Clinical and cost effectiveness of endoscopic bipolar radiofrequency ablation for the treatment of malignant biliary obstruction: a systematic review

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Scientific summary

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Scientific summary

Background

The aim of this research was to establish the expected value of undertaking additional research to determine the clinical effectiveness, cost-effectiveness and safety of endoscopic bipolar radiofrequency ablation (RFA) for the treatment of malignant biliary obstruction.

Objectives

- To carry out a systematic review to assess the clinical effectiveness and potential risks of endoscopic bipolar RFA for malignant biliary obstruction.
- To undertake a systematic review to assess the cost-effectiveness of endoscopic bipolar RFA for malignant biliary obstruction.
- To develop a decision model to estimate cost-effectiveness based on the data derived from the systematic reviews.
- To assess the value of further research by undertaking a value of information analysis from the data and results generated by the decision model.

Methods

Clinical effectiveness review

The systematic review followed robust published methods, was registered on PROSPERO (reference CRD42020170233) and is reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance.

Eligibility criteria

Population

- Patients with biliary obstruction caused by any form of unresectable malignancy.

Intervention

- Endoscopic biliary RFA used to ablate malignant tissue that obstructed the bile, either to fit a stent (primary RFA) or to clear an obstructed stent (secondary RFA). Studies that used RFA that was not endoscopic were excluded.

Comparator

- Insertion of a stent to clear the bile or standard care where patients had an occluded stent.

Primary outcomes

- Survival, quality of life and procedure-related adverse events (AEs).

Secondary outcomes

- Technical success, relief of biliary obstruction, pain, nausea, resource use, number of further interventions, length of hospital stays and reintervention and re-admission rates.

Study design

- Controlled studies, uncontrolled observational studies and case reports.

Search strategy

A robust search strategy was designed using a range of bibliographic databases, grey literature resources and trial registries, which were searched to January 2021 to identify eligible studies. Searches were carried out from 2008 because endoscopic biliary RFA was not available before then. References of relevant systematic reviews and included studies were checked for eligible studies. All results were downloaded to EndNote (Clarivate Analytics, Philadelphia, PA, USA) and de-duplicated.

Data selection and extraction

Two reviewers independently screened the titles and abstracts of the search results and two reviewers independently screened the full texts of studies that were deemed relevant. Disagreements were resolved by discussion or reference to the Clinical Advisory Board.

Data were extracted by one reviewer and checked by a second reviewer.Where studies were reported in multiple publications, we checked all publications for relevant data, but considered all data as from a single study. Where data were missing or unclear, authors were contacted for clarification. The following data items were extracted: citation information, study design, participant demographic and clinical characteristics, intervention characteristics (including of the stent and the RFA procedure), comparator characteristics (including details of stent and of 'standard care'), our primary and secondary outcomes, and details of study methods to facilitate an assessment of risk of bias.

Risk-of-bias assessment

Risk-of-bias assessment was conducted by two reviewers independently at a study level, using the Cochrane Risk of Bias 2.0 tool for randomised controlled trials (RCTs) and the ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tool for non-RCTs. Non-comparative studies and abstracts were not formally assessed using a specific tool, but were given less weight in the synthesis.

Data synthesis

A summary of study characteristics, study design, risk-of-bias assessments and results was presented. The primary analysis was meta-analysis of the hazard ratio (HR) of mortality using a random-effects generic inverse variance model, with planned separate analyses for primary and secondary RFA. Meta-analyses were conducted with and without adjustment for bias. Without adjustment for bias, consideration was given to whether or not it was meaningful to combine studies of very different quality. The key confounding factor was whether or not patients received chemotherapy, as chemotherapy also affects survival. Non-randomised studies were combined with RCTs if they controlled for chemotherapy. Analyses were also carried out for time to occlusion and for AE rates using Mantel–Haenszel weighting and a random-effects model. Heterogeneity between studies was assessed by visual inspection of plots of the data, from the chi-squared test for heterogeneity and the I2-statistic. Possible reasons for heterogeneity were explored. Subgroup analyses were planned according to the type of probe, the type of stent (i.e. metal or plastic) and the type of cancer.

Where studies did not provide appropriate data for the meta-analysis, we used narrative synthesis. The effectiveness estimates fed into the economic model.

Cost-effectiveness review

Similar methods were followed as for the clinical effectiveness review. The same search strategy was used as for the clinical effectiveness review, with the addition of the economic studies filter used to populate the NHS Economic Evaluation Database. The only difference in eligibility criteria was in study designs, as only full economic evaluations were included. However, no eligible studies were located.

Development of cost-effectiveness model

The primary economic objective was to evaluate the cost-effectiveness of RFA for patients with unresectable biliary malignancies, as follows:

- bile duct cancer patients receiving primary RFA
- bile duct cancer patients receiving secondary RFA
- pancreatic cancer patients receiving primary RFA
- pancreatic cancer patients receiving secondary RFA.

The secondary economic objective was to estimate the population expected value of perfect information (PEVPI), which is an estimate of the maximum value that could be gained from undertaking future research on RFA from a decision-maker's point of view regarding the adoption of RFA.

There was sufficient evidence to develop only a model specifically for bile duct cancer patients receiving primary RFA.

No cost-effectiveness models for RFA in these populations was found in the systematic review of cost-effectiveness studies and so a de novo economic model was developed to evaluate the cost-effectiveness of RFA with endoscopic stent insertion compared with endoscopic stent placement alone.

A Markov model was developed to model the cost and quality-of-life outcomes associated with RFA over the remaining lifetimes of the patients. An NHS and Personal Social Services perspective was adopted for the analysis. Costs and benefits were discounted at an annual rate of 3.5%. The price year was 2018/19.

The key effectiveness outcomes for RFA were survival and time to occlusion (blockage). It is possible that a patient may experience more than one occlusion, requiring more than one intervention. Effectiveness evidence was available for time to the first occlusion. Consequently, the model included a state for reintervention following the first occlusion, and a state for subsequent reinterventions following subsequent occlusions. Following a reintervention, patients enter a post-intervention state until another occlusion occurs or they die. The cycle length was 1 month. Effectiveness data were obtained from the meta-analyses in the systematic review of effectiveness. Plausible adjustments of the effectiveness estimates were made for bias based on clinical expert opinion and reviewer bias assessments.

A probabilistic analysis was conducted to estimate the incremental cost-effectiveness ratio (ICER) for RFA and the probability that RFA was cost-effective at different cost-effectiveness thresholds. The PEVPI was also estimated in total and for the effectiveness parameters (*Figure i*).

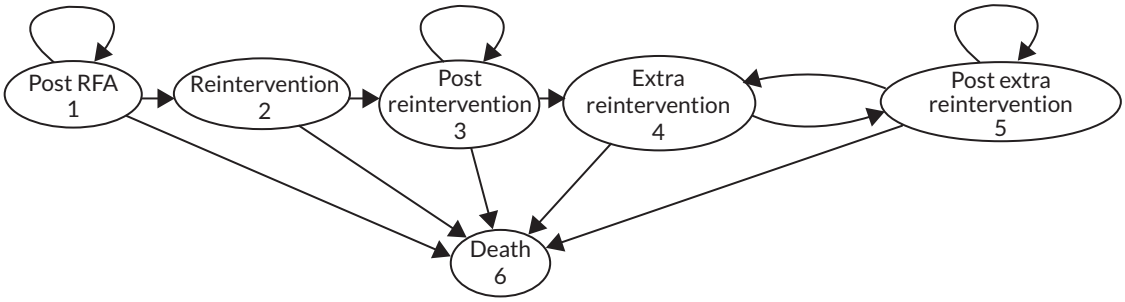

FIGURE i Markov model structure.

Results

Clinical effectiveness review

The search retrieved 4131 results after de-duplication, and update searches retrieved a further 287 de-duplicated results, giving a total of 4418 results. A total of 697 full-text results were screened in EndNote, and a total of 68 studies were included in the review. Eighteen studies were comparative studies and 50 were non-comparative studies, including a total of 1742 patients (plus one study that did not report participant numbers). A majority (53%) of results were conference abstracts with no peer-reviewed published report. Twenty-four studies were conducted in Asia, 20 in European countries, 20 in the USA, two in South American countries and two in Australia. Most patients had biliary obstruction arising from cholangiocarcinoma (where reported). The most commonly reported probe used for the ablation procedure was the Habib™ EndoHPB catheter (Boston Scientific Corporation, Marlborough, MA, USA) (n = 35), although many studies did not report the detail of the equipment used. Studies reported the insertion of a first stent (primary RFA; n = 40), the unblocking of an existing stent (secondary RFA; n = 15) or both (n = 11), but this was unclear in two studies.

Risk-of-bias assessment

One of the two published RCTs was judged to be at high risk of bias overall and one gave rise to 'some concerns'. Four of the five published non-RCTs were judged to be at moderate risk of bias and one was judged to be at low risk of bias.

Survival

Eighteen comparative studies reported a measure of survival. Of these 18 studies, two RCTs, one retrospective case–control study and three retrospective cohort studies reported a HR of death for primary RFA compared with stent-only control. Four of these studies were for the base-case meta-analysis, which showed that RFA reduced the hazard of dying by 66% [pooled HR 0.34, 95% confidence interval (CI) 0.21 to 0.55]. There was moderate heterogeneity (I^2 = 53%). The effect sizes across the studies were consistently in favour of RFA.

Where survival was not reported, most studies reported mean or median survival time, and results were mixed. There was little evidence of prolonged survival in patients who received secondary RFA compared with stent only.

Quality of life

Two studies reported the Karnofsky Performance Score and one study described this as a quality-of-life measure, although it is designed to measure physical functional performance. Both studies reported a higher Karnofsky Performance Score (i.e. better function) in patients who received RFA than in patients who received stent only, up to 9 months after the procedure.

Adverse events

The most commonly reported AEs were cholangitis (i.e. an inflamed bile duct), pancreatitis (i.e. an inflamed pancreas) and cholecystitis (i.e. an inflamed gallbladder). Five of 16 comparative studies reported no evidence of differences in AEs between groups, but the studies did not specify particular AEs. Seven studies specified the number of specific AEs in both intervention and control arms, and were pooled in meta-analyses.

Radiofrequency ablation appeared to carry a higher risk of cholecystitis than stent placement alone. None of the control group patients had cholecystitis in four studies that explicitly reported cholecystitis, and the remaining seven studies reported cholecystitis in the RFA group only.

There was no evidence of any difference in incidence of cholangitis or pancreatitis between groups. Between 6% and 33% of patients experienced cholangitis, and between 4% and 7% of patients reportedly developed pancreatitis.

Mild, self-limiting abdominal pain was reported in five studies, ranging from a small percentage to most patients.

Technical success

Although the majority of the included studies did not report the 'technical success' outcome explicitly, the inference was made if study authors reported the RFA procedure as 'being successful', having 'no complications' or 'no technical problems', or described other similar phrases implying technical success. The vast majority of studies reported 100% technical success. One study reported that 59% of procedures were successful, but in some of the remaining cases the procedure was not attempted. A further study reported 89% success.

Occlusion

In four RCTs and a cohort study, there was no evidence of improvement in stent patency from primary RFA. The reported range of time to occlusion across studies of primary RFA was 23 days to 22 months.

There was limited evidence from a case–control study and a cohort study of improvement in stent patency for patients undergoing secondary RFA. The reported range of time to occlusion across studies of secondary RFA was 2–10 months.

Cost-effectiveness model

In the base-case analysis, the average discounted cost for the RFA intervention was £2659 more than the average discounted cost for the stent-only control. The average discounted quality-adjusted life-years (QALYs) for the RFA intervention was 0.18 more than the average discounted QALYs for the stent-only control. The ICER for RFA was £14,736 per QALY. The probability that RFA plus stent is cost-effective is 0.82 at a £20,000 per QALY cost-effectiveness threshold and is 0.92 at a £30,000 per QALY cost-effectiveness threshold. The PEVPI for the base-case analysis is £9.14M at a cost-effectiveness threshold of £20,000 per QALY and is £5.66M at a cost-effectiveness threshold of £30,000 per QALY, indicating that there may be value in undertaking further research.

Radiofrequency ablation was cost-effective at a threshold of £30,000 per QALY across all scenario analyses and cost-effective at a threshold of £20,000 per QALY across almost all scenarios. Three factors significantly increased PEVPI: (1) adjusting for bias in the effectiveness estimates, (2) increasing the probability of complications and, therefore, staying overnight in hospital for several days from 10% to 20% and (3) reducing the utility of living with advanced cancer from 0.61 to 0.5. The source of the vast majority of decision uncertainty lay in the uncertainty associated with the effect of RFA on stent patency, and this is reflected in the population expected value of partial perfect information values of £8.3M at a £20,000 per QALY threshold and £4.5M at a £30,000 per QALY threshold. This is more than a clinical trial would cost. A clinical trial would not eliminate uncertainty in the effectiveness estimate. However, decision uncertainty could almost be eliminated by demonstrating RFA non-inferiority in stent patency in a quality clinical study.

Conclusions

Primary RFA appears to improve survival and is likely to be cost-effective; however, the evidence for this is mainly in patients with bile duct cancers rather than in patients with pancreatic cancers. Only 6 of 18 comparative studies could be included in the meta-analysis looking at survival because of the differences in outcome measures, but none reported a decrease in survival in the RFA group. There was no increased risk of cholangitis or pancreatitis following RFA, but possibly an increased risk of

cholecystitis. There was a lack of high-quality data examining similar outcomes in patients undergoing secondary RFA. For both primary and secondary RFA, there were insufficient data to determine the effect of RFA on quality of life. Recommendations for further research include the following:

- Prospective RCTs of primary RFA should be conducted, with a specific focus on quality of life and accurate reporting of AEs in each group. Patients with pancreatic cancers should be classified separately from patients with bile duct cancers, to determine the effects of RFA in each group.
- The mechanism by which primary RFA has a beneficial effect on survival should be explored.
- Consideration should be given to whether or not a repeat application of RFA at a specified interval may further improve outcomes in patients with both pancreatic and bile duct cancers.
- High-quality prospective RCTs of secondary RFA should be carried out to determine whether or not there is benefit to survival and quality of life, including accurate reporting of AEs. These RCTs should also incorporate an assessment of cost-effectiveness.
- If benefit is shown in secondary RFA, an exploration of the mechanism should be carried out.

Study registration

This study is registered as PROSPERO CRD42020170233.

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This report

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