strategies for early stage HCC, defined according to EASL[2] and AASLD[21] guidelines as solitary HCC <5 cm or multifocal HCC, ≤3 nodules ≤3 cm, and assess their impact on both recurrence-free survival (RFS) and overall survival (OS). A subgroup analysis considering treatment strategies for solitary (either single lesion < 3 cm or <5 cm) and multifocal (≤3 nodules ≤3 cm) HCC was also performed.

## Methods

### Search strategy

A systematic search of PubMed, EMBASE, Cochrane Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews, and the ClinicalTrials.gov database databases were conducted on the 23rd January 2020 by two independent investigators (SKK, JB). The search terms used were 'early stage' or 'small' and, 'hepatocellular carcinoma', or 'liver cancer' and 'randomised', or 'randomized, or 'randomised controlled trials' individually or in combination. Search terms used for this review are presented in Supplementary Table 1. The 'related articles' function was used to broaden the search, and all citations were considered for relevance. A manual search of reference lists of included trials and related reviews were also undertaken. This paper is reported according to the PRISMA guidelines (Fig. 1).[22]

### Inclusion and exclusion criteria

Inclusion criteria were: (i) RCT's comparing different treatment strategies in human subjects for early stage HCC within the BCLC staging system (i.e. solitary HCC ≤5 cm or multifocal HCC, ≤3 nodules ≤3 cm)[23] and (ii) studies published in the English language. Exclusion criteria were: (i) Conference abstracts, review articles, and case reports (<5 patients); (ii) non-comparative or non-randomised studies; (iii) studies including patients outside the BCLC staging system for early stage HCC; and (iv) studies including Child-Pugh C patients - also deemed outside BCLC early stage HCC. After excluding duplicates, two researchers (SKK, JB) independently reviewed the titles and abstracts of studies identified by the literature search. Where a study was considered to be potentially relevant to the research question a full copy of the publication was obtained for further review. The reference lists of all included studies were hand-searched in order to identify other potentially relevant studies. Any areas of disagreement between the two primary researchers were resolved through discussion with all authors.

### Study outcomes

The primary outcome measure was overall survival. Overall survival was defined as time from intervention to date of last follow-up or death. The secondary outcome was recurrence-free survival, defined time from intervention to date of recurrence which includes local, intrahepatic or extrahepatic recurrence.

### Data extraction

Two researchers (SKK, JB) extracted data on study characteristics (author, year of publication, country of origin, study design, patient number), patient demographics (age, sex), method and details of treatment strategies and reported overall and recurrence-free survival.

### Assessment of methodological quality

The Cochrane Collaboration's tool for assessing the risk of bias in the trial was used,[24] which includes the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. Two reviewers independently assessed trial quality (SKK, JB), and disagreements were resolved by referring to a third assessor (SAW). The quality of evidence (ie, certainty in the estimates) was evaluated using the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation).[25]

### Statistical analysis

This systematic review and network meta-analysis was conducted in accordance with the recommendations of the Cochrane Library and PRISMA guidelines.[22] Hazard ratios from the included trials were extracted. Logarithmic transformed HRs

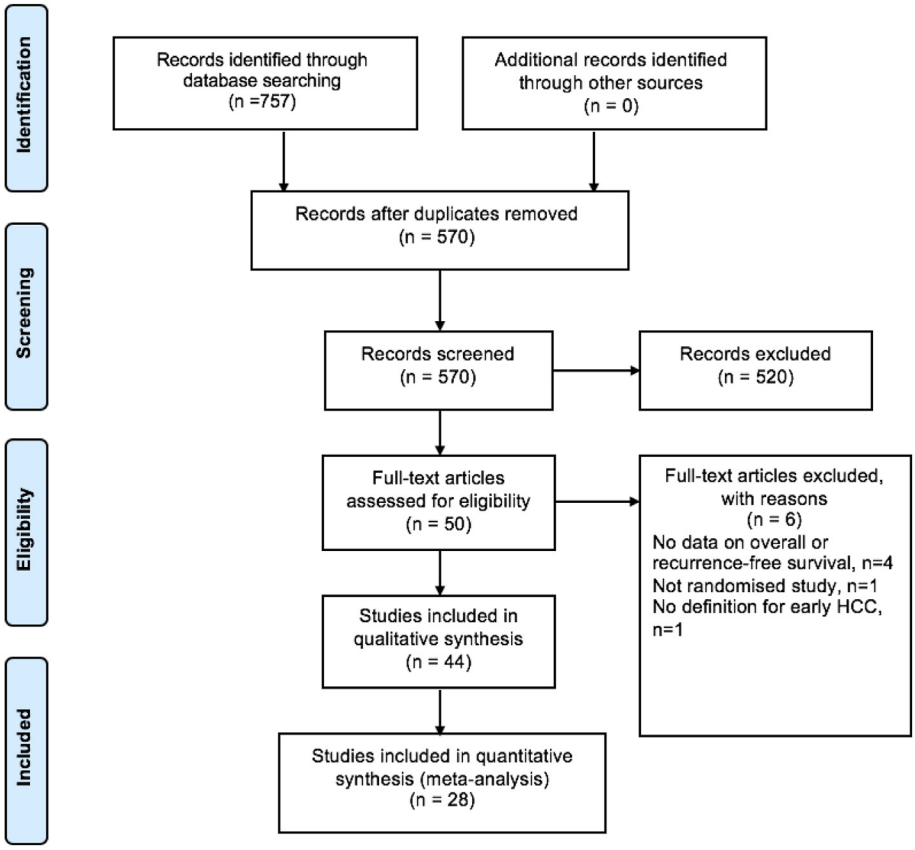


**Figure 1** PRISMA diagram of included studies

were pooled using the Der-Simonian and Laird random-effects model. Following this, a network meta-analysis were performed based on a random-effects consistency model as described by White *et al.*[26] following a multi-variate meta-regression approach to pool evidence from direct and indirect comparisons. For each outcome, graphical representations of treatments (nodes) and comparisons (lines) were mapped. Network maps were then analysed for closed loops to be entered into network analyses. Networks were then examined for the presence of inconsistency, allowing for comparisons between direct and indirect treatment effects. Firstly, by checking for overall inconsistency throughout the entire network. Then by the fitting of node side-splitting models to check for loop inconsistency, within all 3-way treatment comparison loops, as described by Dias and colleagues.[27] If p-values were >0.05, representing acceptance of the null hypothesis, consistency was assumed and networks were entered into consistency modelling. Consistency models utilised a restricted maximum likelihood model, generating network forest plots. Treatment strategies for early HCC were then ranked using the P-score provided by the *netmeta* package, as previously reported to be similar to the surface under the cumulative ranking areas for all outcomes to assess the probability of the superiority of each treatment.[28–30] Two sensitivity analyses were performed: (i) studies published in the last decade (2010–2019) and (ii) studies reporting outcomes for solitary and multifocal HCC separately. Statistical significance was considered when $p < 0.05$. Statistical analyses were undertaken using R Foundation Statistical software (R 3.2.1) as previously described.[31]

## Results

### Study selection

A total of 767 titles and abstracts were identified by the screening electronic search strategy, of which 50 full-text articles met the eligibility for assessment (Fig. 1). Following full-text assessment, six articles were excluded. Of these, four articles[32–35] did not have either OS or RFS estimates, one study[36] was not a randomised trial and the 6th study[37] did not report a definition for early HCC. Forty-four RCT's were included in the qualitative synthesis. Of these, 16 were excluded from the NMA, which ultimately included 28 RCT's[10,38–64] (Fig. 1). Excluded RCT's included one retracted study, 12 studies which included patients with multi-focal tumours ≤4cm[12,65–68] or ≤5 cm[69–75] and two studies[76,77] which included

solitary tumours ≤7 cm, all of which were beyond the accepted definitions for early HCC. Supplementary Table 2 summarises study characteristics included in the qualitative synthesis.

### Study characteristics

The 28 RCT's included into the network meta-analysis comprised 3618 patients. Supplementary Table 2 summarises the baseline characteristics of the included studies. The median age of patients included in the study ranged from 49 to 74 years old and the proportion of male patients ranged from 57% to 93%. All studies included patients with either Child-Pugh Grade A or B liver disease. Median follow-up was reported in 22 studies, ranging from 12 to 93 months. Ten papers only included solitary HCC and the remaining 18 papers included a mixture of solitary and multifocal tumours. The underlying aetiology for HCC were reported in only 14 studies (n = 2095), of which 1080 patients had hepatitis B and 796 patients had hepatitis C. One study by Kobayashi *et al.* reported hepatic artery occlusion using a 5-french balloon catheter with outer diameter measuring as 9 mm[47] Supplementary Table 3 summarises the risk of bias assessment for the included studies.

### Intervention for recurrence

Only seven studies[40,42,46,49,52,56,62] described repeat treatments for recurrent HCC, defined as residual HCC following primary treatment. Five studies repeated primary treatment in the presence of recurrent HCC. For instance, Yin *et al.*[62] (comparing hepatic resection vs TACE) reported 68 patients who received a repeat TACE after an interval of 2–3 months and Di Costanzo *et al.*[42] (comparing RFA vs laser ablation) reported four patients receiving a repeat RFA and 12 patients receiving a repeat laser ablation. Only two of these seven publications reported additional treatments after the primary intervention. For example, Ng *et al.*[56] reported RFA as the primary treatment with ten patients then having hepatic resection, 30 patients receiving TACE, and three patients undergoing liver transplantation. Likewise, Lee *et al.*[49] reported RFA as the primary treatment, one patient then receiving hepatic resection, ten patients receiving PEI, 77 patients receiving TACE, and one patient undergoing liver transplantation. Notably, the patients reported by Ng *et al.* and Lee *et al.* received more than one of these repeat treatments, which have been accounted for in survival analyses.

### Recurrence-free survival

Recurrence free survival was reported in 26 studies comparing 14 different techniques. Three techniques from two RCTs (i.e. transarterial chemoembolisation) could not be evaluated as recurrence-free survival was not reported. Following a network meta-analysis, RFA-I was ranked best overall when compared to other techniques followed by TACE in combination with resection and RFA in combination with hepatic artery occlusion (Fig. 2A). Sensitivity analysis including RCT's published from 2010 to 2019 demonstrated RFA-I ranked best overall followed by surgical resection (Supplementary Fig. 1A).

### Overall survival

Overall survival was reported in 24 studies comparing 13 different treatment strategies (Fig. 3). Five techniques from four RCT's (i.e RFA in combination with either hepatic artery occlusion, percutaneous MWA, laser ablation, and liver resection) could not be evaluated as overall survival was not reported. Following a network meta-analysis, RFA with a combination of iodine-125 (RFA-I) was ranked best overall when compared to other techniques, followed by RFA in combination with PEI and resection (Fig. 2B). Sensitivity analysis for RCT's published from 2010 to 2019 demonstrated RFA-I ranked best overall followed by surgical resection (Supplementary Fig. 1B).

### Subgroup analysis: solitary HCC ≤3 cm

All RCTs included in the NMA included some patients with a solitary HCC. For subgroup analyses of solitary HCC ≤3 cm, data was only available for seven studies on overall survival and three studies on recurrence-free survival. In a network meta-analysis for the seven studies reporting overall survival, RFA-I ranked best associated with improved survival compared to RFA only (Supplementary Fig. 2).

### Subgroup analysis: solitary HCC 3.1–5.0 cm

For subgroup analyses of solitary HCC 3.1–5.0 cm, data was available for three studies on overall survival and two studies on recurrence-free survival. Given the small number of studies reporting this, a network meta-analysis was not possible.

### Subgroup analysis: multifocal (≤3 nodules ≤3 cm) HCC

There were 15 studies including patients with multifocal HCC within the included RCTs into the NMA. For subgroup analyses of multifocal HCC, data was available for four studies on overall survival but none on recurrence-free survival. In a network meta-analysis on overall survival, resection was ranked best (Supplementary Fig. 3). However, given the lack of reporting of outcomes for other treatment strategies, their effectiveness could not be assessed.

### Risk of bias

A qualitative assessment was performed by assessing various indicators for each individual study using the Cochrane tool for risk of bias.[24] Overall, the trials were deemed to be at low risk for bias, except for detection bias, for which only 2 trials had blinded assessment of outcomes, whereas the others were either not blinded or were unclear.

## Discussion

To date, several comparisons of different interventions for the treatment of HCC treatment have been published. Current EASL,[2] AASLD[21] and Asia–Pacific[5] recommendations advocate

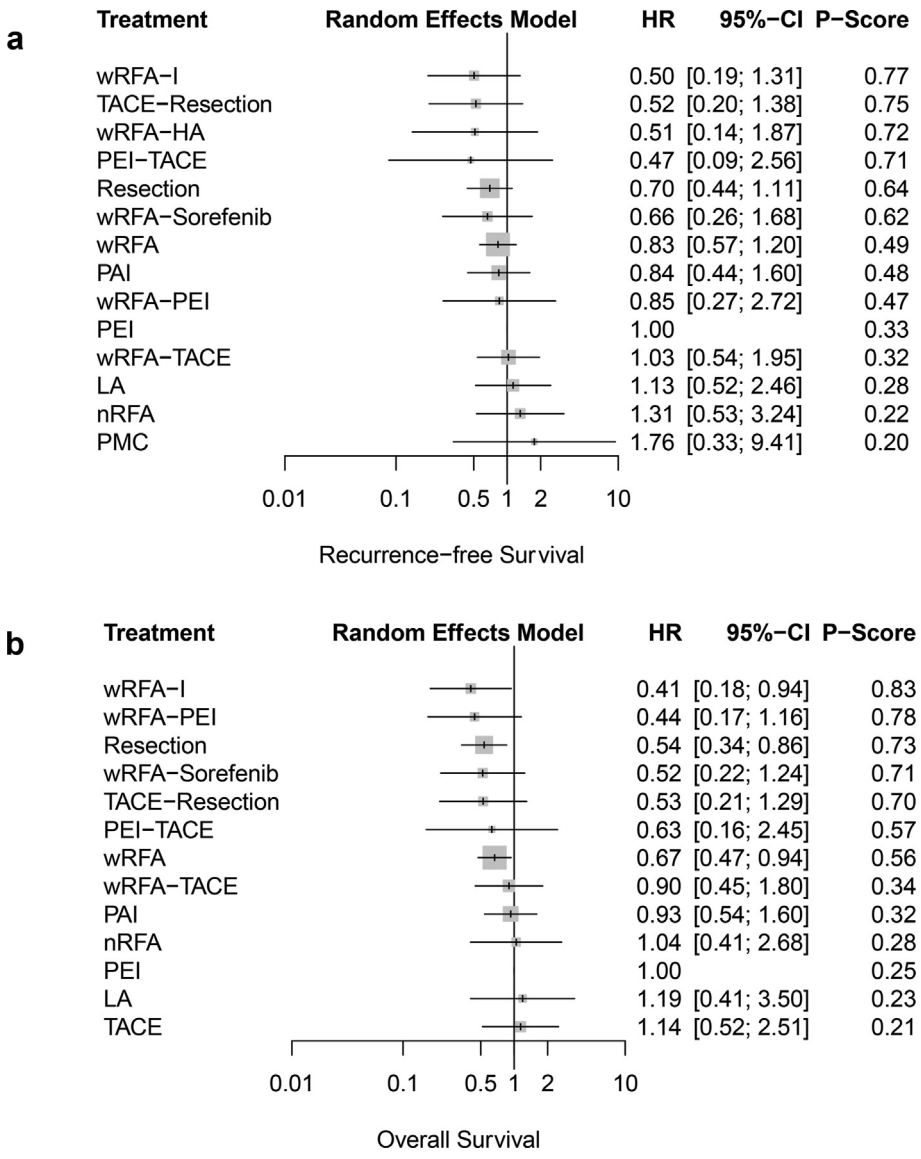


**Figure 2** Summary of hazard ratio of forest plots comparing different treatment strategies for early hepatocellular carcinoma (a) Overall survival (b) Recurrence-free survival

the use of RFA in patients with early HCC (i.e. solitary or multifocal HCC ≤3 nodules, providing nodules are not larger than 3 cm). However, more recent RCTs have compared new adjuncts combined with RFA, although it is accepted that their efficacy has not been rigorously evaluated. This network meta-analysis included 28 RCTs and demonstrates that RFA in combination with Iodine-125 was ranked best for OS and RFS for early stage HCC. These findings were consistent in sensitivity analyses including RCTs published during the last decade (2010–2019). Owing to limited data reported for multifocal HCC, subgroup analysis was not feasible. However, findings from this study if duplicated in western cohorts will warrant a review of current international guidelines regarding best practice for the management of early stage HCC.

Previous network meta-analyses have been performed, although their conclusions should be interpreted in an informed fashion.[18,19,78,79] Firstly, some previous NMAs included trials which evaluated patients beyond early stage HCC criteria (i.e. solitary HCC >5 cm or multifocal HCC >3 cm). Secondly, some NMA's excluded recently published studies evaluating RFA with adjunctive treatments - such as with either iodine-125, hepatic arterial occlusion[47] or TACE. It should also be noted, that previous NMA's have not provided descriptions of subgroup analyses, which may limit some of their conclusions, as treatment approaches or success may differ for solitary versus multifocal HCC, even though both are classed as 'early stage'.

For early stage HCC, liver resection remains the gold standard treatment but is associated with high morbidity and mortality in

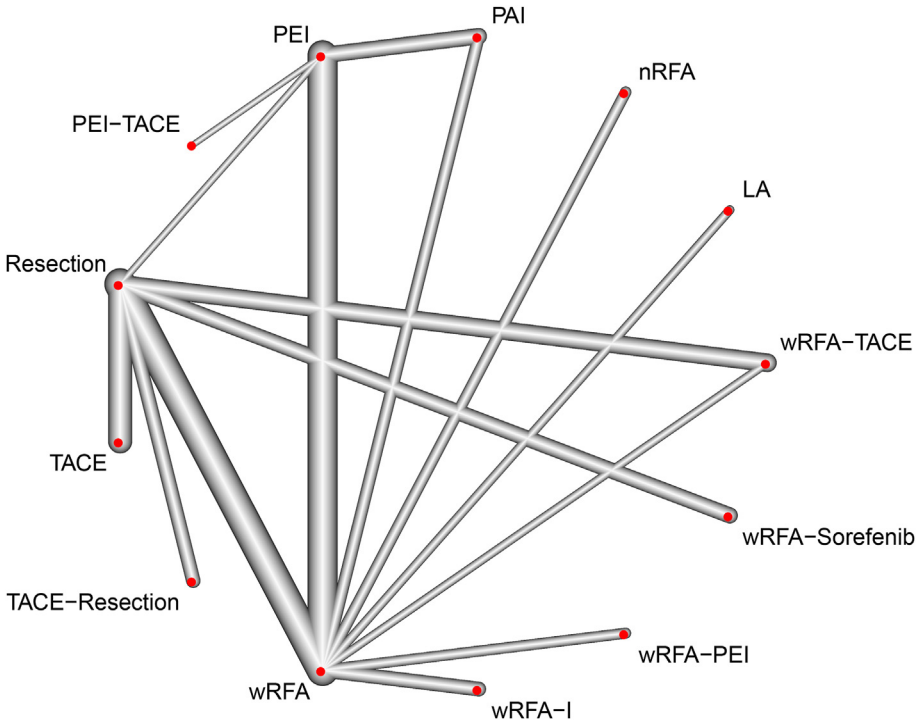


**Figure 3** A network map summarising different interventions reported in randomised controlled trials for early stage hepatocellular carcinoma for overall survival

those patients with advanced cirrhosis.[80] Local ablative techniques such as MWA and RFA have both gained popularity in the treatment of early-stage HCC, with the latter most commonly used in North America.[81] Several studies have indicated that RFA is better than PEI[82,83] and comparable to MWA,[84] but inferior to hepatic resection for early-stage or small HCC (i.e < 3 cm).[85] Studies have compared the impact of MWA, RFA and hepatic resection. A recent meta-analysis considering studies evaluating MWA, RFA resection suggested that MWA may be superior to hepatic resection in some settings, as it is at least as effective as resection in terms of RFS and OS, but associated with fewer complications and less morbidity.[86] MWA is also reportedly better than RFA when treating larger (3–5 cm) tumours (OS; HR: 0.73, 95%CI: 0.45–1.19).[16] Differences in the practice of ablative techniques may reflect etiologic differences. In Eastern cohorts, hepatitis B (HBV) HCC predominates, rather than hepatitis C (HCV) HCC, which is commoner in the North America or Europe. Multifocal disease at presentation, with a higher yearly de novo incidence rate, is more typical of HCV,[87–89] with the wider ablative zone delivered by MWA and the simultaneous treatment of multiple lesions in a shorter procedural time,[90] an attractive option.

Newer non-invasive ablative techniques, such as high intensity focussed ultrasound (HIFU) have also been developed, inducing instantaneous cell death by two major mechanisms having both thermal and mechanical effects.[91] As yet, HIFU has not been evaluated in early stage HCC, where the usefulness of local thermal ablative therapies might be limited by collateral damage to the bile ducts or gall bladder.[92,93] Irreversible electroporation (IRE) delivers short pulses of energy that damages the lipid bilayer of cells, inducing death by apoptosis rather than thermal ablation[94,95] It potentially has a role in the treatment of small HCC (<3 cm) adjacent to major veins or hilar structures,[96] although longer-term data demonstrating oncologic efficacy is lacking.

This NMA, which is focused, unbiased and sensitive, addresses some of the limitations of previous studies and compares many of these techniques, has identified ablation in combination with iodine125 ($RFA^{-125}I$) as a superior treatment for early stage HCC. As such, this technique is worthy of more detailed consideration. Chen *et al.*[41] describe the procedure, which includes a detailed tumour volume evaluation with CT approximately two weeks beforehand. RFA up to 15 min was delivered, after 18–69 temperature sterilised radioactive seeds (0.8 mm by 4.5 mm) were implanted, using up to 45 needles, spaced 1 cm apart, in tumour and adjacent non-tumour tissue. $RFA^{-125}I$ treatment is no simple undertaking and requires a skilled radiation oncologist, interventional radiologist and surgeon. The proposed synergies between radiofrequency and thermal energy, however, are quite compelling, including a number of mechanisms which may contribute to its superior results in experienced hands. These include reciprocal zones of efficacy.[97] RFA delivers it major impact centrally, to the tumour core, where central tumour hypoxia resists radiation induced cytotoxicity. Conversely, sublethal temperatures at the outer margin of the

tumour can limit thermal ablation cytotoxicity, while increasing blood flow and oxygen that improves the efficacy of irradiation treatment. Radiotherapy also impairs cell damage repair, with persistence of free radicals as markers of ongoing oxidative stress and consequently greater targeted tumour injury during combination therapy.[98] Finally, the RFA-$^{125}$I combination most likely induce a greater anti-tumour immune system response that RFA alone, with increased tumour cell killing mediated by an increase in CD8+ T-cell populations,[99] reprogramming of anti-tumour macrophages,[100,101] and generation of tumour-specific cytotoxic T lymphocytes (CTL)[102] after iodine-125 implantation.

This study does also have its limitations. Some are technical, relating to the availability of data – or lack of it – in the published studies. The reporting of RFS and OS outcomes were incomplete and inconsistent in some of the included studies, owing to varying median follow-up. For instance, the study by Chen *et al.* (2005) comparing RFA-PEI with RFA alone had a median follow-up of 29 months, which may limit interpretation of longer survival outcomes at 5-years which are important for HCC. Further, the study by Chen *et al.* (2014) reporting the RFA-I technique were performed in only one study, requiring validation of data in further RCT's. The current meta-analysis was done with summary statistics rather than individual patient data. There may, therefore, have been un-reported covariates at the individual patient level affect the treatment outcomes, which could not be adjusted for in the current network meta-analysis. For instance, this review only included patients with Child-Pugh A or B status, but no further stratified data by Child-Pugh status is available as this may likely affect long-term survival. The other limitation which remains difficult to overcome, is that of regional variation. While the NMA accounts for a number of patient factors, it is not appropriate to translate these findings, arising from a single expert centre in Asia treating patients with viral hepatitis related HCC, average age 50 years, to a typical western population, age 70+ years with comorbidities obesity and type 2 diabetes, and cirrhosis arising on a background of obesity and or alcohol excess. To improve outcomes globally for patients with early stage HCC, more international collaboration would help to validate exciting findings such as these, identifying those subgroups of patients most likely to benefit from one treatment versus another.

## Conclusion

In conclusion, this network meta-analysis demonstrates RFA in combination with iodine-125 is a superior treatment, in terms of both RFS and OS, for early stage HCC, especially solitary HCC. This treatment combination warrants further evaluation in both Asian and Western patients with early stage HCC.

### Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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## Conflicts of interest

None declared

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.10.031.