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Abstract

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

Fiona Beyer,[1] Stephen Rice,[1] Giovany Orozco-Leal,[1] Madeleine Still,[1] Hannah O'Keefe,[1] Nicole O'Connor,[1] Akvile Stoniute,[1] Dawn Craig,[1] Stephen Pereira,[2] Louise Carr[3] and John Leeds[1,3*]

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Background: Early evidence suggests that using radiofrequency ablation as an adjunct to standard care (i.e. endoscopic retrograde cholangiopancreatography with stenting) may improve outcomes in patients with malignant biliary obstruction.

Objectives: To assess the clinical effectiveness, cost-effectiveness and potential risks of endoscopic bipolar radiofrequency ablation for malignant biliary obstruction, and the value of future research.

Data sources: Seven bibliographic databases, three websites and seven trials registers were searched from 2008 until 21 January 2021.

Review methods: The study inclusion criteria were as follows: patients with biliary obstruction caused by any form of unresectable malignancy; the intervention was reported as an endoscopic biliary radiofrequency ablation to ablate malignant tissue that obstructs the bile or pancreatic ducts, either to fit a stent (primary radiofrequency ablation) or to clear an obstructed stent (secondary radiofrequency ablation); the primary outcomes were survival, quality of life or procedure-related adverse events; and the study design was a controlled study, an observational study or a case report. Risk of bias was assessed using Cochrane tools. The primary analysis was meta-analysis of the hazard ratio of mortality. Subgroup analyses were planned according to the type of probe, the type of stent (i.e. metal or plastic) and cancer type. A de novo Markov model was developed to model cost and quality-of-life outcomes associated with radiofrequency ablation in patients with primary advanced bile duct cancer. Insufficient data were available for pancreatic cancer and secondary bile duct cancer. An NHS and Personal Social Services perspective was adopted for the analysis. A probabilistic analysis was conducted to estimate the incremental cost-effectiveness ratio for radiofrequency ablation and the probability that radiofrequency ablation was cost-effective at different thresholds. The population expected value of perfect information was estimated in total and for the effectiveness parameters.

Results: Sixty-eight studies (1742 patients) were included in the systematic review. Four studies (336 participants) were combined in a meta-analysis, which showed that the pooled hazard ratio for mortality following primary radiofrequency ablation compared with a stent-only control was 0.34 (95% confidence interval 0.21 to 0.55). Little evidence relating to the impact on quality of life was found.

There was no evidence to suggest an increased risk of cholangitis or pancreatitis, but radiofrequency ablation may be associated with an increase in cholecystitis. The results of the cost-effectiveness analysis were that the costs of radiofrequency ablation was £2659 and radiofrequency ablation produced 0.18 quality-adjusted life-years, which was more than no radiofrequency ablation on average. With an incremental cost-effectiveness ratio of £14,392 per quality-adjusted life-year, radiofrequency ablation was likely to be cost-effective at a threshold of £20,000 per quality-adjusted life-year across most scenario analyses, with moderate uncertainty. The source of the vast majority of decision uncertainty lay in the effect of radiofrequency ablation on stent patency.

Limitations: Only 6 of 18 comparative studies contributed to the survival meta-analysis, and few data were found concerning secondary radiofrequency ablation. The economic model and cost-effectiveness meta-analysis required simplification because of data limitations. Inconsistencies in standard reporting and study design were noted.

Conclusions: Primary radiofrequency ablation increases survival and is likely to be cost-effective. The evidence for the impact of secondary radiofrequency ablation on survival and of quality of life is limited. There was a lack of robust clinical effectiveness data and, therefore, more information is needed for this indication.

Future work: Future work investigating radiofrequency ablation must collect quality-of-life data. High-quality randomised controlled trials in secondary radiofrequency ablation are needed, with appropriate outcomes recorded.

Study registration: This study is registered as PROSPERO CRD42020170233.

Funding: This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 27, No. 7. See the NIHR Journals Library website for further project information.

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Glossary

Bacteraemia Presence of bacteria in the bloodstream.

Bile duct A thin tube that goes from the liver to the small intestine.

Cholangiocarcinoma Cancer of the bile duct.

Cholangitis Inflammation of the bile duct system.

Cholecystitis Inflammation of the gallbladder.

Cohort study A prospective or retrospective non-randomised comparative study.

Gallbladder A small, pear-shaped organ on the right side of the abdomen, beneath the liver.

Haemobilia Bleeding in the biliary tree.

Hepatic abscess A mass filled with pus inside the liver.

Hyperamylasaemia An elevated level of serum amylase beyond the upper limit of the normal range.

Liver infarction Areas of coagulative necrosis from hepatocyte cell death.

Lumen The cavity or channel within a tube or tubular organ.

Necrosis A form of cell injury that results in the premature death of cells in living tissue.

Oesophageal tumours Tumours in the oesophageal area. The oesophagus is the long tube that carries food from the throat to the stomach.

Pancreatitis Inflammation in the pancreas.

Perforation A hole that develops through the wall of a body organ.

Photodynamic therapy A treatment that involves light-sensitive medicine and a light source to destroy abnormal cells.

Stenosis Narrowing or restriction of a blood vessel or valve that reduces blood flow.

List of abbreviations

AE	adverse event
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRD	Centre for Reviews and Dissemination
EQ-5D	EuroQol-5 Dimensions
ERCP	endoscopic retrograde cholangiopancreatography
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
HR	hazard ratio
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
PEVPI	population expected value of perfect information
PEVPPI	population expected value of partial perfect information
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RFA	radiofrequency ablation
ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions
SE	standard error

Plain language summary

What was the question?

The bile and pancreatic ducts transport fluids to the intestines to help people digest their food properly. Some types of cancer can cause these ducts to become totally or partially blocked.

We wanted to know if endoscopic radiofrequency ablation is safe and works well to treat people who have one of these blockages that cannot be removed by surgery.

Radiofrequency ablation burns away a blockage by hitting it with radio waves. Endoscopic means that the radio waves are directed to the blockage using a thin, tube-like wire with a camera at the end. During radiofrequency ablation, a person might have a small tube called a stent put into their bile or pancreatic duct to keep it open or to replace an already blocked stent.

What did we do?

We searched for research studies that looked at (1) whether or not radiofrequency ablation was able to remove blockages from the ducts, (2) if radiofrequency ablation allowed people to live longer, (3) if patients had a better quality of life after radiofrequency ablation, (4) if radiofrequency ablation caused any side effects and (5) how much it costs to treat people with radiofrequency ablation.

What did we find?

We found that treatment with radiofrequency ablation before giving a person a stent helped them to live a little longer with their cancer.We did not find any evidence that radiofrequency ablation increased pain or swelling in the bile duct or pancreatic duct. Radiofrequency ablation might cause more swelling in the gall bladder than having a stent without radiofrequency ablation, but there was not enough research available for us to be certain of this.

What does this mean?

Radiofrequency ablation before inserting a stent could be a safe option to add to treatment of bile and pancreatic duct blockages caused by cancer. There is limited research evidence and so we are unable to recommend radiofrequency ablation as a treatment for standard clinical practice.

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*).

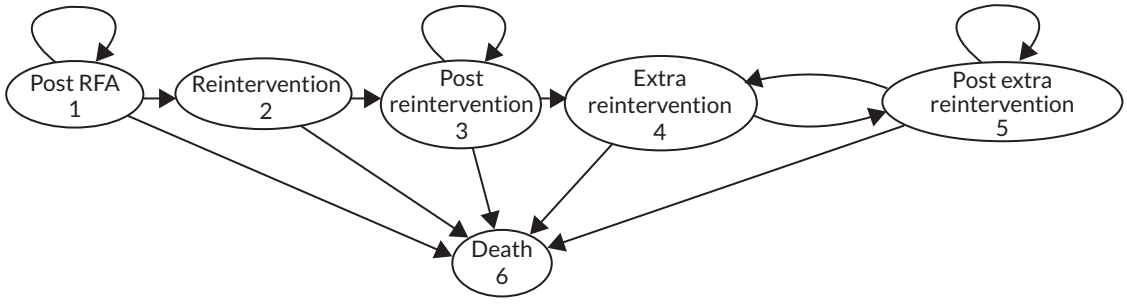

FIGURE i Markov model structure.

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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Chapter 1 Background

Description of hepatobiliary cancers

The majority of malignant obstructions of the bile duct are caused by a variety of cancers, including ampullary carcinoma, cholangiocarcinoma, adenocarcinoma of the pancreatic head and carcinoma of the gall bladder, which are inoperable in the majority of scenarios (e.g. < 30% of cholangiocarcinomas and 20% of pancreatic carcinomas are resectable at the time of diagnosis).[1] Furthermore, evidence that the incidence of gall bladder cancer and cholangiocarcinoma is increasing in the Western world and globally.[2,3]

Despite years of research, survival in this group of patients continues to be poor, even with chemotherapy and/or radiotherapy and, therefore, palliation of symptoms becomes a key aspect of therapy.[4]

Description of current service provision

In patients with inoperable disease, current standard of care involves the insertion of one or more stents during endoscopic retrograde cholangiopancreatography (ERCP), which restores bile flow, alleviating symptoms associated with obstructive jaundice.[5] Around 60,000 ERCPs are performed in the UK per annum, with about 20% being for malignant biliary obstruction. Metal stents are preferred over plastic stents because they remain patent longer.[6] Metal stents remain patent for an average period of about 6–9 months, after which repeat intervention may be necessary.[7] Metal stents necessitate repeated hospital admissions, cause considerable morbidity and expose the patient to further procedure related risks. Efforts have been ongoing to develop adjunctive interventions for improving the patency period of metallic biliary stents.[4] Some interventions that have been studied include photodynamic therapy and intraductal radiotherapy; however, there are many drawbacks to these treatments, and they are usually delivered in multiple sessions.[8]

Description of radiofrequency ablation

Delivery of radiofrequency ablation (RFA) in the bile duct has emerged as a promising modality in the last few years.[9] RFA produces coagulative necrosis of tissue and, therefore, reduces tumour volume in the bile duct. RFA has been used both prior to placing biliary stent (i.e. primary RFA) and for management of blocked biliary stents (i.e. secondary RFA) in malignant bile duct obstruction.[9,10] RFA is part of standard care in the treatment of hepatocellular cancer or liver tumours that are unsuitable for resection (including metastatic liver tumours, oesophageal tumours and colorectal cancers).[11] As overall survival in pancreatic and biliary cancers is poor, additional treatments are urgently needed.

Primary RFA delivered at the time of stent insertion is technically straightforward to perform, and feasibility studies have already shown high levels of technical success.[9,10] If primary RFA can improve survival and duration of stent patency, then this has the potential to reduce the rate of repeated admissions and interventions and could conceivably lead to improvements in quality of life in people with unresectable disease.

Secondary RFA is employed in the management of occluded metal stents to treat the cancerous tissue that has grown back into the lumen, causing recurrent obstructive jaundice and often infection (cholangitis). This is often an emergency situation and patients may take several weeks to recover from such an event. In addition, because of the recurrent jaundice, patients may not be able to receive chemotherapy, which may further adversely affect their outcome.[7]

There are two commercially available RFA probes that can be used during ERCP, both of which come at additional cost on top of that of standard care. The two RFA probes have slightly different characteristics and, therefore, may not deliver the same outcomes for patients. Furthermore, there have been case reports of adverse events (AEs) occurring in patients undergoing biliary RFA but it is difficult to ascertain whether this is in excess to that expected from standard care at ERCP.

Primary radiofrequency ablation

Initial investigation of RFA delivered at the time of ERCP has shown that this is a technically feasible adjunct with acceptable safety and stent patency rates at 90 days.[9] Two studies[9,10] have suggested that RFA prior to stent insertion may confer a doubling in overall survival. The studies,[9,10] however, are small single-centre studies that are not randomised and, therefore, are not of sufficient quality to change clinical practice. Many of the data have arisen from retrospective analysis of clinical usage and primarily in patients with cholangiocarcinoma.[12] Review of the previous studies in this area with respect to size, trial design, control group selection and outcomes reveals considerable heterogeneity and a lack of high-quality study design. Only two[9,13] of the studies have been of prospective design and only four studies[14–17] used a control group. Some studies[14–16] used historic controls, and one study[17] used the Surveillance, Epidemiology, and End Results database. Given the poor survival of most patients with pancreatic and biliary cancers, more information is urgently required concerning RFA, particularly with reference to any survival benefits, AEs and effects on quality of life. Pilot data from two UK centres (Aberdeen Royal Infirmary and the Hammersmith Hospital) have shown that delivery of RFA during ERCP has a high technical success rate and a low AE rate, and suggests overall improvement in survival.[9,10] The addition of RFA was also acceptable to patients during ERCP. How RFA leads to such effects is not fully understood. It is thought that RFA causes tissue necrosis and increases the diameter of biliary strictures. Drainage and stent insertion may be aided by this.[13,16] Previously noted increased survival times cannot be attributed to this mechanism alone. Rat models of metastatic colorectal cancer have shown that antigen release after RFA can lead to antitumour immunity against hepatocellular carcinoma.[18] The technical feasibility, safety and efficacy of primary RFA have been confirmed; however, very few prospective randomised studies exist.

Secondary radiofrequency ablation

With respect to treatment of tumour ingrowth and subsequent occlusion of biliary metal stents, there are several case series demonstrating technical feasibility and safety of RFA in this setting.[19] Data from Newcastle have shown that RFA significantly increases the stricture diameter, allowing for better flow.[20] However, similar to primary RFA, many of the data have been derived from small single-centre retrospective studies with heterogeneous cohorts and often without suitable control groups. One study[19] examined secondary RFA purely in patients with occluded metal stents and matched to control subjects in whom plastic stents were inserted across the occluded metal stent. The study[19] found improved stent patency at 90 days and longer overall stent patency, but did not report survival in the two groups. Secondary RFA may improve stent patency and time to further intervention, but overall survival has not been well studied. Indeed, this is likely to be difficult, as, in contrast to patients treated with primary RFA (delivered prior to stent insertion), in patients undergoing secondary RFA (delivered within a previously placed stent), the period since diagnosis of the malignancy will generally be longer, and such patients are therefore likely to have more advanced tumours. There is also the question as to whether or not a further stent (and, therefore, additional time and cost) is required following secondary RFA, as the rates of stent reintervention in current studies appears to vary.

Rationale

Although there appears to be a suggestion from some studies[13,44] that primary RFA may improve survival, it is currently unclear if this is cost-effective or associated with an increased AE rate. In addition, true impact on quality of life is not known. For secondary RFA, there is a suggestion of improving stent patency duration, but, again, cost-effectiveness, AE rates and quality of life have not been well studied.

This evidence synthesis will evaluate the existing data with respect to these outcomes to determine if there is sufficient evidence for RFA in these circumstances or if further research, and its directions, are required.

Aims and objectives

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 interventions for the treatment of malignant biliary obstruction.

The key objectives were as follows:

- To undertake a systematic review assessing the clinical effectiveness and potential risks of RFA in patients with malignant biliary obstruction (see *Chapter 2*).
- To undertake a second systematic review assessing the cost-effectiveness of RFA in patients with malignant biliary obstruction (see *Chapter 3*).
- To develop a decision model to estimate cost-effectiveness based on the data derived from the systematic reviews (see *Chapter 6*).
- To assess the value of further research by undertaking a value of information analysis from the data and results generated by the decision model (see *Chapter 7*).

Chapter 2 Methods of clinical effectiveness review

A robust systematic review was carried out in accordance with the methods outlined in guidance from the Centre for Reviews and Dissemination (CRD).[21] A protocol was developed and signed off by the project team and Clinical Advisory Board. The review was registered on PROSPERO (reference CRD42020170233) and was reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and SwiM (Synthesis Without Meta-analysis) guidance.[1,22] The review aimed to evaluate the impact of RFA, compared with inserting a stent without RFA, on survival, quality of life and AEs. Two patient and public involvement (PPI) colleagues were members of the Clinical Advisory Board (including author LC). The two PPI colleagues contributed to the design of the protocol, in particular helping to identify and prespecify patient-related outcomes that were subsequently reported as an important gap in the literature. In addition the PPI colleagues also contributed to interpretation of results, writing of the *Plain English summary* and the final report.

Search strategy

An experienced information specialist designed the search in MEDLINE in collaboration with the project team. The search used the following concepts:

- population: people with cancer that could cause biliary obstruction
- intervention: endoscopic biliary RFA.

The search was designed using database thesaurus headings and keywords, and the strategy was translated as appropriate to other databases. An example of the full search strategy can be found in *Appendix 1*.

As the intervention was not available prior to 2008, the search dates were restricted from 2008 to present. No other limits or restrictions were applied to the search. All search results were downloaded to EndNote (Clarivate Analytics, Philadelphia, PA, USA) and de-duplicated.

Update searches were restricted to bibliographic databases and de-duplicated against the primary search results.

Bibliographic databases

- MEDLINE (OVID), 1946 to May 19 2020 (searched 20 May 2020, updated search 21 January 2021).
- EMBASE (OVID), 1996 to 2020 week 20 (searched 20 May 2020, updated search 21 January 2021).
- The Cochrane Library (Wiley) (searched 20 May 2020, updated search 21 January 2021):
    - Cochrane Database of Systematic Reviews
    - Cochrane Central Register of Controlled Trials
    - Cochrane Clinical Answers.
- Scopus (searched 22 May 2020, updated search 21 January 2021).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO*host*) (searched 20 May 2020, updated search 21 January 2021).
- Health Technology Assessment database (CRD) (searched 22 May 2020).
- Database of Abstracts of Reviews of Effects (CRD) (searched 22 May 2020).

Grey literature databases

- OpenGrey (searched 12 June 2020).
- Web of Science Conference Proceedings Index (searched 17 June 2020).

Specific websites

- Royal College of Surgeons.
- Health Management Information Consortium.
- Annual conference meetings:

    - digestive disease week (accessed 12 June 2020).
    - united European gastroenterology week (accessed 12 June 2020)
    - International Digestive Endoscopy Network (accessed 12 June 2020)
    - the British Society of Gastroenterology (accessed 12 June 2020).

Trial registries

A range of trials registers were searched to ensure that international trials were identified:

- ClinicalTrials.gov (accessed 17 June 2020)
- European Union Drug Regulating Authorities Clinical Trials (accessed 17th June 2020)
- International Standard Randomised Control Trials Number registry (accessed 12 June 2020)
- International Conference on Harmonization in Good Clinical Practice (accessed 17 June 2020)
- Korean Clinical Research Information Service (accessed 12 June 2020)
- National Institute of Public Health Japan Primary Registry Network (accessed 12 June 2020)
- Thai Clinical Trials Registry (accessed 12 June 2020).

Reference lists/hand-searching

The references of included studies and relevant systematic reviews were checked for eligible studies potentially missed in the search.

As the intervention was not available prior to 2008, the search dates were restricted from 2008 to present. All search results were downloaded to EndNote and de-duplicated.

Inclusion and exclusion criteria

Population

Studies that recruited the following types of patients were included:

- patients with biliary obstruction caused by any form of unresectable malignancy who were ineligible for surgical resection (malignancies could include cancer of the pancreas, bile duct, gall bladder and duodenum, and also ampullary and metastatic cancers)
- patients undergoing a first procedure or patients with recurrent obstruction of a previously inserted stent
- adult patients aged ≥ 18 years
- patients with either first diagnosis or previous history of cancer, including patients receiving ongoing treatment
- patients with underlying health issues, such as diabetes or asthma.

Studies that recruited the following types of patients were excluded:

- Patients with benign biliary obstruction (studies with patients presenting with both benign and malignant strictures were included if the malignant data were reported separately)
- Patients with hepatocellular cancer or liver tumours, unless there was also biliary obstruction.

Interventions and comparators

Interventions

Endoscopic biliary RFA used to ablate malignant tissue that obstructed the bile or pancreatic ducts, either to fit a stent (metal or plastic) or to clear obstructed stents.

Studies that used RFA that was not endoscopic were excluded.

Comparators

Comparators include insertion of a stent to clear the bile or pancreatic duct or standard care of patients with an occluded stent. 'Standard care' was deemed likely to be different between different countries and at different time points (e.g. 'standard' types of chemotherapy would be different now from types of chemotherapy 10 years ago, even in the same hospital). Where detail was available about what was provided as 'standard care', this was extracted.

Outcomes

Outcomes were defined in consultation with clinician and PPI colleagues during the first Clinical Advisory Group meeting. Studies that reported any of the following primary outcomes were included:

- survival
- quality of life
- procedure-related AEs (e.g. bleeding, perforation, liver infarction, infection, pancreatitis, cholangitis or biliary leakage).

Studies were combined in a meta-analysis only if outcome measures matched; otherwise the studies were included in the narrative synthesis. Secondary outcomes included 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

Scoping had uncovered a limited and heterogeneous literature, and so we considered all articles except editorials, letters and opinion pieces to make the most use of available data. Studies reported in abstract form were considered for inclusion if sufficient data were available to extract.

Data collection

Selection of studies

Two reviewers (FB, JL, NOC, HOK, GOL or MS) independently screened the title and abstracts of the studies retrieved by the search in Rayyan (Doha, Qatar), a software designed to aid screening of results for systematic reviews.[23] A set of 253 records were pilot screened, and reviewers met to resolve disagreements and to clarify eligibility criteria. For studies deemed eligible, or where it was impossible to decide eligibility from the abstract, the full text was retrieved, and two reviewers independently assessed the full text for inclusion. Any disagreements were resolved through discussion or by reference to a third reviewer or the Clinical Advisory Board.

Data extraction

Data were extracted by one reviewer and checked by a second reviewer, and, when required, discrepancies were resolved by consultation with a third reviewer.Where studies were reported in multiple publications, relevant data were extracted from all publications, but they were considered as one study. Where data were missing or unclear, authors were contacted to request details or clarification.

For the effectiveness review, we extracted the following data from included studies:

- citation information
- study design
- participant characteristics (e.g. diagnosis, source and extent of obstruction, new or existing stent, disease stage, age, other relevant treatments, clinical measurements that are proposed as a mechanism of action of the RFA)
- intervention characteristics (e.g. type of stent, RFA settings used, duration of ablation, type of probe used, detail of proposed mechanism of action)
- comparator characteristics (e.g. type of stent, alternative treatment details, details of 'standard care' provision)
- primary outcomes [e.g. survival, relief of biliary obstruction, time to occlusion or reocclusion, AE details (quantitative or qualitative)]
- secondary outcomes, where reported (e.g. technical success, relief of biliary obstruction, pain, nausea, resource use, number of further interventions, length of hospital stays, reintervention and readmission rates)
- carer perspectives, where available (e.g. personal costs in terms of personal and physical health, well-being, financial impacts of the disease on patients and carers)
- details of study methods to facilitate an assessment of risk of bias.

Risk-of-bias assessment of included studies

Risk-of-bias assessment was conducted by two reviewers independently at a study level using the following tools, according to study design:

- Randomised controlled trials (RCTs) were assessed using the Cochrane Risk of Bias 2.0 tool.24 Domains under consideration included risk of bias arising from the randomisation process, from deviations from intended assignment to interventions, from missing outcome data and the way the outcome was measured, and in selection of the reported result.
- Non-randomised controlled studies were assessed using criteria based on the ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tool.25 Domains under consideration included risk of bias arising from confounders, from selection of participants into the study, from classification of and deviation from interventions, from missing outcome data, and in selection of the reported result.
- Uncontrolled studies were not formally assessed using a specific tool.
- Studies published only as abstracts were not formally assessed for risk of bias, as there was a risk that brevity of reporting would confound the assessment.

Disagreements were resolved by the two reviewers or in team discussions.

Data analysis

In the first instance, data were presented as study characteristics, results and risk-of-bias assessments in a series of structured tables to give a clear picture of the available evidence.

For the clinical effectiveness synthesis, controlled studies were prioritised. The primary analysis estimated the hazard ratio (HR) of mortality using a random-effects generic inverse variance model, with separate analyses for primary and secondary RFA. All meta-analyses were conducted using RevMan software (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Chemotherapy was identified as a key confounding factor. The base-case analysis was restricted to full-text papers and studies that were RCTs or were non-randomised controlled trials that adjusted for chemotherapy treatment if the study included some patients receiving chemotherapy treatment, as these were considered better-quality studies. The result of the analysis was included in the economic model for patients not receiving chemotherapy treatment, as the economic model distinguished between patients receiving chemotherapy treatment and patients not receiving chemotherapy treatment. Results from conference abstracts and non-randomised studies that did not adjust for chemotherapy but did include chemotherapy patients were included in a sensitivity analysis.

Adverse events were analysed using an exploratory approach, utilising all reported AEs so as not to bias the results of the review with the author preconceptions. AE data were pooled in a random-effects meta-analysis using Mantel–Haenszel weighting. Heterogeneity between studies was assessed by visual inspection of plots of the data, from the chi-squared test for heterogeneity and the I^2-statistic. Possible reasons for heterogeneity were explored where possible, such as differences in the populations studied (e.g. concomitant treatments, cancer type and stage), the interventions (whether patients were receiving primary RFA with a stent being newly inserted or secondary RFA to unblock an existing stent), the detail of 'standard care' provided and the way in which the outcomes were assessed.

A sensitivity analysis included studies that were reported in conference abstracts because there were usually insufficient data to fully assess the risk of bias in the studies. Subgroup analyses were also planned according to the type of probe, stent (i.e. metal or plastic) and cancer. However, during the review, it became clear that there were insufficient data to carry out these subgroup analyses.

Where there were insufficient data or it was inappropriate to pool data because of differences between studies in comparisons or reported outcomes, a narrative synthesis of the data was provided, structured by outcome. The effectiveness estimates fed into the economic model.

Meta-analyses were conducted with and without adjustment for bias. On average, the characteristics of participants (e.g. average age, severity of disease and whether or not people receive adjuvant treatment in each group) should be similar in both arms of a RCT because of the randomisation process. Conversely, in a non-randomised study, it is useful to adjust for the potential differences between groups that may occur in the absence of randomisation.

The key confounding factor, raised in the initial Clinical Advisory Board meeting, was whether or not patients received chemotherapy, as this has its own impact on survival. Non-randomised studies were included in the primary meta-analyses only if they had adjusted for the chemotherapy given to patients or if no or similar chemotherapy was received by patients in each group.

Chapter 3 Methods of cost-effectiveness review

A second systematic review was planned, looking at economic evaluations of RFA for malignant biliary obstruction. Searches and screening were carried out as described below, but no studies were found for inclusion.

Search strategy

An experienced information specialist designed the search in MEDLINE in collaboration with the project team. The search used the following concepts:

- Population: people with cancer that could cause biliary obstruction.
- Intervention: endoscopic biliary RFA.

Bibliographic databases

- MEDLINE (OVID), 1946 to 19 May 2020 (searched 20 May 2020).
- EMBASE (OVID), 1996 to week 20 2020 (searched 20 May 2020).
- Scopus (searched 22 May 2020).
- CINAHL (EBSCOhost) (searched 20 May 2020).
- NHS Economic Evaluation Database (NHS EED) (CRD) (searched 22 May 2020).

The search was designed using database thesaurus headings and keywords. The strategy was translated, as appropriate, to other databases. An example of the full search strategy can be found in *Appendix 2*.

Grey literature databases

- Web of Science Conference Proceedings Index (accessed 17 June 2020).
- Cost-Effectiveness Analysis Registry (accessed 12 June 2020).
- DEAS (Research Papers in Economics) database (accessed 12 June 2020).

Reference lists/hand-searching

References were checked from previous relevant systematic reviews.

An economic study filter was applied (NHS EED, MEDLINE using OvidSp) and the search was restricted from 2008 (as the intervention was not available prior to 2008). No other limits or restrictions were applied.

All search results were downloaded to EndNote and de-duplicated.

Inclusion and exclusion criteria

Population

Studies had to include patients with biliary obstruction caused by any form of unresectable malignancy who were ineligible for surgical resection (see *Chapter 2*, *Population*, for further details).

Interventions

Studies were included where endoscopic biliary RFA was used to ablate malignant tissue that obstructed the bile or pancreatic ducts, either to fit a stent (metal or plastic) or to clear obstructed stents (see *Chapter 2*, *Interventions and comparators*, for further details).

Outcomes

The aim was to include full economic evaluations, including trial- and model-based evaluations. No restrictions were imposed on the type of economic evaluation (i.e. cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses, cost–consequences analyses), as long as the studies fitted the Drummond *et al.*[26] definition of a full economic evaluation (i.e. a comparative analysis of alternative courses of action in terms of costs and consequences).

Data collection

Selection of studies

Two reviewers (FB and GOL) independently screened the title and abstracts of the studies retrieved by the search in Rayyan.[23] For studies deemed eligible or where it was impossible to decide eligibility from the abstract, the full text was retrieved and two reviewers independently assessed the full text for inclusion.

Data extraction

We planned to extract the following data from included studies using a standardised data extraction form:

- citation information
- study design
- participant characteristics (e.g. diagnosis, source and extent of obstruction, new or existing stent, disease stage, age, other relevant treatments, clinical measurements that are proposed as a mechanism of action of the RFA)
- intervention characteristics (e.g. type of stent, RFA settings used, duration of ablation, type of probe used, detail of proposed mechanism of action)
- comparator characteristics (e.g. type of stent, alternative treatment details, details of 'standard care' provision)
- primary outcomes [e.g. survival, relief of biliary obstruction, time to occlusion or reocclusion, AE details (quantitative or qualitative)]
- method of economic evaluation
- principal study findings.

Risk-of-bias assessment of included studies

We planned to use the Drummond *et al.*[26] checklist to assess the risk of bias in the included economic evaluations.

Data synthesis

We planned to assess the transferability of the included evaluations and to carry out a narrative synthesis.

Chapter 4 Results of 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. After title and abstract screening, a total of 697 results were deemed potentially eligible for inclusion.

EndNote was used to assist the full-text screening of 697 records. All records were screened in duplicate by independent reviewers, blinded to each other's decisions. After removal of the blind, conflicting decisions were resolved by discussion or by a third reviewer if an agreement could not be reached (see *Appendix 3* for excluded studies).

Characteristics of included studies

Following eligibility assessment, 68 studies were included in this review (*Figure 1*, and see *Appendix 4*).

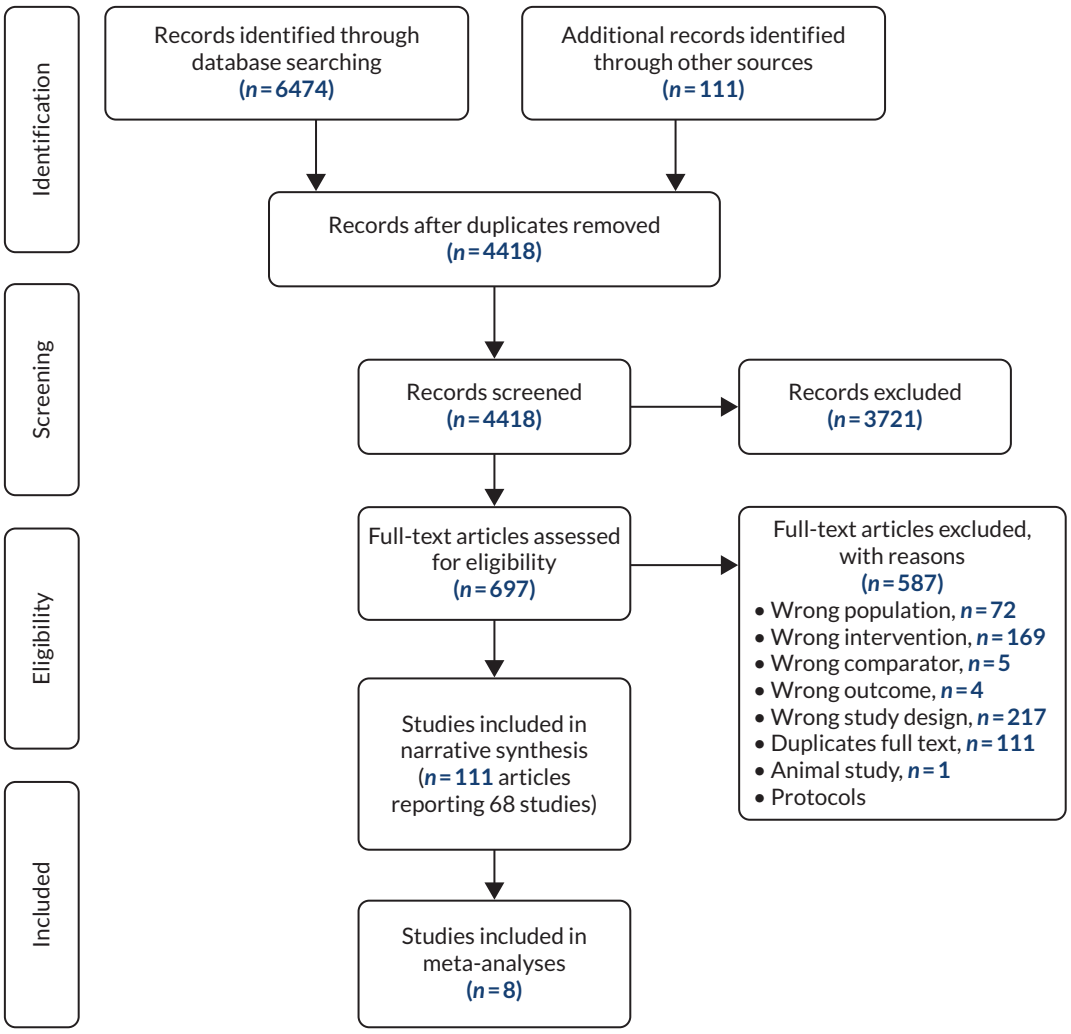

FIGURE 1 Flow of studies through the effectiveness review. Reproduced with permission from Moher *et al.*[116] This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The figure above includes minor additions and formatting changes to the original figure.

Less than half (*n* = 32, 47%) of the studies were reported as peer-reviewed published articles, and the rest (*n* = 36, 53%) were available only as conference abstracts. In total, there were 18 comparative and 50 non-comparative studies, with a total of 1742 patients (plus one study that did not report numbers). The studies were conducted in Asia (*n* = 24), European countries (*n* = 20), the USA (*n* = 20), South America (*n* = 2) and Australia (*n* = 2) (*Table 1*). Most patients had biliary obstruction arising from cholangiocarcinoma (where reported). The most commonly reported probe used for the ablation procedure was the Habib™ EndoHPB[27] (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 (i.e. primary RFA; *n* = 40), the unblocking of an existing stent (i.e. secondary RFA; *n* = 15) or both (*n* = 11); this aspect was unclear in two studies.

Risk-of-bias assessment of included studies

Two full-text RCTs were assessed for risk of bias using the Cochrane Risk of Bias 2.0 algorithm.[28,29] One study[28] was judged to be at a high risk of bias overall and one study[29] was judged to be of 'some concern'. More detailed results for each domain of the Risk of Bias 2.0 tool can be seen in *Figure 2*.

In the case of Yang *et al.*,[29] concerns were around the intervention being reported differently in the paper compared with its cited trial registry record.[29] It was not possible to establish why this was the case, however, and, as the paper matched our inclusion criteria, it was included, with concerns raised in the risk-of-bias judgement.

The Gao *et al.*[28] study was deemed at high risk of bias because patients and clinicians delivering the intervention were not blinded to the intervention received.[28]

A total of five full-text non-randomised studies[12,14,16,34,35] were assessed for risk of bias (*Figure 3*). Four[12,16,34,35] of these studies were judged to be at moderate risk of bias overall, whereas the study by Kallis *et al.*[14] was judged to be at low risk.

Risk of bias was not formally assessed for studies for which only abstracts were available.

Summary of clinical effectiveness results

Primary outcomes

Survival

Of the 18 comparative studies, 16 reported a measure of survival. Two RCTs,[28,29] one case–control study[14] and three cohort studies[16,34,37] reported a HR for death for primary RFA compared with stent-only control. Four[16,28,29,34] of these (full-text papers and either RCTs or non-randomised controlled studies that adjusted for receiving chemotherapy treatment where necessary) were used for the base-case meta-analysis, two[14,37] were used only in a sensitivity analysis (one was an abstract[37] and one did not report a Cox proportional regression estimate).[14]

The pooled HR in the base-case analysis (336 participants) was 0.34 [95% confidence interval (CI) 0.21 to 0.55], meaning that RFA reduces the hazard of dying by 66%, and this is statistically significant at a 95% level of confidence (*Figure 4*). There was moderate heterogeneity, indicated by an I^2-value of 53%. Heterogeneity was not apparent in the characteristics of the participants where reported (age), but stage of cancer, comorbidities and sex were all poorly reported. The individual study effect sizes were consistently in favour of RFA.

TABLE 1 Characteristics of studies included in the effectiveness review

Study	Paper/abstract	Prospective?	Study design; number of participants	Country	Diagnosis	Primary/secondary RFA	Type of probe
Gao *et al.*[28]	Paper	Yes	RCT; 174	China	Extrahepatic CCA; AC	Primary	Habib EndoHPB
Yang *et al.*[29]	Paper	Yes	RCT; 65	China	Extrahepatic hilar CCA, except Bismuth III–IV	Primary	Habib EndoHPB
Hu *et al.*[30]	Abstract	Yes	RCT; 63	China	Hilar CCA; mid-CBD tumour; AC	Primary	NR
Hucl *et al.*[31]	Abstract	Yes	RCT; 31	Czech Republic	CCA; PC	Primary	NR
Teoh *et al.*[32]	Abstract	Yes	RCT; 47	China	Malignant distal biliary obstruction at least 2 cm away from the hilum	Primary	NR
Yang *et al.*[33]	Abstract	Yes	RCT; 59	China	Extrahepatic CCA	Primary	NR
Bokemeyer *et al.*[12]	Paper	No	Case control; 32	Germany	Hilar CCC; PC; GBC; other malignancy	Primary	NR
Kallis *et al.*[14]	Paper	No	Case control; 69	UK	PC	Primary	Habib EndoHPB
Sharaiha *et al.*[16]	Paper	No	Case control; 66	USA	CCA; PC; GBC; gastric cancer; liver metastases from colon cancer	Primary	Habib EndoHPB
Dutta *et al.*[34]	Paper	No	Cohort; 31	UK	MBO	Primary/secondary	Habib EndoHPB
Kadayifci *et al.*[35]	Paper	No	Cohort; 50	USA	MBO	Secondary	Habib EndoHPB
Andalib *et al.*[36]	Abstract	No	Cohort; 406	USA	CCA	Primary	NR
Buerlein *et al.*[37]	Abstract	No	Cohort; 47	USA	Perihilar CCA	Primary	NR
Kallis *et al.*[38]	Abstract	No	Cohort; 24	UK	CCA; PC	Primary	NR
Nair *et al.*[39]	Abstract	Yes	Cohort; unclear	India	Hilar CCA	Primary	TaeWoong RFA catheter (TaeWoong Medical Co., Ltd, Gyeonggi-do, Republic of Korea)
Sampath *et al.*[40]	Abstract	No	Cohort; 26	USA	Unresectable perihilar CCA	Primary	NR
Schwarzer *et al.*[41]	Abstract	No	Cohort; 9	Austria	CCA	Primary	NR
Wu *et al.*[42]	Abstract	No	Cohort; 39	China	Malignant distal biliary obstruction	Secondary	NR
Alis *et al.*[43]	Paper	No	Non-comparative; 10	Turkey	CCA	Primary	NR

continued

TABLE 1 Characteristics of studies included in the effectiveness review (*continued*)

Study	Paper/abstract	Prospective?	Study design; number of participants	Country	Diagnosis	Primary/secondary RFA	Type of probe
Dolak *et al.*[44]	Paper	No	Non-comparative; 58	Austria	Klatskin tumour; distal CCA; pancreatic adenocarcinoma; central HCC; mixed HCC/CCA; GBC; metastatic colorectal cancer	Primary/secondary	Habib EndoHPB
Figueroa-Barojas *et al.*[13]	Paper	Yes	Non-comparative; 20	USA	CCA; PC; intraductal papillary mucinous neoplasm with high grade dysplasia; gastric cancer with metastatic tumour in the bile duct	Primary	Habib EndoHPB
Han *et al.*[45]	Paper	Yes	Non-comparative; 21	Republic of Korea	Combined HCC with bile duct invasion	N/A	StarMed (Intersurgical Ltd, Wokingham UK)
Lee *et al.*[46]	Paper	Yes	Non-comparative; 30	Republic of Korea	CCA; PC; GBC	Primary	ELRA™ (TaeWoong Medical Co., Ltd, Gyeonggi-do, Republic of Korea)
Ogura *et al.*[47]	Paper	No	Non-comparative; 12	Japan	PC; CCA	Primary	Habib EndoHPB
Sharaiha *et al.*[17]	Paper	No	Non-comparative; 69	USA	CCA; PC	Primary	Habib EndoHPB
Steel *et al.*[9]	Paper	Yes	Non-comparative; 22	UK	PC; CCA	Primary/secondary	Habib EndoHPB
Tal *et al.*[48]	Paper	No	Non-comparative; 12	Germany	Malignant bile duct obstruction of the hepatic hilus (Klatskin-like tumours); intrahepatic CCA (Bismuth stage IV); CCA; GBC; metastases of gastric small cell carcinoma	Unclear	Habib EndoHPB
Battish *et al.*[49]	Abstract	No	Non-comparative; 19	USA	CCA; PC; HCC; metastatic colon cancer, pancreatobiliary origin; metastatic breast cancer	Primary/secondary	NR
De Nucci *et al.*[50]	Abstract	No	Non-comparative; 6	Italy	Extrahepatic CCA (with or without ongoing chemotherapy)	Primary	Habib EndoHPB
Ermerak *et al.*[51]	Abstract	Yes	Non-comparative; 9	Australia	MBO	Primary	Habib EndoHPB
Han *et al.*[52]	Abstract	No	Non-comparative; 9	Republic of Korea	Perihilar CCA	Primary	StarMed
Hashimoto *et al.*[53]	Abstract	Yes	Non-comparative; 12	Japan	Malignant hilar biliary obstruction	Primary	NR

TABLE 1 Characteristics of studies included in the effectiveness review (*continued*)

Study	Paper/abstract	Prospective?	Study design; number of participants	Country	Diagnosis	Primary/secondary RFA	Type of probe
Kahaleh *et al.*[54]	Abstract	No	Non-comparative; 62	USA	CCA; PC; GBC; gastric cancer; liver metastasis from colon cancer	Primary/secondary	Habib EndoHPB
Kallis *et al.*[55]	Abstract	No	Non-comparative; 11	UK	PC; CCA; hepatic metastases	Secondary	NR
Ribeiro[56]	Abstract	No	Non-comparative; 16	USA	CCA; liver metastases of PC; colon cancer metastasis; GBC; HCC	Primary	Habib EndoHPB
Samuel *et al.*[57]	Abstract	No	Non-comparative; 8	USA	CCA; PC; colon cancer; papillary neoplasm of CBD with type I choledochal cyst	Primary	Habib EndoHPB
Saraswat *et al.*[58]	Abstract	No	Non-comparative; 10	India	GBC; CCA	Primary	Habib EndoHPB
Ueno *et al.*[59]	Abstract	No	Non-comparative; 16	Japan	Malignant biliary stricture	Primary/secondary	NR
Laquière *et al.*[60]	Paper	No	Non-comparative; 12	France	Extrahepatic CCA	Secondary	Habib EndoHPB
Martí Romero *et al.*[61]	Paper	No	Non-comparative; 3	Spain	CCA	Primary	SpyGlass® (Boston Scientific Corporation, Marlborough, MA, USA)
Mukund *et al.*[62]	Paper	N	Non-comparative; 2	India	Rising serum bilirubin and signs of cholangitis secondary to occlusion of MBS	Secondary	NR
Nayar *et al.*[20]	Paper	N	Non-comparative; 7	UK	Pancreaticobiliary cancer; blocked biliary stents	Primary/secondary	ELRA
Lewis *et al.*[63]	Abstract	No	Non-comparative; 5	USA	Primary CCA; biliary implant of colon adenocarcinoma to the left hepatic duct	Primary	Habib EndoHPB
Morales *et al.*[64]	Abstract	No	Non-comparative; 10	Mexico	Malignant biliary stenosis	Primary/secondary	Habib EndoHPB
Mukund *et al.*[65]	Abstract	No	Non-comparative; 8	India	Adenocarcinoma; malignant hilar obstruction	Secondary	Habib EndoHPB
Watson and Habr[66]	Abstract	No	Non-comparative; 3	USA	Hilar CCA	Primary	Habib EndoHPB
Bastos *et al.*[67]	Paper	No	Case report; 1	Brazil	CCA	Primary/secondary	Habib EndoHPB
Gunasingam *et al.*[68]	Paper	No	Case report; 1	Australia	CCA	Primary	Habib EndoHPB
Han *et al.*[69]	Paper	No	Case report; 1	Republic of Korea	Advanced hilar CCA	Primary/secondary	ELRA

continued

TABLE 1 Characteristics of studies included in the effectiveness review (*continued*)

Study	Paper/abstract	Prospective?	Study design; number of participants	Country	Diagnosis	Primary/secondary RFA	Type of probe
Inoue *et al.*[70]	Paper	No	Case report; 1	Japan	Obstructive jaundice due to malignant hilar biliary obstruction	Primary	Habib EndoHPB
Kruger and Krishna[71]	Paper	No	Case report; 1	USA	Extrahepatic CCA and recurrent malignant biliary strictures	Secondary	Habib EndoHPB
Lee *et al.*[72]	Paper	No	Case report; 1	Republic of Korea	Adenocarcinoma	Primary	StarMed
Lorenzo *et al.*[73]	Paper	No	Case report; 1	France	Stenosis of the main pancreatic duct	Secondary	Habib EndoHPB
Lui and Li[74]	Paper	No	Case report; 1	China	CCA	Secondary	NR
Mansilla-Vivar *et al.*[75]	Paper	No	Case report; 1	Spain	Cryptogenic liver cirrhosis; spontaneous bacterial peritonitis; hilar CCA	Primary	ELRA
Mok *et al.*[76]	Paper	No	Case report; 1	USA	CCA	Secondary	NR
Monga *et al.*[77]	Paper	No	Case report; 1	India	CCA; adenocarcinoma	Primary	Habib EndoHPB
Ogura *et al.*[78]	Paper	No	Case report; 1	Japan	CCA with liver metastasis	Primary	Habib EndoHPB
Linz *et al.*[79]	Abstract	No	Case report; 1	USA	Metastatic PC involving the head of the pancreas	Secondary	NR
Ludvik *et al.*[80]	Abstract	No	Case report; 1	USA	Pancreatic adenocarcinoma with numerous metastases	Secondary	NR
Morais *et al.*[81]	Abstract	No	Case report; 1	Portugal	Perihilar CCA	Primary	Habib EndoHPB
Musquer *et al.*[82]	Abstract	No	Case report; 1	France	Peritoneal carcinomatosis	Secondary	Habib EndoHPB
Saumoy *et al.*[83]	Abstract	No	Case report; 1	USA	CCA	Primary	NR
Schlosser *et al.*[84]	Abstract	No	Case report; 1	Switzerland	Klatskin tumour	Secondary	ELRA
Sonpal *et al.*[85]	Abstract	No	Case report; 1	USA	Klatskin tumour	Secondary	Erbe (Erbe Medical UK Ltd, Leeds, UK)
Tian *et al.*[86]	Abstract	No	Case report; 1	China	Periampullary carcinoma	Primary	Habib EndoHPB
Tyberg *et al.*[87]	Abstract	No	Case report; 1	USA	MBS	Primary	Habib EndoHPB
Yoon and Brugge[88]	Abstract	No	Case report; 1	Republic of Korea	Malignant occlusion in the common hepatic duct	Primary	Habib EndoHPB

AC, ampullary cancer; CBD, common bile duct; CCA, cholangiocarcinoma; CCC, cholangiocellular carcinoma; GBC, gall bladder carcinoma; HCC, hepatocellular carcinoma; MBO, malignant biliary obstruction; MBS, malignant biliary stricture; N/A, not applicable; NR, not reported; PC, pancreatic cancer.

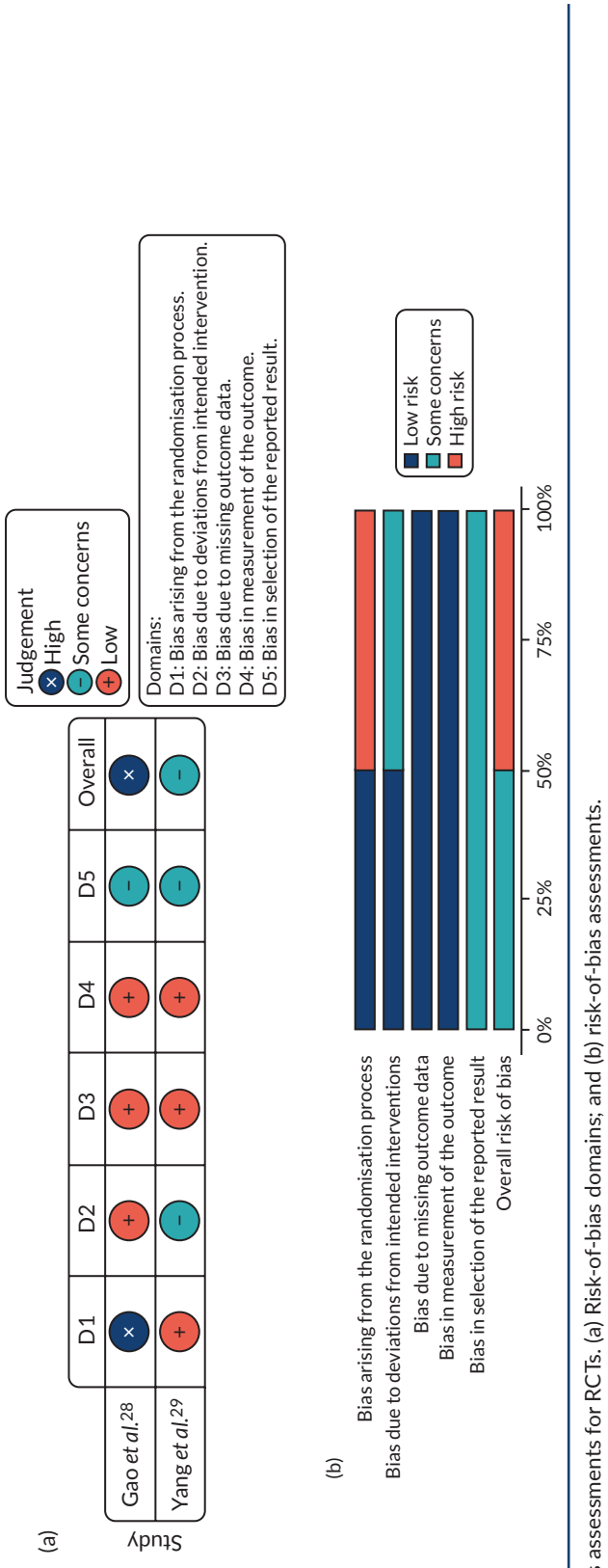

FIGURE 2 Risk-of-bias assessments for RCTs. (a) Risk-of-bias domains; and (b) risk-of-bias assessments.

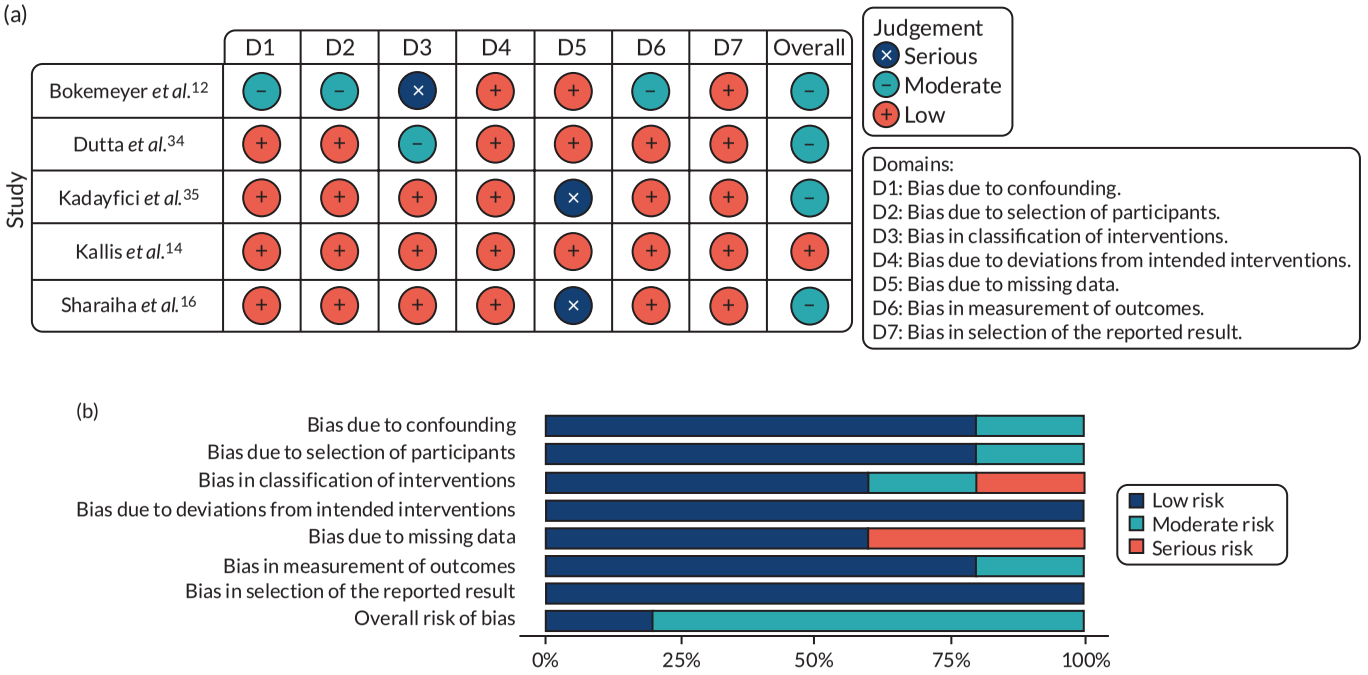

FIGURE 3 Risk-of-bias assessments for non-randomised comparative studies. (a) Risk-of-bias domains; and (b) risk-of-bias assessments.

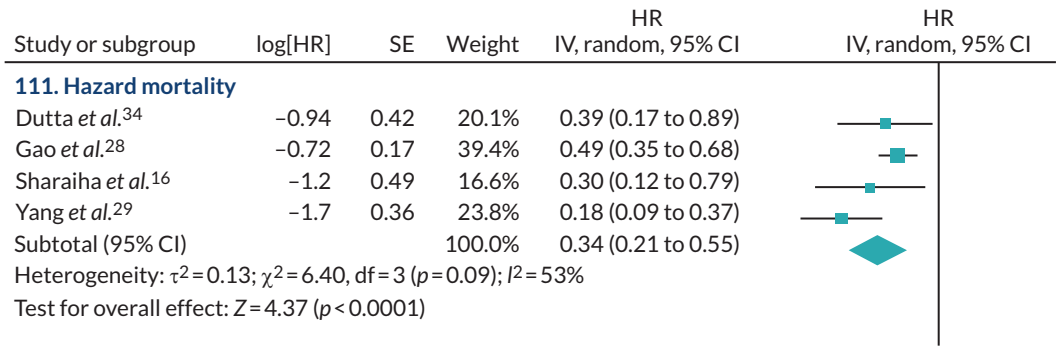

FIGURE 4 Hazard ratio of mortality, base-case meta-analysis (336 participants). SE, standard error.

The sensitivity analysis that included the studies at higher risk of bias (452 participants) showed a potentially slightly less beneficial effect of RFA, with the pooled HR estimated at 0.39 (95% CI 0.27 to 0.57) and this was statistically significant at a 95% level of confidence (*Figure 5*). There was moderate heterogeneity indicated by an I^2-value of 53%. The effect sizes are consistently in favour of RFA.

Of the 12 comparative studies that did not report a HR, most reported mean or median survival times and results were mixed. Of the four prospectively designed studies, two RCTs reported no difference in survival,[30,32] whereas one RCT and one prospective cohort study reported significantly prolonged survival in patients who received RFA.[33,39] Seven retrospective comparative studies[12,35,36,38,40–42] reported similarly mixed results.

None of the studies that assessed secondary RFA reported HRs, and so this planned meta-analysis was not possible. Two cohort studies[35,42] reported survival following secondary RFA, and neither reported a significant difference in survival between groups.

Of the 15 non-comparative studies[9,13,17,20,43–48,50,54,60–62] that reported a measure of survival, 11 reported mean or median survival and four reported the proportion of patients who died.

Quality of life

None of the studies reported quality of life using a conventional tool. Two studies[28,29] reported Karnofsky Performance Score as a measure of quality of life. Karnofsky Performance Score is designed to measure functional status from a clinician perspective rather than quality of life from a patient perspective. In both studies,[28,29] Karnofsky Performance Scores were reported to be significantly higher] ($p < 0.001$) in the RFA groups up to 9 months after the intervention.

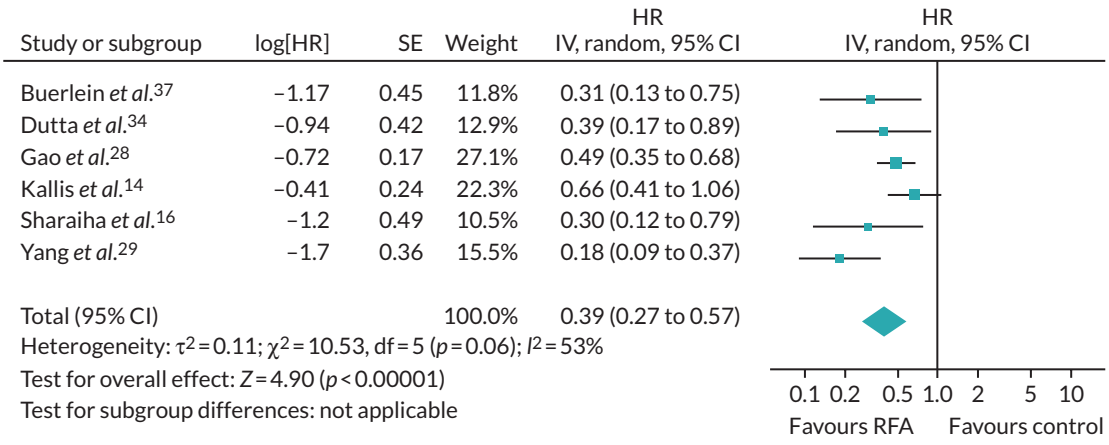

FIGURE 5 Hazard ratio of mortality, subgroup analysis including studies at higher risk of bias (452 participants). SE, standard error.

Adverse events

The most commonly reported AEs were cholangitis, pancreatitis and cholecystitis (*Figure 6*).

Sixteen comparative studies reported AEs. Five studies[32,33,36,39,42] reported that there were no statistically significant differences in AEs between groups, but did not specify particular AEs. Three comparative studies reported events in the RFA group only[12,38] or events in all participants without specifying whether they were in the control or intervention groups.[16] One study reported that no patients experienced any AEs.[35] Seven studies[14,28–31,34,37] specified the number of AEs in both intervention and control arms and were pooled in meta-analyses.

We found 24 non-comparative studies[9,13,17,20,43–62] and 14 single case reports[68,70–73,76,78–85] that reported AEs.

Cholangitis

Cholangitis is typically inflammation and fibrosis of the biliary tract, commonly caused by infection.[89] Cholangitis was reported in 15 studies.[12,14,28–30,34,37,44,46–48,52,58–60] Data from five comparative studies[14,28–30,34] were pooled in a meta-analysis (*Figure 7*), which showed no evidence of difference between groups (risk ratio 1.15, 95% CI 0.63 to 2.12). One further study[12] reported AEs in the intervention group only.

Eight non-comparative studies[44,46–48,52,58–60] reported that between 6% and 33% of patients experienced cholangitis.

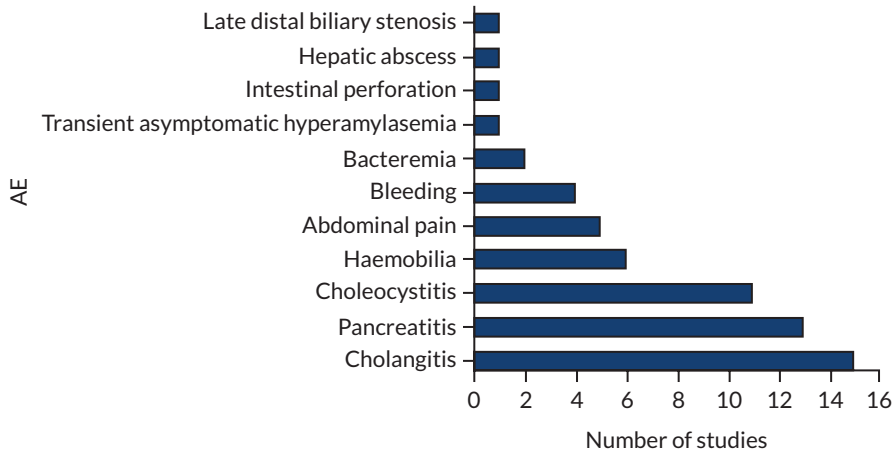

FIGURE 6 Frequency of reported AEs.

Study or subgroup	RFA Events	RFA Total	Control Events	Control Total	Weight	Risk ratio M–H, fixed, 95% CI
Dutta *et al.*[34]	1	15	0	16	2.9%	3.19 (0.14 to 72.69)
Gao *et al.*[28]	10	87	9	87	53.2%	1.11 (0.47 to 2.60)
Hu *et al.*[30]	4	32	6	31	36.1%	0.65 (0.20 to 2.07)
Kallis *et al.*[14]	1	23	0	46	2.0%	5.88 (0.25 to 138.84)
Yang *et al.*[29]	2	32	1	33	5.8%	2.06 (0.20 to 21.64)
Total (95% CI)		189		213	100.0%	1.15 (0.63 to 2.12)
Total events:	18		16			

Heterogeneity: $\chi^2 = 2.62$, df = 4 ($p = 0.62$); $I^2 = 0\%$
Test for overall effect: $Z = 0.46$ ($p = 0.65$)
Test for subgroup differences: not applicable

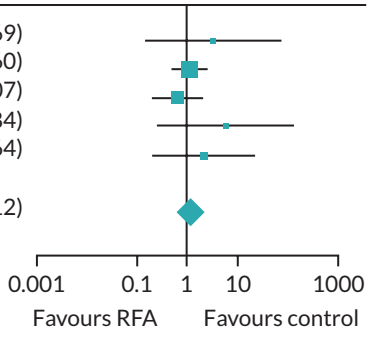

FIGURE 7 Risk of cholangitis.

Pancreatitis

Pancreatitis is an inflammation of the pancreas with many aetiologies.[90] Pancreatitis (mild or severe) was reported in 13 studies.[9,12–14,16,17,28,30,34,38,43,46,71] Four comparative studies[14,28,30,34] contributed data to a meta-analysis (*Figure 8*), which showed no evidence of a significant difference between groups (risk ratio 1.34, 95% CI 0.55 to 3.25). Three studies reported AEs in either the intervention group only or across all participants without distinction between the groups.[12,16,38] One study[38] reported that the incidence of pancreatitis was similar between groups.

Six observational studies[9,13,17,43,46,71] reported that between 4% and 7% of patients experienced pancreatitis.

Cholecystitis

Cholecystitis is an inflammation of the gallbladder, commonly due to a blockage.[91] Eleven studies[12,13,16,17,28,30,31,38,50,52,54] reported incidence of cholecystitis. Three comparative studies[28,30,31] contributed data to a meta-analysis. The estimate was very imprecise and none of the studies reported any cholecystitis in control group patients, but it seems likely that RFA carries a higher risk of cholecystitis than stent placement alone (risk ratio 11.47, 95% CI 2.28 to 57.66) (*Figure 9*).[28,30,31] A further three studies[12,16,38] reported cholecystitis in either the intervention group only or in participants from both groups. One study[38] reported that the incidence of cholecystitis was similar between groups.

Five non-comparative studies[13,17,50,52,54] reported that between 2% and 17% of patients experienced cholecystitis.

Abdominal pain

Two studies[17,75] reported that a small number of patients experienced mild, self-limiting abdominal pain after the RFA procedure. One study[16] reported a small number of instances of abdominal pain across the intervention and comparator groups, one study[58] reported that most (9/10) patients experienced abdominal pain and abdominal pain was also reported in a case study patient.[71]

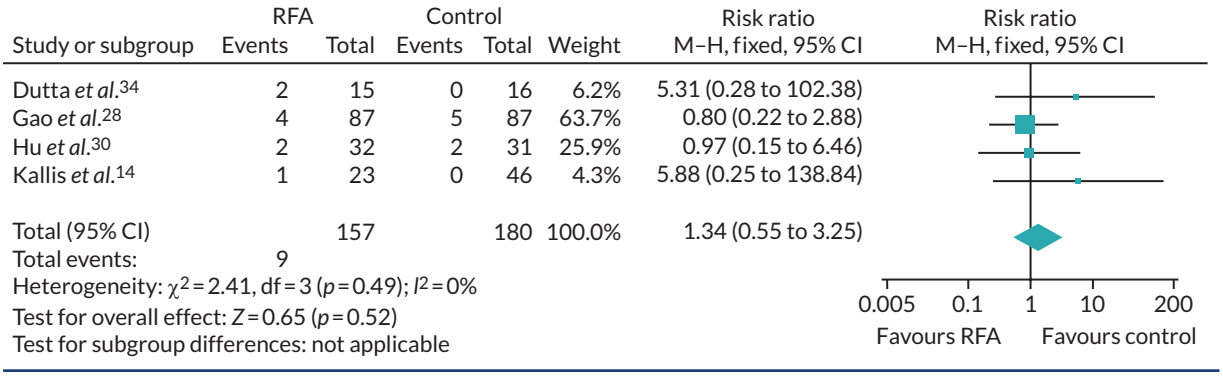

FIGURE 8 Risk of pancreatitis.

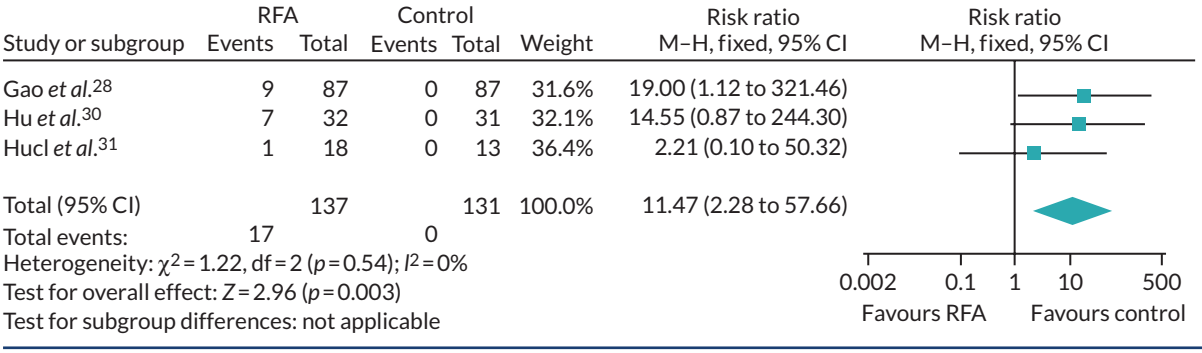

FIGURE 9 Risk of cholecystitis.

Secondary outcomes

Technical success

Even though the majority of the included studies did not report the 'technical success' outcome explicitly, the inference about it was made if study authors reported the RFA procedure as 'being successful' or as having 'no complications' or 'no technical problems', or described it in other similar phrases implying technical success. The vast majority of studies reported 100% technical success. Two studies[43,52] explicitly reported a different rate of technical success. One study[43] reported that 10 out of 17 RFA procedures were successful. In the remaining cases, RFA was either not attempted or not successful. A second study[52] reported that eight out of nine RFA procedures were successful, but 'functional success was not achieved in one patient'.

Time to occlusion or reocclusion

Occlusion occurs when a stent becomes blocked and reocclusion is when a stent becomes blocked again having been cleared. Two RCTs[28,29] reported mean stent patency and were included in a meta-analysis that showed no evidence of improvement in stent patency with primary RFA (*Figure 10*). In the two studies,[28,29] the direction of effect was different and statistical heterogeneity was high, with an I^2-value of 79%. The uncertainty in the estimate is consequently very high, and very little can be concluded from this analysis. Two further RCTs[30,33] and one comparative cohort study[14] also reported no benefit of primary RFA in terms of stent patency. None studies reported mean duration and so this could not be included in the meta-analysis.

One cohort study[42] and one case–control study[35] reported a benefit of secondary RFA compared with stent only in stent patency (median 152 vs. 83 days, p = 0.024; and mean 119.5 vs. 65.3 days, p = 0.01, respectively).

Five non-comparative studies and one case report[43,45,47,52,55,86] described different measures of time to occlusion for primary RFA, ranging from 22 months to 23 days.

One cohort study and two case reports[60,65,85] described time to reocclusion for secondary RFA, ranging from 2 to 10 months.

Two cohort studies[9,59] reported time to occlusion or reocclusion for a population that had received either primary or secondary RFA.

Other secondary outcomes

Very few data were reported about nausea, resource use, number of further interventions, length of hospital stays, and reintervention and re-admission rates.

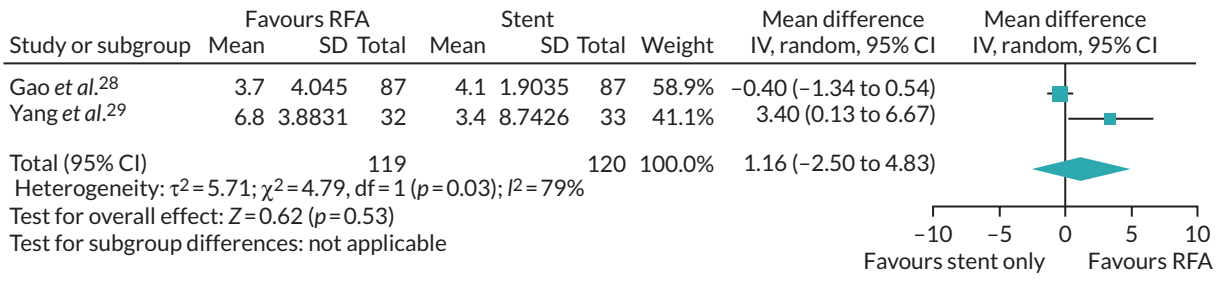

FIGURE 10 Time to occlusion (months).

Chapter 5 Results of cost-effectiveness review

A search retrieved 73 results after de-duplication (see *Appendix 5*). Rayyan was used to assist title and abstract screening of 73 records.[23] All records were screened in duplicate by independent reviewers, blinded to each other's decisions. After removal of the blind, conflicting decisions were resolved by discussion or by a third reviewer where an agreement could not be met. A total of 13 results were deemed potentially eligible for inclusion at this stage.

EndNote was used to assist full-text screening of 13 records. All records were screened in duplicate by independent reviewers, blinded to each other's decisions. After removal of the blind, conflicting decisions were resolved by discussion or by a third reviewer where an agreement could not be met. No records were deemed eligible for inclusion in the review (see *Appendices 5* and *6*).

Chapter 6 Development of a cost-effectiveness model

The objectives of the economic analysis were to (1) evaluate the cost-effectiveness of endoscopic RFA for the treatment of malignant biliary obstruction and (2) estimate the value of information that may be obtained from conducting future research. RFA alongside stent placement is compared with stent placement alone. Analyses were planned for four populations:

1. patients with pancreatic cancer and receiving primary stent placement
2. patients with pancreatic cancer and receiving secondary stent placement
3. patients with cholangiocarcinoma causing a blockage along the biliary tree and receiving primary stent placement
4. patients with cholangiocarcinoma causing a blockage along the biliary tree and receiving secondary stent placement.

Owing to a lack of effectiveness evidence for secondary stent placement, analyses could be run for primary stent placement only.

As the cost-effectiveness analysis used the effectiveness and AE evidence obtained from the systematic review to inform the consequences of endoscopic RFA compared with no RFA, an economic model was required to estimate the survival for each technology and to estimate the quality of life and cost outcomes over time. The systematic review of economic evaluations found no published model-based economic evaluations of endoscopic RFA interventions. Therefore, a de novo decision-analytic model was developed. The model was developed in TreeAge Pro (TreeAge Software, Inc., Williamstown, MA, USA). The model was probabilistic, meaning that most of the input parameters were entered into the model as probability distributions to reflect parameter uncertainty (i.e. uncertainty in the mean estimates).

The perspective of the economic analyses was the NHS and Personal Social Services perspective. The measure of benefit was quality-adjusted life-years (QALYs) and the time horizon was lifetime. Costs and benefits were discounted at an annual rate of 3.5%.

The effectiveness and adverse effects associated with endoscopic RFA with stent placement compared with stent placement alone were obtained from the systematic review. Value of information analyses estimate the value of reducing or eliminating decision uncertainty.

Key uncertainty in an economic analysis is the uncertainty in the effectiveness estimate. If a study is at risk of bias, there is uncertainty about whether or not the effectiveness estimate accurately estimates the true effect in the study population. The uncertainty associated with bias is not captured in the standard errors (SEs) or CIs of an effectiveness estimate. As the existing clinical studies of endoscopic RFA were anticipated to be at high risk of bias for the study populations, the effectiveness estimates from the clinical studies were adjusted for bias, as described in *Chapter 2*.

Model structure

A cohort Markov model with time-varying mortality and occlusion probabilities was developed to estimate the cost-effectiveness of endoscopic stent insertion and RFA (primary RFA) in a cohort of patients with unresectable cholangiocarcinoma receiving or not receiving chemotherapy. A cohort Markov model was selected, rather than a discrete event simulation, because (1) the only heterogeneity factor for mortality included was use of chemotherapy, and no evidence for this factor influencing the

effectiveness of RFA was available; (2) no time-dependent heterogeneity factors were identified by the clinical advisors; (3) the only time-to-occlusion statistic available was mean time to occlusion for patients who experienced an occlusion, which meant that the simplest method to model this was using a Markov model and checking that the model predictions were reasonably accurate (competing risk could not be explicitly modelled); and (4) the quality of the evidence available meant that the impact of model uncertainties on the results needed to be addressed through scenario analyses, and it is far quicker to run a cohort Markov model than to run a discrete event simulation, especially when conducting expected value of partial perfect information (EVPPI) analyses. A microsimulation state-transition model would be more time-consuming to run than a discrete event simulation.

All patients receive a stent at the start of the model. The difference between the cohorts is whether or not patients also receive RFA. The structure of the Markov model is shown in *Figure 11*. The ellipses in *Figure 11* represent the six states in the Markov model. All patients start in the 'post initial stent' state, meaning that patients have had a stent inserted and the occlusion has been cleared. Patients may transition between states at every cycle of the model. A 1-month cycle length was chosen because of the short life expectancy of the patients and the short time to occlusion and reintervention. Considering the short cycle length, a half-cycle correction was not expected to make a significant difference in the results and, hence, was not applied. The arrows in *Figure 11* indicate the state to which patients may transition during a cycle. Patients start the next cycle period in the new state. If an arrow points back to the same state, then the patient remains in that state. There is a monthly probability of making a transition to another state or remaining in the same state. As no-one can leave the dead state, the proportion of the population cohort that is in the dead state increases over time.

The key outcomes for RFA were survival and time to occlusion (i.e. blockage). The Markov states, therefore, represent whether patients have an occlusion and require a reintervention or they do not. Patients may die at any time. The utility of a patient who does not experience an occlusion is assumed to remain constant and no occlusion or stent or RFA costs are incurred. When a patient has an occlusion and has a reintervention (i.e. a new stent with or without RFA), they enter a reintervention state for 1 month. The utility for this month is a weighted average of the utilities accounting for the procedure and the risk of AEs. The cost incurred during this 1-month period is a weighted average of the cost of the procedure and the cost of treating AEs.

It is possible that a patient may experience more than one occlusion, requiring more than one reintervention. Effectiveness evidence was available for time to the first occlusion. Consequently, the model included a state for reintervention following the first occlusion (see *Figure 11*, state 2), and a state for subsequent reinterventions following subsequent occlusions (see *Figure 11*, state 4). This provides the option of making the risk of a second or third occlusion different from the risk of the first occlusion. Following a reintervention, patients enter a post-intervention state until another occlusion occurs, or they die. Following the first reintervention, patients enter the 'post-reintervention' state. Following an extra reintervention, patients enter the 'post extra reintervention' state. No patient experiences a reintervention within a month of the previous reintervention because of the method of modelling the risk of an extra reintervention (see *Time to occlusion*).

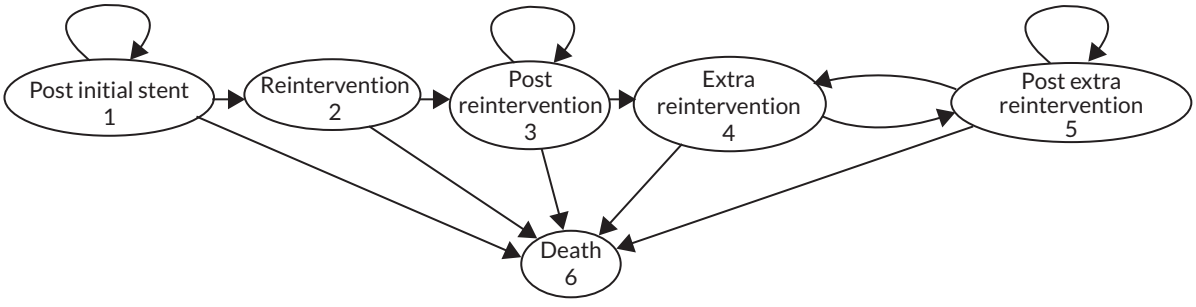

FIGURE 11 Economic model diagram.

The population cohort is divided into patients who receive palliative chemotherapy and patients who do not (either because they are not fit to receive chemotherapy or because they choose not to receive chemotherapy). Patients who are fit enough to receive chemotherapy are expected, on average, to survive longer than patients who are not fit enough to receive chemotherapy (see *Chemotherapy*). For the month when a patient is in a reintervention state, it is assumed that the chemotherapy regimen is halted and is resumed the following month. No cost of chemotherapy is incurred during the month. It is also assumed that the risk of dying changes to the risk for someone who is not fit to receive chemotherapy.

Survival

Time to death

Effectiveness

The HR of mortality was estimated by conducting a meta-analysis of the studies reported in the systematic review (see *Figure 4*). The effectiveness evidence was expected to be poor quality and so bias-adjusted meta-analysis was also planned (see Reviewer risk-of-bias assessment). Only one of the included studies in the meta-analysis was conducted in the UK, and it is possible that there are treatment practices that differ from those in the UK, which may affect the outcome. The type of stent is one possible confounding factor, although this is more likely to factor in secondary RFA.

The HR was modelled on the log-scale using a normal distribution. A HR of mortality was estimated for only bile duct cancer.

No patient-level data were available to test different survival models. In the base-case analysis, proportional hazards were assumed. Visual observation of the Kaplan–Meier plots suggested that this was a reasonable assumption. Of the four[16,28–29,34] studies included in the HR meta-analysis, three reported Kaplan–Meier curves. Of these, two graphs showed increasing divergence of survival curves consistent with proportional hazards until the survival curves converged with 100% dead in both groups within a short period of each other. The other Kaplan–Meier graph showed parallel survival curves to begin with, indicating a falling HR, before diverging until the end of follow-up.

The baseline hazard rate was very high from 15 months (> 4) and so, even with a HR of 0.34, the survival curves for RFA and no RFA followed a pattern seen in the reported Kaplan–Meier curves. The survival curves with and without RFA are reported in *Figure 12*.

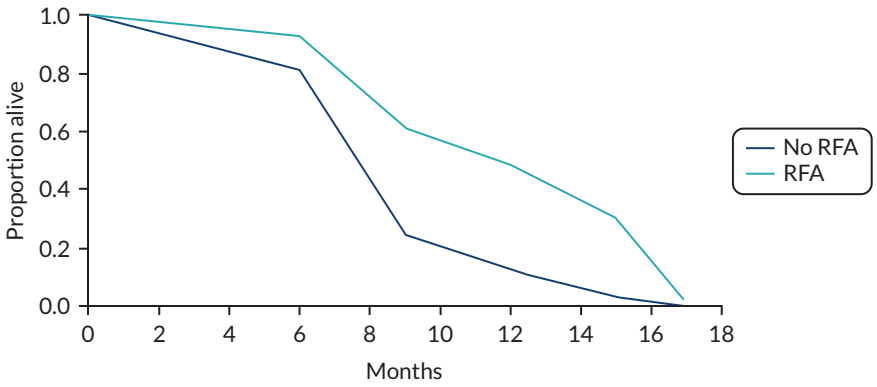

FIGURE 12 Survival curve without RFA and with RFA.

Chemotherapy

The clinical experts on the Project Advisory Group were consulted on the proportion of patients in the study populations who might receive chemotherapy or radiotherapy. In the base case, we assumed that 20% of patients would receive chemotherapy. Alternative values of 10% and 40% were used in sensitivity analyses.

PubMed was searched for systematic reviews of studies evaluating the difference in mortality outcomes in patients who receive chemotherapy (i.e. patients who are fit to receive chemotherapy and who choose to receive chemotherapy) and in patients who do not receive chemotherapy (i.e. patients who are either not fit to receive chemotherapy or choose not to receive chemotherapy) in patients with unresectable bile duct cancer or unresectable pancreatic cancer. No systematic reviews were found.

A simple search of Google (Google Inc., Mountain View, CA, USA) was conducted to identify studies that evaluated the HR of mortality for patients receiving chemotherapy in advanced, unresectable cancer with biliary obstruction. Two studies[92,93] were identified. Two studies[16,94] were also identified from the clinical effectiveness review in this study. A random-effects meta-analysis of the HR of mortality on the log-scale was conducted using the generic inverse variance method in R statistical software (The R Foundation for Statistical Computing, Vienna, Austria). The HR of mortality estimates extracted from the four studies[16,92–94] were estimated in those studies using multivariable regression methods that adjusted for confounding factors. The study populations and type of chemotherapy of the four studies[16,92–94] are reported in *Table 2*. The HRs and the 95% CIs for each study are reported in the forest plot (see *Figure 12*), along with the results of the meta-analysis. The pooled estimate from the random-effects meta-analysis was 0.6123 (95% CI 0.47 to 0.8), indicating that patients who receive chemotherapy are likely to survive for longer than patients who do not receive chemotherapy. There was a moderate degree of heterogeneity indicated by an I^2-value of 44.3%.

The time to death in the stent-only arm among patients who did not receive chemotherapy was modelled using the survival curve for the stent-only group in Yang *et al.*,[29] as this was the only study included in the meta-analysis that excluded patients on chemotherapy, excluded secondary RFA patients and provided sufficient data to model time to death. The exclusion of patients on chemotherapy was necessary, as both patients receiving and not receiving chemotherapy were modelled. A HR of mortality for chemotherapy compared with no chemotherapy was included in the model. The probability of death

TABLE 2 Study characteristics of studies included in meta-analysis of mortality HRs for chemotherapy vs. no chemotherapy

Study	Population	Chemotherapy regimen
Sharaiha *et al.*[16]	Patients with biliary obstruction from advanced stage pancreatic cancer or cholangiocarcinoma. Median survival 5.9 months	Not stated
Afshar *et al.*[93]	Patients who underwent biliary stenting for obstructive jaundice related to advanced malignant disease. Curative surgery patients excluded	Not stated
Yonemoto *et al.*[92]	Unresectable, locally advanced or metastatic adenocarcinoma arising from intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gall bladder cancer or papilla of Vater cancer	Gemcitabine used in analysis because of greatest sample size. HR reported for gemcitabine 0.53 (95% CI 0.34 to 0.82) and CDDP 0.49 (95% CI 0.36 to 0.99)
Liang *et al.*[94]	Patients with confirmed extrahepatic biliary adenocarcinoma but who are ineligible for curative surgery because of locally advanced or metastatic disease or because they are unfit for or not willing to undergo a major operation	22 gemcitabine/cisplatin combinations; 18 other gemcitabine based; and 13 fluoropyrimidine based

CDDP, Cisplatin based regimen.

was calculated for the time periods of 1–6 months, 7–9 months, 10–12 months and 13–15 months from the Kaplan–Meier curve, as the survival probabilities were reported after 6, 9, 12 and 15 months. The rate per cycle was derived for each period using the formula:

$$rate = \frac{-\ln(1-p)}{t}, \quad (1)$$

where t is the number of months in the period to which the probability applies. For example, the probability of dying over the first 6 months was 0.182 and t = 6. The hazard rate for the period following 15 months was assumed to the same as the 13- to 15-month period. Regardless of the number reinterventions (the model state), the probability of dying was related to the time since the start of the model.

Sensitivity analyses were conducted in which the probability of death was increased and decreased by 10% over each time period. For example, the probability of dying during the first 6 months was increased from 0.182 to 0.2 in one analysis and decreased to 0.164 in another. The survival curves for the stent-only group for the base case and scenario analyses are presented in *Figures 13* and *14*. The survival curves show a significant increase in the hazard rate of mortality from 6 to 9 months. All patients have died by month 17.

Occlusion

Effectiveness

Occlusion and death are competing risks. If a study has sufficient sample size, competing risk survival analysis can be conducted to estimate the HR of occlusion for RFA plus stent compared with stent only. The comparative studies included in the systematic review were small and did not conduct competing risk time-to-occlusion analysis, nor did the studies conduct standard time-to-occlusion analysis. Two studies[28,29] included in the systematic review reported average time to occlusion. A random-effects meta-analysis was conducted in the systematic review (see *Chapter 4*, *Survival*) and the forest plot is shown in *Figure 10*. The pooled estimate of the difference in time to occlusion was 1.16 (95% CI −2.5 to 4.83) months, and this was modelled using a normal distribution, with parameters of a mean of 1.16 and a SE of 1.87.

In the base-case analysis, this estimate of difference in time to occlusion was applied to additional RFA procedures, as well as to the initial RFA procedure. Owing to a lack of evidence on the effectiveness of RFA for additional procedures, this estimate of effectiveness was halved for additional procedures in a scenario analysis.

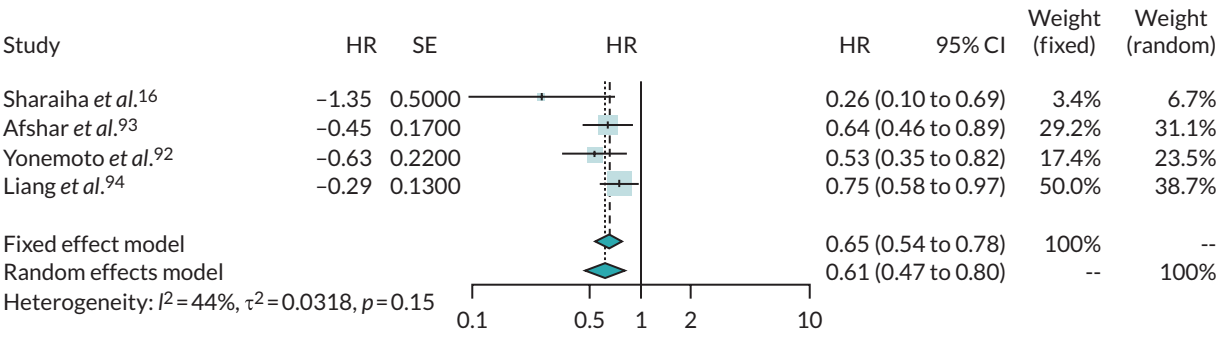

FIGURE 13 Random-effects meta-analysis of mortality HRs for chemotherapy vs. no chemotherapy.

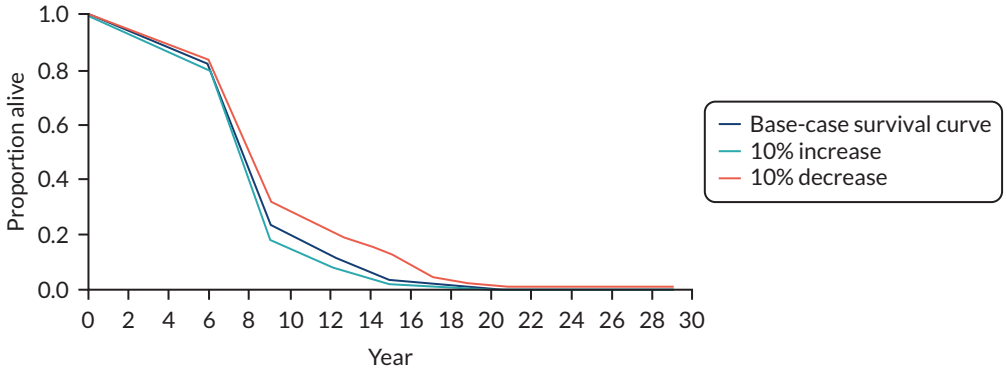

FIGURE 14 Survival curves for stent only: base case and sensitivity analyses (% changes in mortality).

Time to occlusion

The mean time to presentation with a blocked stent (i.e. occlusion) in the stent-only group was obtained from Yang *et al.*[29] The study by Yang *et al.*[29] was the only study, to the best of our knowledge, that provided the mean and 95% CI for time to occlusion in the stent-only group. The time to occlusion was 3.4 (95% CI 2.4 to 6.5) months. It was not clear from the paper how the 95% CI was calculated, as the bounds are not equidistant from the mean on the natural timescale or when converted to the log-scale. It is possible that this was a sample interval, which would be consistent with a follow-up period of 18 months, a mean of 3.4 months, a sample group size of 33 and with 82% of patients still alive at 6 months. Despite this, to model the mean time to occlusion, a normal distribution was used (mean = 3.4, SE = 1.05), as this would overestimate the uncertainty in the mean if the 95% CI actually reflects sample variation.

The probability of an occlusion for the stent-only group was modelled using a gamma distribution. The mean of the gamma distribution was derived from the normal distribution. The variance of the gamma distribution was 1.1, based on the assumption that the 95% CI, stated above, reflects sample variation. Exponential, gamma and log-normal distributions were considered for modelling time to occlusion. Parameter values for the distributions were sought to match the mean and variance of the distribution to a mean of 3.4 and a sample variance of 1.1. Although this was not possible for the exponential distribution, it was possible for the log-normal and gamma distributions. The gamma distribution was selected as it had a broader lower tail. The best fit distributions for each of the three distributions are presented in *Figure 15*. The parameters of the gamma distribution were derived from the mean and SE of time to occlusion. The gamma distribution parameters were α = 10.5 (shape) and

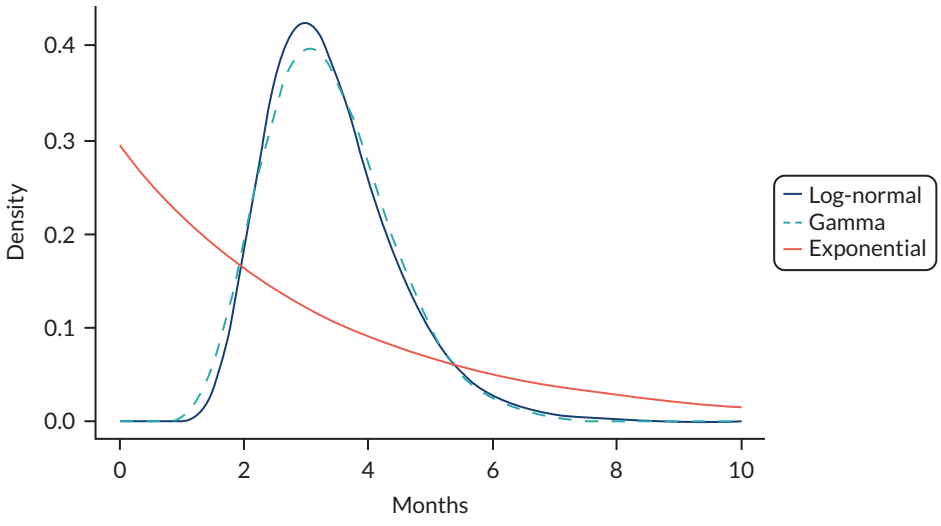

FIGURE 15 Density plots for exponential, gamma and log-normal distributions.

β = 3.1 (rate). The probability of occlusion in each cycle was the difference in the cumulative probability before and after each cycle obtained from the cumulative gamma distribution function. The probability of occlusion was conditional on survival in the model.

For RFA, mean time to occlusion was modelled as the sum of the time to occlusion in the stent-only group and the difference in time to occlusion between RFA and no RFA. The evidence for difference in time to occlusion is described in *Effectiveness*. Monte Carlo simulation ensured that the uncertainty in mean time to occlusion was propagated through the model. The gamma distribution has two parameters, which can be derived from the mean and variance of the distribution. The mean for the gamma distribution was obtained by adding the difference in mean time to occlusion to the stent-only group time to occlusion. The variance was assumed to be the standard deviation of the mean time to occlusion in the RFA group (1.17 months), obtained from Yang *et al.*,[29] again, assuming the variance to represent the sample variation.

Time to occlusion following a reintervention and subsequent reinterventions was assumed to be the same as following the initial intervention in the base-case analysis. However, the above approach to modelling time to occlusion, using a cumulative gamma distribution, cannot be adopted following subsequent reinterventions when a cohort modelling approach is used. The gamma distribution could be used only if microsimulation analysis was conducted and the time at which individuals experience a reintervention was tracked for each individual. As we conducted a cohort analysis, an exponential distribution was used to produce a constant risk of an occlusion each month following the first reintervention.

One of the problems with using an exponential distribution in this context is that the probability of an occlusion is far higher in the first and second months (roughly 0.25) following an intervention than when using the gamma distribution (0.0007 for month 1 and 0.07 for month 2), and this is a problem because this increases the cumulative probability of subsequent occlusions. The earlier some people have an occlusion, the greater the likelihood they will have yet another occlusion later on. To address this, it was assumed that the probability of an occlusion during the first month after a reintervention was zero. This is why a patient cannot remain in the 'extra reintervention' state in the model in *Figure 11*.

Bias adjustment

The clinical studies included in the systematic review were expected to be at risk of bias during the project planning stage. The reason for this was the small sample and often poor study design of published clinical studies, which often are non-randomised or have poor randomisation and may not adjust for confounding factors. Risk of bias produces uncertainty in the validity of the results, which is not reflected in the CI statistics reported for the effectiveness estimates. Risk of bias can mean that uncertainty in the cost-effectiveness of a technology is underestimated and the value of future research is underestimated. This section describes the methods used to adjust the HR of mortality and the difference in time to occlusion effect estimates for bias. The outcomes that were the object of the bias elicitation was the HR of mortality and the mean difference in time to occlusion. Every study included that informed the HR of mortality and mean difference in time to occlusion was included in the exercise.

As there were expected to be few comparative studies of RFA and the risk of bias was expected to be significant, the effect of bias on the cost-effectiveness and value of information results was investigated in two ways. The first way involved trying to quantify the bias elicited from clinical experts. The second way involved quantifying plausible degrees of bias based on reviewers' internal risk-of-bias assessments and external risk of bias from the clinical experts and study populations.

Expert elicitation of bias

Four clinical experts were included in the expert elicitation exercise. Three of the clinical experts (Irfan Ahmed, Manu Nayar and Kofi Oppong) were in the Advisory Group, and one of the clinical experts (SP) was in the Advisory Group and was an author for the project. A review of bias adjustment methods by Verde *et al.* was identified.[95] The most practical method for adjustment of individual elements of internal and external bias of individual study results before a meta-analysis is conducted was considered to be that of Turner *et al.*[96] The method by Turner *et al.*[96] involved three steps. The first step was a consideration of the presence of bias-related factors in the studies. The second step was a group meeting of the clinical experts to discuss the bias elements. The third step was a qualitative assessment of the level of each bias on the outcome statistic of interest (i.e. HR of mortality, difference in time to occlusion) for the populations of interest (i.e. advanced bile duct cancer, advanced pancreatic cancer) and a marking on a scale to quantify that bias (*Figures 16* and *17*, and see *Appendix 7*). The internal bias elements included were selection bias, performance bias, attrition bias and detection bias. The external bias elements included were population bias, intervention bias, control bias and outcome bias.

Unfortunately, owing to late finalisation of the comparative studies to be included in the systematic review, the tight timelines from the end of the review to the end of the project and difficulty in arranging for the clinical experts to be available at the same time to discuss the bias results, the step 2 discussion did not happen. The clinical experts also needed more guidance on the assessment and marking of bias. In addition, the review update included a study that could not be reviewed by the clinical experts because of project time constraints.

The result was that there was only one response where the bias quantification could be assessed as consistent with the assessed bias factors in each study, and this did not include an assessment of the study by Gao *et al.*[28] Where only a qualitative assessment was provided, a quantitative value was inferred. A value of 1 indicates no bias. A value of 0.6 indicates that bias may reduce the hazard rate of mortality with a HR of 0.6 when, in fact, the intervention has no effect (HR 1). A range such as 0.85–0.6 indicates bias (0.6) more likely to favour RFA than the comparator. The qualitative and quantitative assessment of bias from this response for the HR outcome for the bile duct cancer population is presented in *Table 3*.

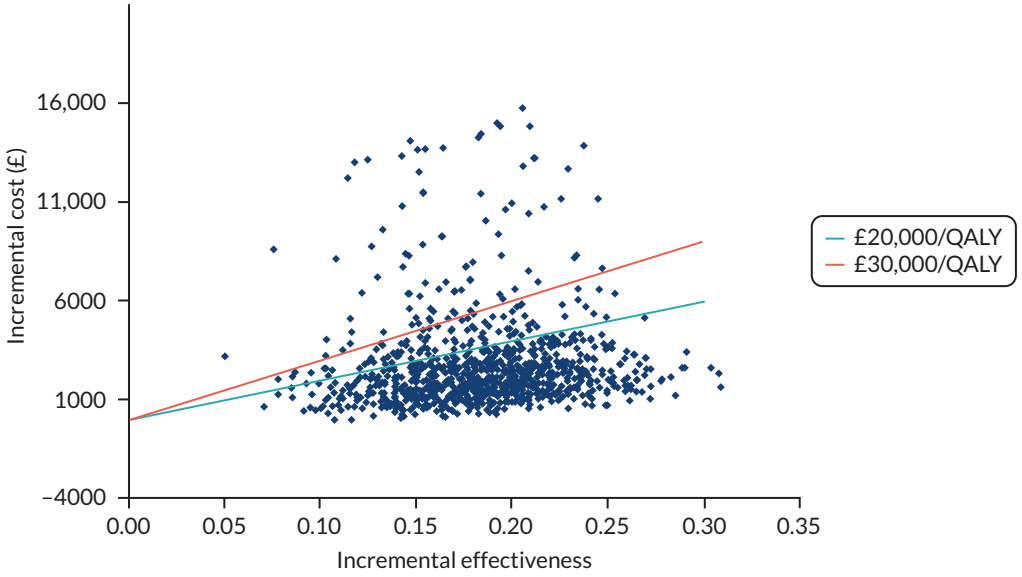

FIGURE 16 Cost-effectiveness plane for RFA vs. no RFA.

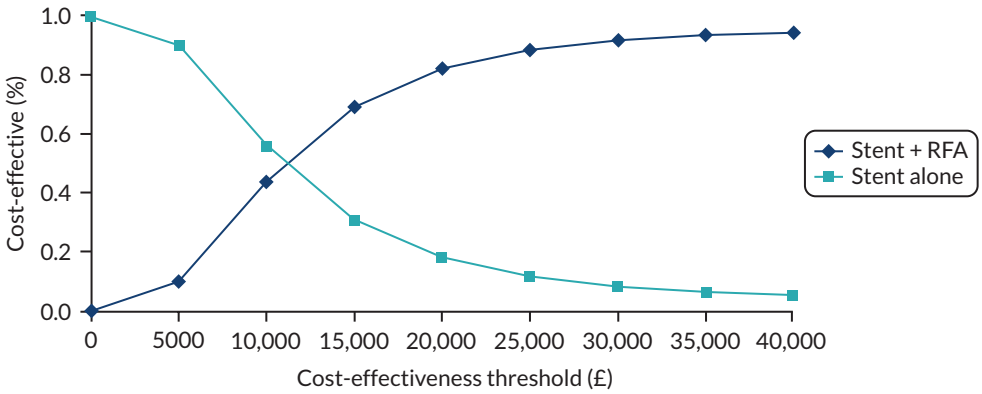

FIGURE 17 Cost-effectiveness acceptability curves for RFA and no RFA.

TABLE 3 Level of bias from a clinical expert assessment

	Yang *et al.*[29]		Dutta *et al.*[34]		Sharaiha *et al.*[16]	
Assessment	**Bias**	**Value**	**Bias**	**Value**	**Bias**	**Value**
Internal						
Selection	None	1	High	0.85–0.6	Medium	0.7–0.7
Performance	None	1	Medium	0.95–0.84	Medium	0.7–0.7
Attrition	None	1	Medium	0.8–0.75	Low	0.9–0.9
Detection	None	1	Medium	0.76–0.76	Medium	0.76–0.76
Other	None	1	None	1	None	1
External						
Population	None	1	Medium	0.8–0.1	Medium	0.76–0.76
Intervention	None	1	None	1	None	1
Control	None	1	None	1	None	1
Outcome	None	1	None	1	None	1

The relationship between the qualitative assessment and quantitative assessment in Turner *et al.*[96] was based on the percentage increase in the SE of the log-odds ratio,[96] and it assumed a rare occurrence of events. Bias assessment for the log-HR and the difference in time to occlusion requires an appropriate scale on which to mark the degree of bias (see *Appendix 7*). The sampling variances of studies with a small sample size from the included studies were used to derive scales comparable to the log-odds ratio scale used in Turner *et al.*[96] and comparable bias quantification guidance [e.g. low (0.92–1)] for the log-HR and the difference in time to occlusion (see *Appendix 7*). Bias was considered either additive or proportional to the outcome. The bias values are presented in *Table 3*.

The effectiveness statistics were adjusted using the formulae presented in Turner *et al.*[96]

No risk of bias was identified for Yang *et al.*[29] for either the HR of mortality or difference in time to occlusion. For the HR of mortality, the bias-adjusted statistic was 0.28 (95% CI: 0.17 to 0.48), and this compares with 0.26 (95% CI 0.16 to 0.42) from a HR meta-analysis including Yang *et al.*,[29] Dutta *et al.*[34] and Sharaiha *et al.*[16] Yang *et al.*[29] had the greatest weight in the meta-analysis unadjusted for bias. As no risk of bias was identified for Yang *et al.*,[29] it increased its weight in the bias-adjusted meta-analysis.

Excluding Gao *et al.*,[28] only Yang *et al.*[29] reported a difference in stent patency. The between-study variance estimate from the meta-analysis including Gao *et al.*[28] was added to the variance of the effect estimate in Yang *et al.*[29] to ensure that the uncertainty in the average effect estimate was adequately captured.

Reviewer risk-of-bias assessment

A reviewer risk-of-bias assessment was conducted because of the limitations of the expert elicitation bias conducted. There were two RCTs[28,29] and two comparative observational studies.[16,34] The risk of bias for the RCTs was assessed using the Risk of Bias 2.0 tool,[24] and the risk of bias for the comparative observational studies was assessed using the ROBINS-I tool.[25]

The risk-of-bias assessments using these tools were mapped to the bias categories used in Turner *et al.*[96] and an estimate of bias at the high end of the range was adopted. For example, a medium risk of bias range for the HR was assumed to be 0.76–0.92. If the risk of bias using the ROBINS-I tool was moderate, then the risk of bias for a bias category was assumed to be 0.76.[25] The objective was to obtain a bias estimate on the high side. Likewise, the assessment 'some concern' from the Risk of Bias 2.0 tool was assumed to be moderate bias with a value of 0.76.[24] There is no 'no bias' option. The lowest assessment is 'low' risk of bias. For 'low' risk of bias, a very small bias effect was assumed of 0.95.

The Risk of Bias 2.0 and ROBINS-I tools assess the risk of internal bias.[24,25] The risk of external bias for the population obtained from the clinical expert response was added to the reviewer risk of internal bias assessment. No assumption was made about the direction of bias. It was assumed that the risk of bias would increase the CIs for the effect estimate, but not change the estimated effect. The bias values are reported in *Table 4*.

The Risk of Bias 2.0 and ROBINS-I tools do not assess whether the biases are additive in nature or proportional to the effect size, and so two bias-adjusted estimates were produced, one assuming that biases are additive and the other assuming that the biases are proportional. Assuming proportional bias, the difference in time to occlusion was 0.58 (95% CI −2.68 to 3.85), and this compares with the results of the meta-analysis presented in *Chapter 4*, *Figure 10* of 1.16 (95% CI −2.50 to 4.83). Assuming additive bias, the difference in time to occlusion was 1.18 (95% CI −2.49 to 4.86).

TABLE 4 Level of bias inferred from reviewer assessment

Assessment	Yang *et al.*[29]	Dutta *et al.*[34]	Sharaiha *et al.*[16]	Gao *et al.*[28]
Internal				
Selection	0.95–0.95	0.6–0.6	0.95–0.95	0.6–0.6
Performance	0.7–0.7	0.95–0.95	0.95–0.95	0.95–0.95
Attrition	0.95–0.95	0.95–0.95	0.95–0.95	0.95–0.95
Detection	0.95–0.95	0.95–0.95	0.95–0.95	0.95–0.95
Other	0.7–0.7	1	0.6–0.6	0.7–0.7
External				
Population	1	0.76–0.76	0.76–0.76	1
Intervention	1	1	1	1
Control	1	1	1	1
Outcome	1	1	1	1

Assuming proportional bias, the hazard rate of mortality was 0.44 (95% CI 0.24 to 0.8), and this compares with 0.34 (95% CI 0.21 to 0.55) from the HR meta-analysis presented in *Chapter 4*, *Survival*, and the estimate of 0.28 (95% CI 0.17 to 0.48) from the expert bias adjustment. Assuming additive bias, the hazard rate of mortality was 0.32 (95% CI 0.15 to 0.69).

The additive bias method hardly affected the mean HR of mortality effectiveness estimate. The CI of the HR was wider. The difference in stent patency CI from the additive bias-adjusted estimate was very similar to the unadjusted CI, and this is because there were only two studies[28,29] in the random-effects meta-analysis and because there is significant statistical heterogeneity. Although the additive bias approach increased the individual SEs of the effectiveness estimates of the trials, this result also reduced the estimate of the between-study variance, and, overall, the CIs were similar.

The proportional bias method reduced the effectiveness estimate for both time to occlusion and HR of mortality and increased the CIs. The proportional bias method, therefore, represents a high estimate of bias and the additive bias method represents a low estimate of bias.

The limitations of the reviewer assessment of bias are summarised as follows: the reviewers are not experts in this clinical area; the reviewers use a risk-of-bias assessment tool that has less flexibility in the grading of bias than in the Turner *et al.*[96] risk-of-bias assessment; the reviewers' assessment results in a categorical assessment of bias, which then needed to be mapped onto the bias scale; the reviewers assessed internal validity, not external validity; and the reviewers' did not assess proportional or additive bias. Despite these limitations, a crude assessment of the potential impact of bias on the results could determined.

Adverse events

Relative risks

The relative risks of cholangitis, cholecystitis and pancreatitis were estimated from meta-analyses, including a subset of studies included in the meta-analyses of AEs reported in *Chapter 4*, *Adverse events*. The reason the estimates used in the economic model were different from the estimates reported in *Chapter 4*, *Primary outcomes* is that the AE meta-analyses were updated at a late stage of the project. The relative risks reported here are less precise, but both the clinical effectiveness and cost-effectiveness results report considerable uncertainty in their estimates. The estimates used in the base-case and scenario economic analyses were as follows: the relative risk of cholecystitis for RFA compared with no RFA was 7.07 (95% CI 1.31 to 38.26) and the relative risk of pancreatitis for RFA compared with no RFA was 2.08 (95% CI 0.55 to 7.89). The very wide 95% CIs reflects the very small numbers of events and sample sizes. No difference in cholangitis risk was assumed in the base case. The base-case analysis was re-run with the updated AE relative risks, as reported in *Chapter 4*, *Primary outcomes*, and the relative risk of cholecystitis for RFA compared with no RFA was 11.47 (95% CI 2.28 to 57.66), the relative risk of pancreatitis for RFA compared with no RFA was 1.34 (95% CI 0.55 to 3.25) and the relative risk of cholangitis for RFA compared with no RFA was 1.15 (95% CI 0.63 to 2.12).

In the base case, the relative risks were modelled on a log-scale as normal distributions with the following parameters: a mean of 1.96 and a SE of 0.86 for cholecystitis, and a mean of 0.73 and a SE of 0.68 for pancreatitis.

Adverse event risk

The risk of an AE was modelled each time a stent was inserted with or without RFA. The cost was a one-off cost. Based on clinical expert opinion, the occurrence of AEs was post procedure or shortly after discharge. There were few to no data on the time to AE or recurrence of AEs in the included studies. The AEs were modelled as one-off events when a stent was inserted.

The risks of cholangitis, cholecystitis and pancreatitis were estimated by conducting meta-analyses of AEs risks in the stent-only groups.

In the base-case analysis and scenario analyses, in the stent-only group, the risk of cholangitis was 0.077 (SE 0.089), the risk of cholecystitis was 0.00016 (SE 0.0015) and the risk of pancreatitis was 0.015 (SE 0.019). These risks were modelled as beta distributions where the parameters of the beta distribution were derived from the means and SEs of the risk estimates.

The studies included in the AE meta-analyses were updated late in the project. The revised mean estimates were 0.0495 (SE 0.03693) for cholangitis, 0.000041 (SE 0.000617) for cholecystitis and 0.03127 (SE 0.02458) pancreatitis, and these were included in a scenario analysis for the base case.

The risk of haemobilia was assumed to be 5%, which was obtained from clinical expert opinion.

Health utility

A focused literature review was conducted to identify utility values for patients with locally advanced or metastatic pancreatic cancer and cholangiocarcinoma, for stent or RFA procedures in these populations and for AEs, such as cholangitis, in these populations.

Web of Science (Clarivate) and EMBASE (Ovid) were searched. The search term 'QALY OR health utility*' was combined with free-text terms for the cancer, 'pancreatic cancer OR pancreatic carcinoma OR cholangiocarcinoma OR bile duct cancer OR biliary tract'; free-text terms for cancer type, 'locally advanced OR metastatic'; and a term for the UK or US context (e.g. 'UK'). Searches were limited to English-language publications and excluded neuroendocrine tumours or resectable (operable) cancers.

The Cost-Effectiveness Analysis Registry was searched for health utilities using the terms 'biliary', 'pancreas' and 'cancer'.

Limited utility data were identified. A set of utilities favourable to RFA was defined and a set of utilities conservative to RFA (i.e. favourable to stent only) was defined, and these were used in two scenario analyses. The scenarios are reported in *Table 5*.

An average utility estimate of 0.61 for people living with unresectable bile duct cancer was used in the base-case analysis, which is conservative to RFA. A utility estimate of 0.71 was used in a scenario analysis favourable to RFA. Martinez *et al.*[97] used an EuroQol-5 Dimensions (EQ-5D) utility estimate for delimited, locally advanced and metastatic pancreatic cancer, obtained from Heiberg *et al.*,[98] of 0.61 for an economic evaluation of stents in patients with locally advanced or metastatic pancreatic cancer presenting with biliary obstruction. Roth and Carlson[99] used a utility estimate for advanced hepatocellular carcinoma, obtained from Connock *et al.*,[100] of 0.71 for an economic evaluation of chemotherapy regimens in patients with advanced biliary tract cancer, and this estimate was derived by mapping Functional Assessment of Cancer Therapy – General scores to time trade-off values.

A utility estimate of 0.18 was assumed for a procedure for a duration of 2 days in the base-case analysis and a procedure for a duration of 3 days in a scenario analysis favourable to RFA. Martinez *et al.*[97] used an EQ-5D utility estimate of 0.18 for patients receiving ERCP, obtained from Jeurnink *et al.*,[101] for patients receiving ERCP and metal or plastic stents, and it was assumed to last for 2 days. No additional specific disutility for symptoms leading to the reintervention was modelled.

No reliable utility estimate was found for AEs in the study populations. A high estimate of 0.57 was used in the base-case analysis and a low estimate of 0.5 was used in a scenario analysis favourable to RFA. An AE was assumed to last for 2 weeks.

TABLE 5 Health utility data for health states and procedures

Condition	RFA conservative	RFA favourable	Source	Time period
Locally advanced cancer	0.61	0.71	0.61 from Martinez *et al.*[97] who reference Heiberg *et al.*[98] (utility study population: delimited, locally advanced, metastatic pancreatic cancer; utility method: EQ-5D-3L index) 0.71 from Roth and Carlson[99] who reference Connock *et al.*[100] (utility study population: advanced hepatocellular carcinoma; utility method: mapping FACT-G scores to TTO values)	Per cycle
Stent/RFA procedure	0.18 for 2 days	0.18 for 3 days	0.18 for 3 days from Martinez *et al.*[97] who reference Jeurnink *et al.*[101] EQ-5D-3L (utility study population: patients receiving ERCP; utility EQ-5D	2 or 3 days
AE[a]	0.57	0.5	Assumption	2 weeks
State				
Reintervention: per month	0.046	0.054	Reintervention (per year)/12	
Reintervention: per month	0.553	0.646	Derived from *Equation 2*	
Post-reintervention: per month	0.051	0.059	Post-reintervention (per year)/12	
Post-reintervention: per month	0.61	0.71	The locally advanced cancer utilities	

EQ-5D-3L, EuroQol-5 Dimensions, three-level version; FACT-G, Functional Assessment of Cancer Therapy – General; TTO, time trade-off.
a Assumes a probability of an AE is 0.02.

The QALYs for the model states are also reported in *Table 5*. A cycle length was 1 month. The QALY gain for a reintervention was a weighted average. For example, for the RFA favourable utility scenario, the QALY gain for a 1-month cycle involving a reintervention was:

$$QALY_{R1} = \frac{3}{365} \times 0.18 + \frac{14}{365} \times 0.65 \times prob_{AE} + \frac{13}{365} \times 0.71 \times prob_{AE} + \frac{27}{365} \times 0.71 \times (1 - pron_{AE}), \quad (2)$$

where $prob_{AE}$ is the probability of an AE. The QALYs for the 'post-reintervention' and 'post extra reintervention' states was the utility for locally advanced cancer over a 1-month period.

Resource use and unit costs

The resource use in the model was limited to the stent and RFA procedures, chemotherapy regimens, treatment for intraoperative complications and treatment for AEs. The unit costs were obtained from the 2018/19 NHS reference costs.[102] The unit costs and the NHS reference cost Healthcare Resource Group (HRG) codes associated with stent insertion are reported in *Table 6*, the total procedure-related costs associated with stent placement alone are reported in *Table 7* and the total procedure-related costs associated with stent insertion with RFA are reported in *Table 8*.

TABLE 6 Endoscopic stent insertion: data sources and unit costs

Parameter	Cost (£)	Source	Description
Day case procedure, no complications	842	NHS reference costs 2018/19102	FE10A Endoscopic Insertion of Luminal Stent into Gastrointestinal Tract with CC Score 7 +; Day Case
Elective inpatient procedure, complications	5320	NHS reference costs 2018/19102	FE10A Endoscopic Insertion of Luminal Stent into Gastrointestinal Tract with CC Score 7 +; Elective inpatient
Base-case total	1289.80		Assuming 10% inpatient stays due to complications
Higher complications scenario	1737.60		Assuming 20% inpatient stays due to complications
Lower complications scenario	1065.90		Assuming 5% inpatient stays due to complications

TABLE 7 Total intervention costs: stent-only arm/reintervention: data sources and unit costs

Resource unit	Unit cost (£)	Source	Description
Diagnostic ERCP	1515	NHS reference costs 2018/19[102]	GB11Z Diagnostic Endoscopic Retrograde Cholangiopancreatography; Elective
Endoscopic stent insertion	1290	NHS reference costs 2018/19[102]	FE10A Endoscopic Insertion of Luminal Stent into Gastrointestinal Tract with CC Score 7+; 90% Day Case and 10% Elective procedures
Total	2805		

TABLE 8 Radiofrequency and stent insertion: data sources and unit costs

Parameter	Cost (£)	Source	Description
Diagnostic ERCP	1515	NHS reference costs 2018/19[102]	GB11Z Diagnostic Endoscopic Retrograde Cholangiopancreatography; Elective
RFA catheter	1203	Navaneethan *et al.*[103]	Cost of a Habib Endo HPB single-use catheter. Original cost: US(2017)$1495 (Navaneethan *et al.*[103]), converted to GBP (£2017) and inflated to 2019 prices using the NHSCII (PSSRU 2019)[104]
Endoscopic stent insertion	1290	NHS reference costs 2018/19[102]	FE10A Endoscopic Insertion of Luminal Stent into Gastrointestinal Tract with CC Score 7+; 90% Day Case and 10% Elective procedures
Total	4007		

NHSCII, NHS Cost Inflation Index; PSSRU, Personal Social Services Research Unit.

The occurrence of stent and RFA procedures was determined by the parameters in the model. The unit cost of stent placement (£2804.80) was assumed to comprise diagnostic ERCP and endoscopic stent insertion, with 90% of patients having a stent insertion as a day case procedure and 10% of patients staying overnight because of complications. The assumption that 10% of patients stay overnight in hospital following an intervention is based on expert opinion, which stated that < 10% of patients would do so. It was also assumed that patients who experienced complications had an intervention with the highest complexity and comorbidity score in the tariff (i.e. a CC score of 7+), which had a mean length

of stay of 8 days. The percentage of patients who had an intervention with complications that required hospital stay was varied in sensitivity analysis. This contrasts with the assumption made in the economic model for the use of stents for the management of biliary obstruction in people with unresectable pancreatic cancer in the National Institute for Health and Care Excellence (NICE) Guideline NG85, Chapter 12,[105] where the mean length of stay for self-expanding metal stent is assumed to vary from 2.5 days to 3.5 days. The assumption used in NICE Guideline NG85[105] was based on evidence from a RCT.[106]

The unit cost of RFA and stent placement (£4007) was assumed to be the unit cost of stent placement plus the cost of a RFA catheter. It was assumed that the standard endoscopic RFA procedure is performed using a single-use Habib EndoHPB catheter. The cost of the catheter was obtained from the literature, and converted to 2019 GBP.[103] The unit costs and the NHS reference cost HRG codes are reported in *Table 8*.

An assumption was made in the model about the proportion of patients receiving chemotherapy. Patients in the cohort receiving chemotherapy incurred a chemotherapy cost every month for 24 months, except for months when a reintervention occurred.

For patients suitable for chemotherapy, the treatment differs according to cancer type. In cholangiocarcinoma, following the ABC-02 trial,[107] cisplatin combined with gemcitabine is administered at in first 2 weeks of a 3-week cycle.[107]

Drug costs were derived from the drugs and pharmaceutical electronic market information tool (2019/20) for 2019.[108] Chemotherapy delivery costs were derived from the 2018/19 NHS reference costs.[102] The unit costs and sources are reported in *Table 9*.

The AEs that may be associated with stent placement or RFA that were most commonly reported in the systematic review were:

- pancreatitis
- cholangitis
- cholecystitis
- haemobilia
- stent migration/occlusion.

TABLE 9 Monthly chemotherapy unit costs

Chemotherapy regimens			
Parameter	**Cost (£)**	**Source**	**Description**
Cholangiocarcinoma first-time chemotherapy delivery	458	Valle *et al.*,[107] eMIT 2019/20,[108] NHS reference costs 2018/19[102]	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance of a gemcitabine plus cisplatine regimen. Doses and cycles based on the ABC-02 trial.[107] 2019 prices obtained from eMIT 2019/20[108]
Cholangiocarcinoma subsequent chemo-therapy monthly cost	580	Valle *et al.*,[107] eMIT 2019/20,[108] NHS reference costs 2018/19[102]	Gemcitabine plus cisplatine regimen. Doses and cycles based on the ABC-02 trial.[107] 2019 prices obtained from eMIT 2019/20[108]

eMIT, electronic market information tool.

Haemobilia is described here as a complication of the procedure. Pancreatitis, cholangitis and cholecystitis are described here as AEs that could occur after hospital discharge.

Pancreatitis, cholangitis and cholecystitis are generally assessed in an inpatient setting and can lead to patients staying for 24–48 hours in the hospital. The HRG code used reflects the cost of a hospital day case or an ordinary stay, assuming that the adverse effects are caused by an infection in the local area. The risk of an AE was obtained from the clinical evidence (see *Chapter 4*, *Adverse events*). The unit cost associated with haemobilia and the other AEs are reported in *Table 10*.

The cost of a procedure, a complication and an AE are all assumed to be incurred during the month in which a reintervention takes place. The cost of the resinsertion state for a stent and RFA procedure is:

$$Cost_{RI} = £1515 + (1 - prob_{comp}) \times £842 + prob_{comp} \times £5,320 + prob_{AE} \times £498. \quad (3)$$

Summary of model parameters

A summary of the model parameters is provided in *Table 11*.

TABLE 10 Postoperative AEs: data sources and unit cost

Parameter	Cost (£)	Source	Description
Cholangitis/pancreatitis/ cholecystitis requiring inpatient stays	498.00	NHS reference costs 2018/19[102]	WH07E Infections or Other Complications of Procedures, without Interventions, with CC Score 4+; Day Case

TABLE 11 Summary of model parameters

Parameter	Value (95% CI)	Distribution	Source
Clinical parameter *Survival HR of RFA*			
Base case	0.34 (0.2 to 0.55)	Log-normal	Meta-analysis
Additive bias	0.32 (0.15 to 0.7)	Log-normal	Meta-analysis
Proportional bias	0.44 (0.24 to 0.8)	Log-normal	Meta-analysis
Survival HR of chemotherapy			
Base case	0.61 (0.47 to 0.8)	Log-normal	Meta-analysis
Proportion receiving chemotherapy			
Base case	20%		Expert opinion
Favourable case	40%		Assumption
Difference in stent patency months	for RFA		
Base case	1.16 (−2.5 to 4.8)	Normal	Meta-analysis
Additive bias	1.18 (−2.49 to 4.86)	Normal	Meta-analysis
Proportional bias	0.58 (−2.68 to 3.85)	Normal	Meta-analysis

TABLE 11 Summary of model parameters (*continued*)

Parameter	Value (95% CI)	Distribution	Source
AE risks stent only			
Cholangitis	0.077 (SE 0.089)	Beta	Meta-analysis
Pancreatitis	0.015 (SE 0.019)	Beta	Meta-analysis
Cholecystitis	0.00016 (SE 0.0015)	Beta	Meta-analysis
Intraoperative haemobilia	0.05		Expert opinion
Utility *Locally advanced cancer*			
Base case	0.61		Martinez *et al.*;[97] Heiberg *et al.*[98]
Favourable case	0.71		Roth and Carlson *et al.*;[99] Connock *et al.*[100]
Moderately low	0.5		Assumption
Very low	0.4		Assumption
Reintervention			
Base case	0.18 for 2 days		Martinez *et al.*;[97] Jeurnink *et al.*[101]
Favourable case	0.18 for 3 days		Martinez *et al.*;[97] Jeurnink *et al.*[101]
AEs			
Base case	0.57 for 2 weeks		Assumption
Favourable case	0.5 for 2 weeks		Assumption
Moderately low	0.46 for 2 weeks		Assumption
Very low	0.36 for 2 weeks		Assumption
Costs *Endoscopic stent insertion*			
Day case procedure, no complications	£842		NHS reference costs 2018/19[102]
Elective inpatient procedure, complications	£5320		NHS reference costs 2018/19[102]
Diagnostic ERCP	£1515		NHS reference costs 2018/19[102]
RFA catheter	£1203		Navaneethan et al.[103]
Stent alone/reintervention	£2805		
RFA plus stent insertion	£4007		
Chemotherapy regimens			
Cholangiocarcinoma first time chemotherapy delivery	£458		Valle *et al.*,[107] eMIT 2019/20,[108] NHS reference costs 2018/19[102]
Cholangiocarcinoma subsequent chemotherapy monthly cost	£580		Valle *et al.*,[107] eMIT 2019/20,[108] NHS reference costs 2018/19[102]
Postoperative AEs			
Cholangitis/pancreatitis/ cholecystitis requiring inpatient stays	£498		NHS reference costs 2018/19[102]

eMIT, electronic market information tool.

Incremental cost-effectiveness analysis

The outcome of the cost-effectiveness analysis is incremental cost per QALY gained and this is calculated as the difference in the total discounted cost between the RFA plus stent group and the stent-only group, divided by the difference in the total discounted utility between the RFA plus stent group and the stent-only group:

$$Incremental\ cost\ per\ QALY = \frac{C_{RFA} - C_{noRFA}}{U_{RFA} - C_{noRFA}}. \quad (4)$$

The incremental cost per QALY gained is the incremental cost-effectiveness ratio (ICER). If the ICER of a health technology is less than the accepted cost-effectiveness threshold, then the health technology is considered to be cost-effective and the decision-maker is willing to adopt the technology. The £20,000 per QALY and £30,000 per QALY cost-effectiveness thresholds recommended by NICE are used as reference cost-effectiveness thresholds in this report.[109]

Analysis of uncertainty

Probabilistic sensitivity analysis

The investigation of how much uncertainty in the evidence influences decision uncertainty, that is uncertainty in whether or not a health-care technology should be adopted, is a key part of economic evaluation. Where evidence is available, we specify probability distributions to represent the uncertainty in the effectiveness estimates. Parameter values for these distributions have been reported in each section. Monte Carlo simulation is then used in the analysis sampling from every distribution 1000 times to produce a joint distribution of the incremental costs and effects of RFA compared with no RFA. All analyses of uncertainty, including value of information, were performed using the TreeAge Pro software.

The production of statistics from the Monte Carlo simulation is probabilistic sensitivity analysis. The sampled incremental cost and incremental QALY estimates are presented on a cost-effectiveness plane. The net benefit of adopting a health technology is calculated for different cost-effectiveness thresholds using the following equation:

$$Net\ benefit = threshold\left(e.g.\frac{£20,000}{QALY}\right) \times QALYs - cost(£). \quad (5)$$

The proportion of the simulation estimates where the intervention has the highest net benefit represents the probability that the intervention is cost-effective. The probability that an intervention is cost-effective at different cost-effectiveness thresholds is presented in a cost-effectiveness acceptability curve (CEAC).[109]

Uncertainty in effectiveness parameters

Some evidence on uncertainty in the effectiveness estimate, as well as a mean estimate, is essential to conduct probabilistic sensitivity analysis that has value in a cost-effectiveness analysis of a health technology. If there is only one study that provides evidence on effectiveness and that study is small, then there will be no evidence on the between-study variance that may arise from conducting several small studies. In that situation, some measure of between-study variance would need to be assumed and sensitivity analysis conducted on the between-study variance value.

For the HR of mortality, there were four studies[16,92–94] included in the meta-analysis. For stent patency, there were only two studies[28,29] and the estimate of between-study variance was high. A lot of uncertainty was reflected in the CI for difference in stent patency.

Uncertainty in the validity of study results is not reflected in the CI or SE of an effectiveness estimate. Consequently, basic estimates of bias were obtained, as described in Bias adjustment, to conduct bias-adjusted meta-analyses, and these provided a high estimate of uncertainty in the effectiveness parameters.

Scenario analyses

Where there is insufficient evidence to inform a probability distribution that can adequately represent the uncertainty in a parameter estimate, then the effect of assuming different values for the parameters on the economic results can be explored. An example is the paucity of evidence informing health utility in this population. This paucity of evidence led us to create favourable and conservative (with respect to RFA) sets of health utility values. The uncertainty in the effect of bias on the effectiveness estimates is another example. The full set of scenario analyses is presented in *Table 12*.

TABLE 12 Scenario analyses

Scenario	Parameter value	Base-case value
A: lower stent patency for secondary stents	Stent patency in stent group: mean 1.7, SE 0.505	Stent patency in stent group: mean 3.4, SE 1.01
	Difference in stent patency (RFA vs. no RFA): mean 0.76, SE 0.73	Difference in stent patency (RFA vs. no RFA): mean 1.52, SE 1.46
B: zero RFA effectiveness in increasing stent patency and zero uncertainty	Difference in stent patency (RFA vs. no RFA): mean 0, SE 0	Difference in stent patency (RFA vs. no RFA): mean 1.16, SE 1.46
C: 20% complications	Probability of a complication requiring inpatient stay: 20%	Probability of a complication requiring inpatient stay: 10%
D: 5% complications	Probability of a complication requiring inpatient stay: 5%	Probability of a complication requiring inpatient stay: 10%
E: low reviewer bias adjustment	HR (mortality): mean 0.32, 95% CI 0.15 to 0.69	HR (mortality): mean 0.34, 95% CI 0.21 to 0.55
	Difference in stent patency: mean 1.18, 95% CI −2.49 to 4.86	Difference in stent patency: mean 1.16, 95% CI −2.5 to 4.83
F: high reviewer bias adjustment	HR (mortality): mean 0.44, 95% CI 0.24 to 0.8	HR (mortality): mean 0.34, 95% CI 0.21 to 0.55
	Difference in stent patency: mean 0.58, 95% CI −2.68 to 3.85	Difference in stent patency: mean 1.16, 95% CI −2.5 to 4.83
G: expert bias adjustment without the Gao *et al.*[28] study	HR (mortality): mean 0.31, 95% CI 0.14 to 0.7	HR (mortality): mean 0.26, 95% CI 0.16 to 0.42
	Difference in stent patency: mean 3.4, 95% CI −1.4 to 8.2	Difference in stent patency: mean 3.4, 95% CI −1.4 to 8.32
H: RFA favourable utilities	Locally advanced cancer utility: 0.71	Locally advanced cancer utility: 0.61
	AE utility: 0.5	AE utility: 0.57
I: moderately low advanced cancer utility	Locally advanced cancer utility: 0.5	Locally advanced cancer utility: 0.61
	AE utility: 0.46	AE utility: 0.57
J: very low advanced cancer utility	Locally advanced cancer utility: 0.4	Locally advanced cancer utility: 0.61
	AE utility: 0.36	AE utility: 0.57
K: greater survival for stent-only intervention	Number dying each period decreased by 10%	Yang *et al.*[29] stent-only survival curve

continued

TABLE 12 Scenario analyses (*continued*)

Scenario	Parameter value	Base-case value
L: lower survival for stent-only intervention	Number dying each period increased by 10%	Yang *et al.*[29] stent-only survival curve
M: greater proportion of patients receive chemotherapy	40%	20%
N: lower proportion of patients receive chemotherapy	10%	20%

The scenarios can be grouped into six broad categories:

1. stent patency
2. stent and RFA cost
3. bias
4. health utility
5. survival
6. chemotherapy.

Stent patency

Stent patency has a significant effect on cost because of the significant cost incurred for a reintervention. Despite the short life expectancy of these patients, around 67% of patients are modelled to have at least one reintervention, and many have two or more. There is no limit on the number of reinterventions in the model, and so the shorter the stent patency duration the more reinterventions there will be. If RFA increases survival, then there may also be an increase in stent reinsertions, and this will not be the case if RFA also increases stent patency by a certain degree. There is risk of bias associated with the stent patency effectiveness estimate, and this is covered in the bias category.

There was considerable uncertainty in the effect estimate for stent patency. The same stent patency for no RFA and stent patency effectiveness was assumed for subsequent reinterventions as for the first intervention. There is a lack of evidence for stent patency and the effectiveness of RFA in secondary RFA. A scenario analysis was designed to halve the duration of stent patency in a secondary RFA population in the stent-only group and halve the effectiveness of RFA in increasing stent patency in a secondary RFA population (see *Table 12*, scenario A).

Given the significance of stent patency on cost, a scenario was specified where the effectiveness of RFA on stent patency was zero and there was no uncertainty in this value (see *Table 12*, scenario B). The purpose of this scenario was to explore the effect of non-inferiority in stent patency on the cost-effectiveness of RFA.

Stent and radiofrequency ablation cost

The effect that increased survival has on the number of reinterventions is important because of the significant cost associated with a reintervention. The cost includes both the cost of a stent and RFA intervention and the cost of treating complications. The effect on the results of varying the cost of stent insertion and RFA was explored by increasing the probability of a complication to 20% (see *Table 12*, scenario C) and reducing the probability of a complication to 5% (see *Table 12*, scenario D).

Bias

The clinical studies identified were expected to be at risk of bias. Consequently, estimates of bias and the effect on the effectiveness estimates were sought. Two scenario analyses (see *Table 12*, scenarios E and F) with different methods of converting reviewer bias assessment of included studies into quantitative values and a scenario (see *Table 12*, scenario G) representing a clinical expert's assessment

of bias were specified to explore the effect of bias on the results. The results of the clinical expert bias assessment were compared with the base-case analysis excluding the Gao *et al.*[28] evidence, as that evidence was identified in the review update.

Health utility

The most important health utility value is the utility of living with advanced cancer, as this determines the value of additional survival that may be a result of RFA. There were limited data on the health utility for advanced bile duct cancer and advanced pancreatic cancer, and for AEs and the duration of events. Consequently, favourable and conservative sets of utilities were produced with respect to RFA. The conservative set was used in the base-case analysis. The favourable set was used in scenario H (see *Table 12*). In addition, lower utilities for cancer were assumed in alternative analyses (see *Table 12*, scenarios I and J).

Survival

Since some patients in the model received chemotherapy and others did not, and some patients received RFA and others did not, survival differed across these groups. The survival of patients in the stent-only group and not receiving chemotherapy was based on one study.[29] High and low survival estimates were assumed in scenario analyses (see *Table 12*, scenarios K and L).

Chemotherapy

Chemotherapy in this population is associated with longer life expectancy, and this may have particular importance in the model in terms of increasing the number of occlusions and reinterventions that may occur. A smaller effect is that any increase in stent patency leads to a longer uninterrupted period of receiving chemotherapy treatment. The proportion of patients fit to receive chemotherapy was based on clinical expert opinion. High and low values were specified in scenario analyses (see *Table 12*, scenarios M and N). These scenario analyses also help to determine the importance of the mortality HR for people who are fit to receive chemotherapy compared with people who are not fit to receive chemotherapy.

Expected value of information

Value of information analysis estimates the value of reducing decision uncertainty and there is an opportunity cost to the selection of the suboptimal intervention. Further information may reveal that an adopted intervention was suboptimal. The expected value of perfect information (EVPI) is the maximum expected gain in net benefit per patient that can be obtained from reducing uncertainty in model parameters.[110]

The maximum expected gain in net benefit that could be achieved across the whole population is the population expected value of perfect information (PEVPI). PEVPI is calculated by multiplying the individual EVPI by the expected future population to benefit from the interventions. The total population to benefit was estimated using the equation:

$$\textit{Population EVPI} = \textit{EVPI} \times \Sigma_t {}^{I_t}\!/_{(1+r)^t}, \tag{6}$$

where I_t is the incidence per year, t is the number of years and r is the annual discount rate.

The number of RFA procedures per year in the UK was assumed to be 2035 based on the number of stent placements reported in the NHS reference costs.[102] The population cost was discounted over a 10-year period and the annual discount rate was assumed to be 3.5%.

If PEVPI is not significantly greater than the cost of doing a specific piece of research, then there is no value in doing that research. A good-quality clinical trial to evaluate the effectiveness of a surgical intervention could cost up to £2M; however, the cost of a RCT varies considerably, and this is at the higher end. Examples of National Institute for Health and Care Research-funded trials of

surgical interventions that cost less than, but close to, £2M are research awards NIHR128768[111] and NIHR128815.[112]

Expected value of perfect information and PEVPI can also be estimated for specific model parameters, either individually or in combination. For example, a clinical trial researching the effectiveness of RFA will likely provide information on both mortality and occlusion. A slightly more costly piece of research could add research into the quality of life of patients. EVPI when applied to a subset of parameters is known as EVPPI, and there is a corresponding value at the population level [i.e. the population expected value of partial perfect information (PEVPPI)]. The EVPPI methods used were those stated in Briggs *et al.*[110]

Chapter 7 Cost-effectiveness results

Models were planned for patients with advanced bile duct cancer and patients with advanced pancreatic cancer, for both primary and secondary RFA. Owing to a lack of evidence surrounding the effectiveness of secondary RFA, no model was produced for secondary RFA. The studies included in the meta-analyses of the HR of mortality in *Chapter 4*, *Survival*, included both patients with bile duct cancer and patients with pancreatic cancer, although there was a higher proportion of patients with bile duct cancer. There was also a lack of evidence on difference in stent patency for pancreatic cancer separately to bile duct cancer. Consequently, one model was developed for primary RFA in patients with bile duct cancer.

Base-case results

Cost-effectiveness results

The cost-effectiveness results for the base-case probabilistic analysis, which does not adjust for bias in the effectiveness estimates, are reported in *Table 13*. The average discounted cost for the RFA intervention is £2659 more than the average discounted cost without the RFA intervention. The average discounted QALYs for the RFA intervention is 0.18 more than the average discounted QALYs without the RFA intervention. The ICER is £14,392 per QALY. The ICER increased to £14,511 when the updated AE risk data, including cholangitis, were used.

The cost-effectiveness plane presenting the joint distribution of the incremental cost and incremental QALY estimates from the probabilistic analysis is presented in *Figure 16*. The scatterplot shows that there is considerable variation in the incremental QALY estimates.

The probability that RFA plus stent is cost-effective at different cost-effectiveness thresholds is presented as a CEAC in *Figure 15*. The probability that RFA plus stent is cost-effective is 0.82 at a £20,000 per QALY cost-effectiveness threshold and 0.92 at a £30,000 per QALY cost-effectiveness threshold.

Population expected value of perfect information results

The PEVPI for the base-case analysis is £9.14M at a cost-effectiveness threshold of £20,000 per QALY and £5.66M at a cost-effectiveness threshold of £30,000 per QALY, indicating that there may be value in undertaking further research. When the updated AE risk data were used in the analysis, the PEVPI was £10.07M at a cost-effectiveness threshold of £20,000 per QALY and £6.64M at a cost-effectiveness threshold of £30,000 per QALY.

Scenario analyses

The cost-effectiveness results of the scenario analyses are reported in *Table 14*.

TABLE 13 Base-case cost-effectiveness results

Intervention	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£/QALY)
Stent	7185		0.46		
RFA plus stent	9845	2659	0.64	0.18	14,392

TABLE 14 Cost-effectiveness results for each scenario analysis

Scenario	Incremental cost (£)	Incremental QALYs	ICER (£)	Probability cost-effective		PEVPI (£M; £/QALY threshold)	
				£20,000	£30,000	£20,000	£30,000
Base case	2659	0.184	14,436	0.82	0.92	9.14	5.66
A: lower stent patency for secondary stents	2753	0.183	15,038	0.73	0.88	9.27	3.66
B: zero RFA effectiveness in increasing stent patency and zero uncertainty	3017	0.183	16,459	0.8	0.99	1.74	0.09
C: 20% complications	2850	0.183	15,565	0.79	0.9	12.02	7.7
D: 5% complications	2615	0.194	14,264	0.83	0.92	8.68	5.5
E: low reviewer bias adjustment	2704	0.196	13,811	0.81	0.92	8.83	5.29
F: high reviewer bias adjustment	2764	0.140	19,758	0.67	0.83	14.94	10.20
G: expert bias adjustment without the Gao *et al.*28 study	1425	0.213	7165	0.94	0.97	2.93	1.85
H: favourable utility to RFA	2670	0.151	12,503	0.86	0.93	7.92	4.89
I: cancer utility 0.5, AE utility 0.46	2687	0.121	17,820	0.74	0.88	11.79	7.47
J: cancer utility 0.4, AE utility 0.36	2666	0.218	22,070	0.62	0.81	10.35	9.45
K: 10% improved survival (stent)	2952	0.141	13,564	0.84	0.92	10.24	6.48
L: 10% worse survival (stent)	2340	0.183	16,604	0.76	0.89	10	6.4
M: 40% fit to receive chemotherapy	2940	0.184	16,037	0.81	0.91	9.66	5.92
N: 10% fit to receive chemotherapy	2595	0.183	14,090	0.82	0.91	10.2	6.51

Stent patency

Halving the time to occlusion for secondary stents without RFA and halving the effectiveness of RFA in increasing stent patency significantly lowers the probability that RFA is cost-effective at the £20,000 per QALY threshold from 0.82 to 0.73 (see *Table 14*, scenario A). Lower stent patency increases the number of reinterventions and, therefore, cost. The number of reinterventions increases more with RFA than without RFA because the expected proportional increase in survival associated with RFA is greater than the expected proportional increase in stent patency. The cumulative first reinterventions and the cumulative additional reinterventions (i.e. extra reinterventions) for the base-case analysis and scenario A are reported in *Table 15*. A person can have more than one extra reintervention. In the base case, 65% of the cohort population have a reintervention during the course of the model in the RFA group not receiving chemotherapy, compared with 61% of the population in the stent-only group, and the difference in the cumulative number of extra reinterventions is greater. Reducing stent patency for secondary interventions further increases the number of additional reinterventions, with a proportionate increase in the RFA and stent-only groups. Halving the time to occlusion without RFA and halving the effectiveness of RFA for secondary stents does not increase the PEVPI because the value of information is related to the expected benefit of RFA and the effectiveness of RFA for secondary stents has been reduced.

TABLE 15 Cumulative reinterventions and extra reinterventions in the base-case and scenario A analyses

Intervention	Base case		Scenario A	
	Cumulative reintervention	Cumulative extra reintervention	Cumulative reintervention	Cumulative extra reintervention
RFA	65%	70%	65%	113%
Stent only	61%	54%	61%	84%

The effectiveness of RFA in increasing stent patency is far less certain than the evidence of the effectiveness of RFA for HR of mortality. The CI for difference in stent patency leaves open the possibility that RFA is associated with shorter stent patency than stent only. To investigate whether the uncertainty in the cost-effectiveness of RFA is to do with RFA needing to be non-inferior or superior to stent only, a scenario analysis was run with zero difference in stent patency between RFA and stent only, and with zero uncertainty. The result was an ICER of £16,459 per QALY (see *Table 14*, scenario B). The probability that RFA is cost-effective would be 0.8 at a £20,000 per QALY threshold and 0.99 at a £30,000 per QALY threshold. Furthermore, the PEVPI reduces from £9.14M to £1.74M at a £20,000 threshold, and from £5.66M to £0.09M at a £30,000 threshold. This indicates that, given the costs associated with an intervention, RFA does not need to be superior to stent only in stent patency for RFA to be cost-effective.

Stent and radiofrequency ablation cost

Increasing the cost of a reintervention by increasing the probability of a person having an intervention with a complication has a greater effect on the PEVPI than on the probability of being cost-effective (see *Table 14*, scenarios C and D). The greater the cost of a reintervention, the greater the cost of making the wrong decision.

Bias

The high estimate of bias from the reviewer assessment (see *Table 14*, scenario F) significantly reduces the probability that RFA is cost-effective and increases the PEVPI. The PEVPI increases from £9.1M to £14.1M at a £20,000 threshold and from £5.7M to £10.2M at a £30,000 threshold. The low reviewer bias estimate does not have much effect on the results (see *Table 14*, scenario E), and this is because of the considerable uncertainty already present in the estimate unadjusted for bias. The scenario analysis with expert bias adjustment (see *Table 14*, scenario G) does not include evidence from Gao *et al.*,[28] as that evidence was identified in the review update late in the project. The probability that RFA was cost-effective was reduced to 0.94 from 0.97 at a £20,000 per QALY cost-effectiveness threshold when compared with the base-case analysis, without the Gao *et al.*[28] evidence.

Health utility

The favourable utility assumption does not have a significant effect on the results (see *Table 14*, scenario H). Reducing the estimated utility for someone with advanced cancer significantly reduces the probability that RFA is cost-effective and increases the PEVPI, but there is no strong evidence that average utility is that low in this population (see *Table 14*, scenarios I and J).

Survival and chemotherapy

Small changes in the median survival in the stent-only group (see *Table 14*, scenarios K and L) and changes in the proportion of patients being fit for chemotherapy (see *Table 14*, scenarios M and N) have little impact on the results. The fact that these changes in the proportion of patients fit to receive chemotherapy have little effect on the results means that the uncertainty in the mortality HR of people fit to receive chemotherapy compared with people not fit to receive chemotherapy will also have little impact on the results.

Population expected value of perfect information

The PEVPI for the base-case analysis is £9.14M at a cost-effectiveness threshold of £20,000 per QALY and £5.66M at a cost-effectiveness threshold of £30,000 per QALY, indicating that there may be value in undertaking further research. The PEVPI associated with each scenario analysis is presented in *Table 14*, and the impact of scenario analyses is described in *Scenario analyses*.

Across all of the scenarios, apart from assuming that there is no effect of RFA on stent patency, the PEVPI is greater than £2M, indicating that a future trial may have some value. The PEVPI increases with plausible levels of bias adjustment in the effectiveness estimates. If the cost associated with an intervention were significantly higher than assumed in the base case, then the PEVPI would be significantly higher. The majority of the PEVPI is removed when the stent patency effectiveness of RFA is assumed to be zero, and this is explored further in the estimation of PEVPPI.

Population expected value of partial perfect information

An EVPPI analysis was conducted for the HR of mortality, difference in stent patency and both parameters combined. These analyses were run for the base-case analysis, the scenario where stent patency and the effectiveness of RFA was halved following secondary RFA, and for the scenario analysis with the high bias estimate. The population EVPPI was calculated each time. The results are reported in *Table 16*. Assuming that the cost of a good clinical trial would be £2M, the PEVPPI for the HR of mortality is £42,084, which is much less than £2M (i.e. the cost of a good-quality clinical trial), indicating that uncertainty in the effectiveness estimate for the HR of mortality is not a reason to do further research on RFA, and this reflects the evidence strongly supporting greater mean survival with RFA.

The majority of the PEVPI is attributable to uncertainty in the effectiveness of RFA in increasing stent patency, and this is reflected in the PEVPPI values of £8.3M at a £20,000 per QALY threshold and £4.5M at a £30,000 per QALY threshold for stent patency. These PEVPPI values are greater than £2M, which is a high estimate of the cost of a good-quality trial. 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.

Summary

A cost-effectiveness model was produced for primary RFA only. The effectiveness evidence came from studies with either a bile duct cancer population or a mixed population of patients with bile duct cancer and patients with pancreatic cancer, but with a higher proportion of patients with bile duct cancer.

TABLE 16 The PEVPPI

Scenario	Parameter	PEVPPI (£)	
		£20,000/QALY threshold	£30,000/QALY threshold
	ln(HR)	42,084	
Base case	Stent patency	8,327,584	4,529,519
	ln(HR) and stent patency	8,457,815	4,166,388
Half-patency duration	ln(HR) and stent patency	3,116,139	767,124
High bias adjustment	ln(HR) and stent patency	14,044,549	10,151,764

The results are most applicable to an unresectable bile duct cancer population. Every study included in the meta-analysis of the HR of survival was at least at moderate risk of bias. Furthermore, only one of four studies[16,28–29,34] was conducted in the UK.

The economic analysis showed that RFA was cost-effective at a cost-effectiveness threshold of £20,000 per QALY in almost all scenarios evaluated and there was moderate uncertainty in the results. If the effect of bias on the effectiveness results is in fact greater than the high estimate derived from the reviewers' assessment of risk of bias due to, for example, unaccounted for external validity bias, then it is possible that the RFA would no longer be cost-effective at a threshold of £20,000 per QALY. With the high estimate of bias assumption, the probability that RFA is cost-effective is 0.69 at a £20,000 per QALY threshold and 0.85 at a £30,000 per QALY threshold. The effectiveness of RFA in increasing time to occlusion was the parameter that had the greatest impact on the results and for which there was very little evidence. Given the design of the economic model and the intervention cost assumptions, it was shown that RFA did not need to be superior to stent only in terms of increasing time to occlusion, but that it should not be significantly inferior. The value of information analysis showed that further research to evaluate the effect of RFA on stent patency may be warranted, and the higher PEVPI estimates after accounting for risk of bias lend greater support to this. There was also very little evidence on health-related quality of life to inform the health states and events in the model. It would be efficient for any future trial investigating the effectiveness of RFA to also evaluate health-related quality of life.

Chapter 8 Discussion

To the best of our knowledge, this is the largest and most comprehensive review of the role of RFA in malignant biliary obstruction to date. Previous reviews have suggested that RFA may be of benefit to overall survival but were based on analysis of largely retrospective, small, single-centre, non-randomised studies. In addition, previous reviews have not conducted an analysis of cost-effectiveness. To better understand the role of RFA in the management of malignant biliary obstruction, a full clinical effectiveness review was combined with a cost-effectiveness analysis using the most up-to-date data from published studies.

Summary

The clinical effectiveness review showed that primary RFA appears to be a beneficial adjunct to standard care in terms of increasing survival, agreeing with previous reviews.[113,114] Primary RFA reduces the hazard of mortality by at least 45% (i.e. the upper limit of CI in the main analysis). Five[16,28,29,34,37] out of six of the studies in the subgroup analysis showed a statistically significant reduction in the hazard of mortality when primary RFA was used. None of the 18 comparative studies[12,14,16,28–42] that reported mortality showed that primary RFA increased the risk of mortality compared with stent placement alone. There was no evidence that primary RFA increased two of the most common AEs (i.e. cholangitis and pancreatitis). Interestingly, there is some evidence that primary RFA may increase rates of cholecystitis, but this was significant in only one of the three studies reporting this outcome.[28,30,31] Cholecystitis is a well-recognised AE that can occur following insertion of covered metal stents at ERCP; however, the same stent types were used in both arms of these studies, suggesting that primary RFA adds to this risk. Cholecystitis was not reported in all studies and deserves further investigation. One possible mechanism is related to increased survival times in the primary RFA group, leading to a higher risk of developing cholecystitis over time. None of the studies reported the interval at which this cholecystitis occurred. The results appear to be generalisable, as the studies were conducted in many different countries and health-care systems.

There was insufficient evidence to be able to perform a meta-analysis for secondary RFA. Evaluation of the limited number of comparative studies in this area showed no difference in mortality rates between patients receiving RFA and patients receiving standard care.[35,42] There was insufficient information in the secondary RFA studies to determine whether or not there was any difference in AE rates.

Perhaps the most important finding was the lack of evidence reported about factors prioritised by our PPI colleagues (e.g. quality of life and well-being, personal costs and financial impact on carers) in either the primary or the secondary RFA studies.

The economic analysis showed that RFA was cost-effective at a cost-effectiveness threshold of £20,000 per QALY in almost all scenarios evaluated, and there was moderate uncertainty in the results. The effectiveness of RFA in increasing time to occlusion was the parameter that had the greatest impact on the results, but for which there was very little evidence. Given the design of the economic model and the intervention cost assumptions, it was shown that RFA did not need to be superior to stent only in terms of increasing time to occlusion. The value of information analysis showed that further research to evaluate the effect of RFA on stent patency may be warranted, and the higher PEVPI estimates after accounting for risk of bias lend greater support to this. There was also very little evidence on health-related quality of life to inform the health states and events in the model. It would be efficient for any future trial investigating the effectiveness of RFA to also evaluate health-related quality of life.

Strengths

This project benefited from a multidisciplinary team with clinical, methodological and expert-by-experience backgrounds. The systematic review of clinical effectiveness used robust methods, which involved a comprehensive search strategy (including for non-English-language studies), independent duplicate screening of results at title and abstract stage, and independent checking of the data extracted by a second reviewer.

The economic analysis used the best available evidence in the development of the economic model. Despite the limited evidence, there was enough evidence to enable the cost-effectiveness of RFA and the value of future research to be evaluated for primary RFA. Given the paucity of effectiveness and quality-of-life evidence for the use of RFA in advanced bile duct cancer and advanced pancreatic cancer populations, a thorough assessment of uncertainty through probabilistic and scenario analyses was conducted. Plausible estimates of the effect of risk of bias in the clinical studies on the effectiveness estimates were obtained to explore the value of doing further good-quality research.

Limitations

There are some limitations to this review. Only a small number of studies (n = 6) could be included in the meta-analysis looking at survival because of the differences in outcome measures, but none of the comparative studies (of a total of 18) reported a decrease in survival in the RFA group. Several studies needed to be excluded from either the base-case analysis and/or the sensitivity analysis because of a number of factors. The most common reasons were a lack of a comparator group[9,13,17,20,43-88] or use of mixed populations within the study.[9,12,13,16,17,28,30,31,38,44,46-49,54,55,57,62,63,69,71,77] Many of the earliest publications were feasibility studies determining whether or not RFA was indeed deliverable in the biliary tract and, therefore, did not have a comparator group. Some studies used a mixture of tumour types (e.g. bile duct and pancreatic cancers) and some studies used both endoscopic and percutaneous methods to deliver RFA.[9,20,34,44,49,54,59,64,67,69] It was usually not possible to extract the data on patients having solely endoscopic RFA in these studies and, therefore, the studies were excluded on this basis. Similarly, it was not possible to extract the differences in outcomes between patients with bile duct cancer and patients with pancreatic cancer within an individual trial, and this may be important, as overall survival is generally longer in patients with bile duct cancer than in patients with pancreatic cancer.[115]

One of the major findings was the lack of data on effectiveness of secondary RFA. There were insufficient data from the current studies to conduct the planned meta-analysis and data from the observational studies did not suggest a difference in survival. Given that patients in this group have had their cancer for longer and may be at a more advanced stage, survival may not be the most appropriate outcome to measure. There was limited evidence that stent patency is increased, but the evidence came from two very small studies.[35,42] There were few data on other potentially important outcomes in this group, such as reintervention rates, re-admission rates and quality of life.

A further limitation was the standard reporting of adverse outcomes. Some studies reported these outcomes as rates, whereas others gave average time to event.[12,14,16,28-39,42] In addition, some studies did not report AE rates between the intervention and control groups, confounding determination of potential harm.[12,34] The lack of detail in AE reports also meant that it was not possible to evaluate the consistency and similarity of case definitions across studies.

One other major limitation was the lack of standard reporting of other factors that may have had a positive effect on survival, particularly the use of chemotherapy. Some studies excluded patients who were suitable for chemotherapy[12,29] and some studies included this as a variable in regression analysis, but this was not consistent.[14,16,34,40]

Some studies used different stents to that of UK practice.[29,33] Metal stents are associated with better drainage and longer patency, and this might be a confounding factor, particularly in the secondary RFA group.[7] Variation in treatment practice that affects survival will also affect the cost-effectiveness results, although uncertainty related to study design and sample size is probably a greater factor.

There were also insufficient data to perform an analysis of outcomes between the different probe types, and this was because the majority of studies used the Habib EndoHPB probe rather than the StarMed (ELRA) probe. These two probes have slightly differing characteristics, with one being purely energy based (Habib EndoHPB)[9] and the other using a temperature sensor to deliver pulsed RFA energy.[20] It is unknown whether or not the outcomes would be different with either probe, and future studies should document probe type and settings accurately.

Perhaps the biggest limitation was the lack of any data concerning quality of life. This is extremely important, as the groups of patients involved in these studies have non-curable cancers and, therefore, although affecting survival is desirable, improving or at least maintaining quality of life in this situation is paramount, and this was also a priority focus from the PPI group members.

The base-case meta-analysis included studies that were full-text papers and had adjusted for the proportion of patients receiving chemotherapy treatment, if that was necessary, given the study population inclusion criteria and the study design. Although the adjustment should ensure that the selection of studies in the base-case analysis is expected to be at less risk of bias than the studies excluded from the base-case analysis but included in the sensitivity analysis, all of the included studies in the base-case analysis were at moderate to high risk of bias, according to the assessments using the risk-of-bias tools. Consequently, there is a risk of bias associated with the meta-analysis estimates.

The lack of effectiveness evidence for RFA in a secondary RFA population also meant that no economic model could be developed for this population and no cost-effectiveness analysis was conducted. Given the different patient population, extrapolation from primary RFA may not be representative. There was also a lack of evidence to support separate economic analyses for patients with advanced bile duct cancer and patients with advanced pancreatic cancer, and this is an important consideration, as survival is generally longer in patients with bile duct cancers than in patients with pancreatic cancers and the majority of patients included in this review had bile duct cancers.[115]

It was expected that the effectiveness evidence identified in the systematic review would be of poor quality. Consequently, a bias elicitation exercise was planned with the clinical experts on the advisory group identified as participants in the exercise. Owing to project delays due to the COVID-19 pandemic, late finalisation of the comparative studies to be included in the systematic review, the tight timelines from the end of the review to the end of the project, and difficulty in arranging for the clinical experts to be available at the same time to discuss the bias results, the step 2 discussion of the exercise did not happen. The clinical experts also needed more guidance on the assessment and marking of bias. In addition, the review update identified a study that could not be reviewed by the clinical experts because of project time constraints.[28] As a result, only one response could be identified where the bias quantification could be assessed as consistent with the assessed bias factors in each study. However, there was moderate uncertainty in the effectiveness results without accounting for bias, and this increased when accounting for the effect of bias estimated from reviewer bias assessments in the systematic review.

The economic model was limited by the available data. Limited data on time to occlusion meant that distribution assumptions needed to be made, and competing risk between death and occlusion could not be explicitly accounted for. There was no evidence on the effect on personal costs to patients and carers and, therefore, the study perspective was necessarily limited to the NHS and Personal Social Services perspective. Given the limitations in the data, the uncertainty associated with some parameters and assumptions could not be reflected in the base-case probabilistic sensitivity analysis results and,

consequently, several scenario analyses were conducted to assess the impact on the cost-effectiveness results of different parameter assumptions. The lack of evidence meant that an economic model for only the primary RFA population, and largely bile duct population, could be developed.

Further research

Primary radiofrequency ablation

Assessment of quality of life in patients undergoing primary RFA at baseline and over the course of a trial is critically needed. High-quality prospective collection of data on AEs, particularly cholecystitis, is needed. An assessment is required of whether or not repeated application of RFA at specific intervals adds a further boost to survival. In all of these aspects, outcomes need to be adjusted for confounders, particularly chemotherapy. Given that stent patency is a crucial determinant of cost-effectiveness, the effect of RFA on stent patency should be accurately documented.

The majority of studies reported on patients with bile duct cancer and, therefore, a trial that allowed assessment of individual cancer types would be very useful.

All of the studies analysed were in unresectable cancers, as per the remit of the review; however, the effect of primary RFA as an adjunct in patients undergoing stent insertion prior to potentially curative surgery should be considered.

Assessment of the mechanism by which primary RFA leads to improved survival should be considered, and this may be achieved by looking at changes in markers for antitumour immunity, as has been previously suggested as a potential mechanism.

Secondary radiofrequency ablation

High-quality prospective RCTs with appropriate outcomes including quality of life, AE rates and survival, are needed. There would need to be adjustment for potential confounders, such as chemotherapy use prior to and after secondary RFA. Tumour type is also very important, with a reasonable proportion in this clinical group having metastatic tumours, such as colorectal cancer, which has generally better outcomes than pancreaticobiliary tract cancers.

Many studies are small and a further study would benefit from an appropriate sample size estimate. If the study has a sufficient sample size, then a study evaluating both time to occlusion and time to death could consider conducting competing risk survival analysis, as well as survival analysis and evaluating average stent duration, to allow comparison with existing studies.

Any future research should account for the research currently in progress.

Chapter 9 Conclusions

The current evaluation of the role of RFA in malignant biliary obstruction shows that there appears to be a significant positive effect on survival, particularly for primary RFA, and RFA is likely to be cost-effective. The cost-effectiveness of RFA seems to depend on RFA increasing stent patency and there is considerable uncertainty in the effect estimate. For primary RFA, there does not appear to be a negative effect on stent patency, but better-quality reporting of this outcome is needed. There appears to be a good AE profile, with no significant differences found in rates of abdominal pain, cholangitis and pancreatitis. There was an increased rate of cholecystitis in the RFA group compared with the stent-only group, which is not easy to explain. However, very few of the studies were large, prospective, multicentre, randomised trials and did not consistently report other important outcomes, including AEs, time to stent reocclusion, reintervention rates and, most importantly, effect on quality of life. As an adjunct to standard care, the addition of primary RFA appears to have a very high technical success rates and no effect on the ability to place a stent for drainage following application.

For secondary RFA, the evidence was far more limited, with no prospective randomised studies to inform decision-making. There was a lack of robust clinical effectiveness data and, therefore, more information is needed for this indication. In designing a trial to examine the effectiveness of RFA in this setting, outcomes would need to reflect the needs of the patients. Consistent reporting of AEs, time to stent occlusion and need for further admissions and interventions would be essential. Most importantly, information is needed on the effect of RFA on quality of life in this setting.

Endobiliary RFA has currently been used only in specialist centres (particularly in the UK) and largely in clinical trial settings, and has been carried out using careful patient selection. Therefore, wider routine clinical use would need to be performed using the same inclusion and exclusion criteria.

Implications for practice/decision-makers

The included studies were mostly assessed to be at moderate to high risk of bias. Despite the risk of bias, primary endobiliary RFA is likely to be cost-effective at the £20,000 per QALY and £30,000 per QALY cost-effectiveness thresholds, as there was a consistent and large survival benefit across the studies. The bias associated with these studies would need to be greater than that considered in this study for RFA to not be cost-effective at these thresholds. Alternatively, RFA would need to be associated with a higher risk of occlusion and, therefore, a shorter time to occlusion. There was some evidence of an increased risk of cholecystitis associated with RFA. The use of secondary RFA is currently lacking good effectiveness data and, as such, cannot be recommended for standard clinical practice.

Implications for research

The evidence for improved survival for primary RFA appears to be strong and RFA does not appear to be associated with an AE profile that would prevent the use of RFA. The evidence for secondary RFA is far less certain because there are far fewer studies examining this usage. There is a lack of data concerning very important outcomes for both primary and secondary RFA. The biggest driver of cost-effectiveness is stent patency, which is intimately related to quality of life, and the evidence for the effectiveness of RFA in increasing stent patency is weak. These areas should be the priority focus of future research.

Further research on endobiliary RFA should include the following:

- Primary RFA effects on quality of life. Improvement in survival is important, but not at the cost of quality of life. Whether primary RFA improves, preserves or reduces quality of life is unknown, and this should be an essential measure in future studies.
- Primary RFA AE profile. Cholecystitis can be a serious condition and is usually treated by surgical removal of the gallbladder. Undergoing such a procedure with an underlying advanced cancer is usually not advisable. Further evaluation of whether or not cholecystitis is related to patient factors, tumour factors or intervention factors should be conducted.
- Mechanism of improved survival in primary RFA. An evaluation of effectiveness should be conducted to determine the mechanism by which primary RFA leads to improved survival.
- Repeated applications of RFA. There is a lack of data on repeated applications of endobiliary RFA. The survival benefit seen could be postulated to be boosted by a further application at given time points, and this hypothesis should be tested.
- Secondary RFA. More and higher-quality data are needed in this area specifically. Larger and higher-quality, preferably, prospective randomised studies with robust and patient-centred outcomes should be conducted to examine the clinical effectiveness and AE profiles. Data are also needed concerning the absolute requirement for further stent insertion in this group.
- Secondary RFA. More and higher-quality data are needed on cost-effectiveness in this area, and this could be incorporated into a study that is examining clinical effectiveness.
- Secondary RFA. If secondary RFA shows clinical effectiveness, as for primary RFA, then an evaluation of the mechanism by which secondary RFA works should be conducted.

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Patient and public involvement statement

Two PPI members were included in the Clinical Advisory Board for this project. Meetings were held via the Zoom video conferencing platform (Zoom Video Communications, San Jose, CA, USA) and chaired by John Leeds. Progress and data were presented with opportunities for Clinical Advisory Board members to give feedback. PPI members contributed to the design of the protocol, interpretation of the results and writing of the *Plain English summary*. Importantly, PPI members consulted on patient outcomes, identifying quality of life and well-being, personal costs and financial impact on carers as crucial outcomes of interest. As a result of PPI involvement, we identified a significant evidence gap surrounding quality-of-life outcomes. It also became apparent that patient-focused outcomes were lacking in all trials, and this has contributed to our recommendations for future research.

Contributions of authors

Fiona Beyer (https://orcid.org/0000-0002-6396-3467**)** (Senior Research Associate, Evidence Synthesis) co-led the writing of the protocol and the final report; led the conduct and write-up of the systematic reviews; supervised the design and running of the literature searches; and co-supervised the meta-analyses.

Stephen Rice (https://orcid.org/0000-0002-6767-0813**)** (Senior Research Associate, Health Economics) co-led the writing of the protocol and the final report; led the development of the cost-effectiveness model and the value of information analysis; and co-supervised the meta-analyses.

Giovany Orozco-Leal (https://orcid.org/0000-0002-7473-7318**)** (Research Assistant, Health Economics) contributed to the screening of studies for the systematic reviews, data extraction for the systematic review, development of the cost-effectiveness model and the value of information analysis.

Madeleine Still (https://orcid.org/0000-0003-0625-6325**)** (Research Assistant, Evidence Synthesis) contributed to the screening of studies, data extraction and risk-of-bias assessments for the systematic reviews; and contributed to the writing of the final report.

Hannah O'Keefe (https://orcid.org/0000-0002-0107-711X**)** (Training Fellow, Evidence Synthesis) designed and ran the searches for the systematic reviews; helped to co-ordinate the screening; produced the PRISMA flow charts; managed the references and referencing; and contributed to the writing of the final report.

Nicole O'Connor (https://orcid.org/0000-0002-6654-7178**)** (Training Fellow, Evidence Synthesis) contributed to screening and data extraction for the systematic reviews; and contributed to writing of the final report.

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Dawn Craig (https://orcid.org/0000-0002-5808-0096**)** (Professor of Practice in Evidence Synthesis) contributed to the design and writing of the protocol; provided advice on the systematic review, model and value of information analyses methods; and contributed to the final report.

Stephen Pereira (https://orcid.org/0000-0003-0821-1809**)** (Consultant Gastroenterologist and Hepatologist) was a clinical member of the Clinical Advisory Board; contributed to the design and writing of the protocol; provided clinical advice throughout; contributed to the bias elicitation assessment; and contributed to the writing of the final report.

Louise Carr (https://orcid.org/0000-0002-6730-4186**)** (PPI expert by experience) was a member of the Clinical Advisory Board; and contributed to the design of the protocol, the plain English outputs, the interpretation of the results and to the writing of the final report.

John Leeds (https://orcid.org/0000-0002-5140-6225**)** (Consultant Gastroenterologist) was the principal investigator and oversaw the running of the project; provided clinical advice throughout; and contributed to the design and writing of the protocol, to the screening and data extraction for the systematic review, to the bias elicitation assessment and to the writing of the final report.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Search strategy: clinical effectiveness search

MEDLINE (via Ovid)

Search date: March 2020

Dates searched: January 2008 to March 2020

Search strategy

1. exp Radiofrequency Ablation/
2. ("radio?frequen* ablat*" or RFA).ti,ab,kw,kf.
3. exp Catheter Ablation/
4. "catheter ablat*".ti,ab,kw,kf.
5. "coagulative necro*".ti,ab,kw,kf.
6. "thermal* ablat*".ti,ab,kw,kf.
7. (bipolar adj4 (catheter* or probe* or ablat*)).ti,ab,kw,kf.
8. or/1-7
9. exp Pancreatic Neoplasms/
10. pancreatic adenocarcinoma.ti,ab,kw,kf.
11. exp Bile Duct Neoplasms/
12. exp Cholangiocarcinoma/
13. gallbladder neoplasms/
14. adenoma, bile duct/
15. duodenal neoplasms/
16. common bile duct neoplasms/
17. cholangiocarcinom*.ti,ab,kw,kf.
18. ((bile or biliar* or endobiliar* or bile duct or pacrea* or choliangio*) adj4 (obstruct* or occlu* or cancer* or carcinom* or adenocarcinom* or tumo?r* or malignan* or lump* or mass or masses or sarcom* or metastas* or stricture*)).ti,ab.
19. exp Biliary tract disease/
20. "stent*".ti,ab.
21. Self Expandable Metallic Stents/
22. ((intraductal or intraluminal or unresect*) adj4 (obstruct* or occlu* or cancer* or carcinom* or adenocarcinom* or tumo?r* or malignan* or lump* or mass or masses or sarcom* or metastas* or stricture*)).ti,ab.
23. or/9-22
24. 8 and 23
25. (EndoHBP or ELRA).ti,ab,kw,kf.
26. 24 or 25
27. exp Animals/ not exp Human/
28. 26 not 27
29. limit 28 to yr="2008-Current"

Appendix 2 Search strategy: cost-effectiveness search

MEDLINE (via Ovid)

Search date: May 2020

Dates searched: January 2008 to May 2020

Search strategy

1. exp Radiofrequency Ablation/
2. ("radio?frequen* ablat*" or RFA).ti,ab,kw,kf.
3. exp Catheter Ablation/
4. "catheter ablat*".ti,ab,kw,kf.
5. "coagulative necro*".ti,ab,kw,kf.
6. "thermal* ablat*".ti,ab,kw,kf.
7. (bipolar adj4 (catheter* or probe* or ablat*)).ti,ab,kw,kf.
8. or/1-7
9. exp Pancreatic Neoplasms/
10. pancreatic adenocarcinoma.ti,ab,kw,kf.
11. exp Bile Duct Neoplasms/
12. exp Cholangiocarcinoma/
13. gallbladder neoplasms/
14. adenoma, bile duct/
15. duodenal neoplasms/
16. common bile duct neoplasms/
17. cholangiocarcinom*.ti,ab,kw,kf.
18. ((bile or biliar* or endobiliar* or bile duct or pacrea* or choliangio*) adj4 (obstruct* or occlu* or cancer* or carcinom* or adenocarcinom* or tumo?r* or malignan* or lump* or mass or masses or sarcom* or metastas* or stricture*)).ti,ab.
19. exp Biliary tract disease/
20. "stent*".ti,ab.
21. Self Expandable Metallic Stents/
22. ((intraductal or intraluminal or unresect*) adj4 (obstruct* or occlu* or cancer* or carcinom* or adenocarcinom* or tumo?r* or malignan* or lump* or mass or masses or sarcom* or metastas* or stricture*)).ti,ab.
23. or/9-22
24. 8 and 23
25. (EndoHBP or ELRA).ti,ab,kw,kf.
26. 24 or 25
27. exp Animals/ not exp Human/
28. 26 not 27
29. limit 28 to yr="2008-Current"
30. Economics/
31. exp "costs and cost analysis"/
32. Economics, Dental/
33. exp economics, hospital/
34. Economics, Medical/
35. Economics, Nursing/

36. Economics, Pharmaceutical/
37. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic $).ti,ab.
38. (expenditure$ not energy).ti,ab.
39. value for money.ti,ab.
40. budget$.ti,ab.
41. or/30-40
42. ((energy or oxygen) adj cost).ti,ab.
43. (metabolic adj cost).ti,ab.
44. ((energy or oxygen) adj expenditure).ti,ab.
45. or/42-44
46. 41 not 45
47. letter.pt.
48. editorial.pt.
49. historical article.pt.
50. or/47-49
51. 46 not 50
52. bmj.jn.
53. “cochrane database of systematic reviews“.jn.
54. health technology assessment winchester england.jn.
55. or/52-54
56. 51 not 55
57. 29 and 56

Appendix 3 Excluded studies list: clinical effectiveness review

No articles were excluded based on language alone.All articles were screened at title/abstract level, regardless of language. Google Translate (Google Inc., Mountain View, CA, USA) was used to assess an article if the title/abstract was not available in English. Full-text articles of potentially eligible articles that were not in the English language were translated by individuals fluent in those languages. Studies were excluded where international interlibrary loans were required because of The British Library's limitations during the COVID-19 pandemic.

The full references for all excluded articles are provided in *Table 17*. Articles were excluded for one of the following reasons (in order of hierarchical importance):

- The paper focuses on an ineligible patient population (*n* = 72).
- The paper did not focus on endoscopic RFA plus stenting as the intervention (*n* = 169).
- The paper focuses on an ineligible comparator (*n* = 5).
- The paper did not focus on the outcomes of interest (*n* = 4).
- The paper describes an ineligible study design (*n* = 217).
- The paper was not retrievable by international interlibrary loan (*n* = 7).
- The paper is an exact duplicate (*n* = 111).
- The paper was an animal study (*n* = 1).

TABLE 17 Clinical effectiveness review: excluded articles

Reason for exclusion	Reference
The paper focuses on an ineligible patient population (*n* = 72)	1. ClinicalTrials.gov. *Destruction of Residual Endo-biliary Dysplastic Buds After Endoscopic Ampullectomy*. URL: https://ClinicalTrials.gov/show/NCT02825524 (accessed 23 September 2022) 2. Abe T, Kajiyama K, Harimoto N, Gion T, Shirabe K, Nagaie T. Intrahepatic bile duct recurrence of hepatocellular carcinoma without a detectable liver tumor. *Int J Surg Case Rep* 2012;**3**:275–8. https://doi.org/10.1016/j.ijscr.2012.03.017 3. Akinci D, Unal E, Ciftci TT, Kyendyebai S, Abbasoglu O, Akhan O. Endobiliary radiofrequency ablation in the percutaneous management of refractory benign bilioenteric anastomosis strictures. *AJR Am J Roentgenol* 2019;**212**:W83–W91. https://doi.org/10.2214/AJR.18.19751 4. Ando K, Sakamoto Y. A case of gallbladder metastasis from hepatocellular carcinoma. *Jpn J Clin Oncol* 2009;**39**:540. https://doi.org/10.1093/jjco/hyp092 5. Annane N, Alibenamara F, Haddad K, Bennani A, Abid L. Radiofrequency ablation of liver metastases of endocrine tumors: what is the limit of the number. a case report. *HPB* 2018;**20**:S352 6. Bartsch F, Baumgart J, Paschold M, Heinrich S, Lang H. Recurrence of intrahepatic cholangiocarcinoma – patterns and therapy. *HPB* 2019;**21**:S556 7. Beard JI, Philips G. An old friend in a new neighborhood: the presentation and management of intraductal hepatocellular carcinoma. *Am J Gastroenterol* 2019;**114**:S1217 8. Benson AB, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, Saenz DA, *et al.* Hepatobiliary cancers, version 1.2017 featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* 2017;**15**:563–73 9. Boonsirikamchai P, Loyer EM, Choi H, Charnsangavej C. Planning and follow-up after ablation of hepatic tumors: imaging evaluation. *Surg Oncol Clin N Am* 2011;**20**:301–15, viii. https://doi.org/10.1016/j.soc.2010.11.007 10. Brandi G, Palloni A, Morganti AG. Should we incorporate ablative radiotherapy in standard treatment of advanced intrahepatic cholangiocarcinoma? *Transl Cancer Res* 2016;**5**:S450–S3

continued

TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	11. Braunwarth E, Schullian P, Haidu M, Primavesi F, Margreiter C, Schneeberger S, *et al.* Intrahepatic cholangiocellular carcinoma: stereotactic radiofrequency ablation vs. hepatic resection. *Zeitschriftfur Gastroenterologie* 2017;**55** 12. Brennan IM, Ahmed M. Imaging features following transarterial chemoembolization and radiofrequency ablation of hepatocellular carcinoma. *Semin Ultrasound CT MR* 2013;**34**:336–51. https://doi.org/ 10.1053/j.sult.2013.04.004 13. Buettner S, van Vugt JL, Ijzermans JN, Groot Koerkamp B. Intrahepatic cholangiocarcinoma: current perspectives. *Onco Targets Ther* 2017;**10**:1131–42. https://doi.org/10.2147/OTT.S93629 14. Buis C, Van Dijk R, Bosker R, Smit F, Liem M. A regional liver surgery program in a secondary teaching hospital in the Netherlands, a feasibility study and critical appraisal. *HPB* 2011;**13**:74 15. Camus M, Napoléon B, Vienne A, Le Rhun M, Leblanc S, Barret M, *et al.* Efficacy and safety of endobiliary radiofrequency ablation for the eradication of residual neoplasia after endoscopic papillectomy: a multicenter prospective study. *Gastrointest Endosc* 2018;**88**:511–18 16. Camus M, Napoleon B, Vienne A, Le Rhun M, Leblanc S, Barret M, *et al.* Efficacy and safety of endobiliary radiofrequency ablation for the eradication of residual neoplasia after endoscopic ampullectomy. Results of a multicenter prospective study. *United European Gastroenterol J* 2017;**5**:A244–A5 17. Chan AT, Williams CS. Covering the Cover. *Gastroenterology* 2018;**155**:241–4 18. Chanez B. Caillol F. Ratone J. *P0267 – Endoscopic Radiofrequency Ablation as Focal Therapy for Pancreatic Metastasis from Renal Cell Carcinoma: A Monocentric Experience (Abstract No. 684)*. UECG; 2019 19. Debongnie JC. Clinical gastroenterology – news in brief, March 2017. *Journal Africain d'Hepato-Gastroenterologie* 2017;**11**:42–5 20. Diaz-Gonzalez A,Vilana R, Bianchi L, Garcia-Criado A, Belmonte E, Rimola J, *et al.* Thermal ablation is a safe and effective treatment for intrahepatic cholangiocarcinoma in patients with cirrhosis. *J Hepatol* 2019;**70**:E599–E 21. Díaz-González Á, Vilana R, Bianchi L, García-Criado Á, Rimola J, Rodríguez de Lope C, *et al.* Thermal ablation for intrahepatic cholangiocarcinoma in cirrhosis: safety and efficacy in non-surgical patients. *J Vasc Interv Radiol* 2019;**30**:N. PAG-N.PAG 22. Gamal GH, Nada OM, Ghany MEA. Combined versus single interventional therapies in treatment of hepatic malignant tumors. *Egypt J Radiol Nucl Med* 2014;**45**:117–22 23. UMIN-CTR Clinical Trial. *Prospective Evaluation of Radiofrequency Ablation for Benign Biliary Strictures*. 2020. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045785 (accessed 16 November 2022). 24. UMIN-CTR Clinical Trial. *Prospective Evaluation of Radiofrequency Ablation for Refractory Benign Pancreatic Duct Strictures*. 2020. URL: https://center6. umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045718 (accessed 16 November 2022) 25. Gereitzig N, Ziegan R-A, Tischendorf JJW. [Successful intraductal radiofrequency ablation of residual adenoma tissue following endoscopic papillectomy.] *Z Gastroenterol* 2020;**58**:241–4 26. Giovannini M, Pesenti C, Caillol F, Ratone JP. Treatment of residual biliary adenomas after endoscopic ampullectomy with ERCP guided radiofrequency ablation. *Dig Endosc* 2020;**32**:157 27. Guo JQ, Zou JJ, Zhu JD, Jiang C, Shao CX. A case report of rectal adenocarcinoma with intrahepatic cholangiocarcinoma of the liver. *J Int Med Res* 2019;**47**:5883–90. https://doi.org/10.1177/0300060519876751 28. Gurusamy KS, Ramamoorthy R, Sharma D, Davidson BR. Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases. *Cochrane Database Syst Rev* 2009;**2**:CD007060. https://doi.org/10.1002/14651858.CD007060.pub2 29. Hassan W, Nishi J, Tomiyasu S, Urakado T, Haraoka K, Yamanaka T, *et al.* Unusual biliary myoepithelial carcinoma in liver-case report and immunohistochemical study. *Int J Clin Exp Pathol* 2014;**7**:2647–53 30. Hu B, Gao DJ,Wu J, Pan YM,Wang TT, Yang XM, *et al.* Intraductal radiofrequency ablation for the resolution of refractory benign biliary stricture. *Gastrointest Endosc* 2013;**77**:AB320

TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	31. Hu B, Gao DJ,Wu J,Wang TT, Yang XM, Ye X. Intraductal radiofrequency ablation for refractory benign biliary stricture: pilot feasibility study. *Dig Endosc* 2014;**26**:581–5. https://doi.org/10.1111/den.12225 32. Hu B, Sun B, Gao DJ,Wu J, Ye X, Xia MX,Wang TT. Initial Experience of ERCP-Guided Radiofrequency Ablation as the Primary Therapy for Inoperable Ampullary Carcinomas. *Dig Dis Sci* 2020;**65**:1453–9. https://doi.org/10.1007/s10620-019-05849-3 33. Iida H, Aihara T, Ikuta S, Yamanaka N. Effectiveness of impedance monitoring during radiofrequency ablation for predicting popping. *World J Gastroenterol* 2012;**18**:5870–8. https://doi.org/10.3748/wjg.v18.i41.5870 34. Ikai I, Kudo M, Arii S, Omata M, Kojiro M, Sakamoto M, *et al.* Report of the 18th follow-up survey of primary liver cancer in Japan. *Hepatol Res* 2010;**40**:1043–59. https://doi.org/10.1111/j.1872-034X.2010.00731.x 35. Inoue T, Ito K, Yoneda M. Radiofrequency ablation combined with multiple biliary metal stent placement using short-type single-balloon endoscope in patients with surgically altered anatomy. *Dig Endosc* 2018;**30**:395–6. https://doi.org/10.1111/den.13016 36. Kamphues C, Seehofer D, Eisele RM, Denecke T, Pratschke J, Neumann UP, Neuhaus P. Recurrent intrahepatic cholangiocarcinoma: single-center experience using repeated hepatectomy and radiofrequency ablation. *J Hepatobiliary Pancreat Sci* 2010;**17**:509–15. https://doi.org/10.1007/s00534-009-0256-6 37. Kjaer J, Stalberg P, Skogseid B, Hellman P, Eriksson B, Norlen O. Long term outcome after resection and radiofrequency ablation of liver metastases in pancreatic neuroendocrine tumours. *Langenbecks Arch Surg* 2018;**403**:406 38. Kobayashi M. Development of a biliary multi-hole self-expandable metallic stent for bile tract diseases: a case report. *World J Clin Cases* 2019;**7**:1323–8. https://doi.org/10.12998/wjcc.v7.i11.1323 39. Kolarich AR, Shah JL, George TJ, Hughes SJ, Shaw CM, Geller BS, Grajo JR. Non-surgical management of patients with intrahepatic cholangiocarcinoma in the United States, 2004–2015: an NCDB analysis. *J Gastrointest Oncol* 2018;**9**:536–45. https://doi.org/10.21037/jgo.2018.02.04 40. Kwan V. Advances in gastrointestinal endoscopy. *Intern Med J* 2012;**42**:116–26 41. Laca L, Dedinska I, Palkoci B, Miklusica J, Janik J. Surgical treatment of intrahepatic cholangiocarcinoma: a retrospective cohort study. *Int J Surg Open* 2016;**4**:10–14 42. Lam VW, Ng KK, Chok KS, Cheung TT,Wat J, Fan ST, Poon RT. Safety and efficacy of radiofrequency ablation for periductal hepatocellular carcinoma with intraductal cooling of the central bile duct. *J Am Coll Surg* 2008;**207**:e1–5. https://doi.org/10.1016/j.jamcollsurg.2008.03.028 43. Lermite E, Lebigot J, Oberti F, Pessaux P, Aube C, Arnaud JP. Radiofrequency thermal ablation of liver carcinoma. Prospective study of 82 lesions. *Hepatol Int* 2011;**5**:388–9 44. Liang R, Ma KX, Sun DG, Liu QL, Gao ZM,Wang LM. Clinical analysis of 15 cases catheter ablation of the cholangiocarcinoma. *HPB* 2013;**15**:189 45. Liang X, Ou YL, Hao J, Hu XG, Jin G, Liu R, *et al.* The clinical experience of surgical treating 9 cases of gastrinoma. *Pancreatology* 2016;**16**:S36–S7 46. Liu J, Zhong M, Feng Y, Zeng S,Wang Y, Xu H, Zhou H. Prognostic factors and treatment strategies for intrahepatic cholangiocarcinoma from 2004 to 2013: population-based SEER analysis. *Transl Oncol* 2019;**12**:1496–503 47. Lou W, Fan Y. Long term survival of pancreatic cancer patients with liver metastasis. *Pancreatology* 2010;**10**:374 48. Mavrogenis G, Deprez PH,Wallon J,Warzée P. Bile duct adenoma causing recurrent cholangitis: diagnosis and management with targeted Spyglass access and radiofrequency ablation. *Endoscopy* 2012;**44**:E290–1. https://doi.org/10.1055/s-0032-1310036 49. UMIN-CTR Clinical Trial. *Usefulness of Radiofrequency Ablation with Infusing the Contract Medium into Bile Duct for Hepatocellular Carcinoma Located Near the Intrahepatic Bile Duct*. 2015. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000020229 (accessed 16 November 2022) 50. Mondragón-Sánchez R, Murrieta-González H, Martínez-González MN, Gómez-Gómez E, Arias-Arias O, Mondragón-Sánchez A, *et al.* [Ablation of malignant liver tumors with radiofrequency. A series of cases in Mexico.] *Rev Gastroenterol Mex* 2009;**74**:212–17

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TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	51. Mondragon-Sanchez R, Murrieta-Gonzalez H, Martinez-Gonzalez MN, Gomez-Gomez E, Arias-Arias O, Mondragon-Sanchez A, *et al.* Radiofrequency ablation of malignant liver tumors. A series of cases in Mexico. *Revista de Gastroenterologia de Mexico* 2009;**74**:212–17 52. ClinicalTrials.gov. *Effectiveness of Microwave Ablation of Hepatocellular Carcinoma as Compared to Radiofrequency Ablation*. URL: https://ClinicalTrials.gov/ct2/show/NCT01340105 (accessed 23 September 2022) 53. Ogura T, Takagi W, Ueno S, Takeuchi T, Fukunishi S, Higuchi K. Endoscopic hemostasis for tumor bleeding using intraductal radiofrequency ablation. *Endoscopy* 2016;**48**:E328–E9 54. Perez-Cuadrado-Robles E, Piessevaux H, Moreels T, Yeung R, Aouattah T, Jouret-Mourin A, *et al.* Intraductal biliary or pancreatic ablation during endoscopic ampullectomy may reduce the long-term recurrence rate. *United European Gastroenterol J* 2017;**5**:A152 55. Pesenti C, Caillol F, Bories E, Ratone JP, Poizat F, Giovannini M. Ampullary radio frequency ablation: a new minimally invasive approach to avoid surgery? *United European Gastroenterol J* 2018;**6**:A605 56. Rao B, Garg M, Gulati A, Singh S, Thakkar S. Successful use of radiofrequency ablation for the management of a recurrent ampullary adenoma with intraductal extension. *Gastrointest Endosc* 2017;**85**:AB128 57. Rustagi T, Irani S, Reddy DN, Abu Dayyeh BK, Baron TH, Gostout CJ, *et al.* Radiofrequency ablation for intraductal extension of ampullary neoplasms. *Gastrointest Endosc* 2017;**86**:170–6 58. Rustagi T, Irani S, Reddy ND, Abu Dayyeh BK, Baron TH, Gostout C, *et al.* Endoscopic radiofrequency ablation for intraductal extension of ampullary neoplasms. *Gastrointest Endosc* 2016;**83**:AB298 59. Shimizuguchi T, Shirai M, Kimura K, Imamura J, Saeki S, Kuruma S, *et al.* A case of successfully treated advanced hepatocellular carcinoma with portal vein tumor thrombus and bile duct obstruction by multimodal therapy. *Acta Hepatologica Japonica* 2011;**52**:139–46 60. Sigal M, Pape UF, Wiedenmann B. Gastroenteropancreatic neuroendocrine neoplasms. *Ther Umsch* 2012;**69**:591–6 61. Suarez AL, Coté GA, Elmunzer BJ. Adjunctive radiofrequency ablation for the endoscopic treatment of ampullary lesions with intraductal extension (with video). *Endosc Int Open* 2016;**4**:E748–51. https://doi.org/10.1055/ s-0042-107665 62. Topazian M, Levy MJ, Patel S, Charlton MR, Baron TH. Hepatic artery pseudoaneurysm formation following intraductal biliary radiofrequency ablation. *Endoscopy* 2013;**45**:E161–2. https://doi.org/10.1055/s-0032-1326644 63. Tringali A, Bove V, Perri V, Bokoski I, Familiari P, *et al.* Radiofrequency ablation (RFA) for intrabiliary extension of adenoma of the papilla of vater: preliminary results. *Dig Liver Dis* 2018;**50**:e144 64. Tsoulfas G, Kastanias E, Georgantis G, Mentesidou N, Kalamaras S, Tsiantzi B, *et al.* Clinical and financial outcomes from the coordinated treatment of primary and metastatic hepatobiliary malignancies: early experience of a new center. *HPB* 2012;**14**:552 65. Uhlig J, Nie J, Stein S, Cha C, Kim K. 3:09 PM Abstract No. 33 Comparison of radiofrequency ablation and stereotactic radiotherapy for primary treatment of intrahepatic cholangiocellular carcinoma: results from the National Cancer Database. *J Vasc Interv Radiol* 2020;**31**:S19 66. Valente R, Urban O, Del Chiaro M, Capurso G, Blomberg J, Löhr JM, Arnelo U. ERCP-directed radiofrequency ablation of ampullary adenomas: a knife-sparing alternative in patients unfit for surgery. *Endoscopy* 2015;**47**:E515–6. https://doi.org/10.1055/s-0034-1392866 67. Valente R, Urban O, Del Chiaro M, Lohr M, Blomberg J, Arnelo U. ERCP directed radio-frequency ablation (RFA) of an intra-pancreatic duct (PD) and intra-bile duct (BD) growing ampullary adenoma. A possible safe and mini invasive alternative to surgical treatment. *Pancreatology* 2015;**15**:S98 68. Wang F, Li Q, Ge X, Yu H, Nie J, Miao L. Choledochoscopic radiofrequency ablation for congenital choledochal cysts. *Endoscopy* 2014;**46**:E373–4. https://doi.org/10.1055/s-0034-1367604

TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	69. Wang Y, Ma K, Zhong A, Xiong Q, Chen J. Hepatopulmonary syndrome after radiofrequency ablation of recurrent intrahepatic cholangiocarcinoma: a case report. *Onco Targets Ther* 2019;**12**:2431–8. https://doi.org/10.2147/ OTT.S86702 70. Wang YH, Zheng YM, Teng LH. Hepatic resection for intrahepatic cholangiocarcinoma after a failed trial of radiofrequency ablation. *Chin Med J* 2013;**126**:3594 71. Weigt J, Kandulski A, Malfertheiner P. Endoscopic intraductal radiofrequency ablation of remnant intrapapillary mucinous neoplasm with acute hemorrhage after incomplete surgical resection. *Endoscopy* 2014;**46**:E489–90. https://doi.org/10.1055/s-0034-1377590 72. Wolfsen HC. Endoscopic ablation therapy: imaging and advanced technology in action. *Gastroenterology* 2009;**137**:1225–8. https://doi.org/10.1053/j.gastro.2009.08.039
The paper did not focus on endoscopic RFA plus stenting as the intervention (*n* = 168)	1. ClinicalTrials.gov. *Radiofrequency Ablation Combined With S-1 for Pancreatic Cancer With Liver Metastasis.* URL: https://ClinicalTrials.gov/show/NCT02634502 (accessed 23 September 2022) 2. ClinicalTrials.gov. *Prospective Evaluation of the Ablation Therapy With Bipolar Radio Frequency for Nonresectable Bile Duct Cancer*. URL: https://ClinicalTrials.gov/show/NCT03679338 (accessed 23 September 2022) 3. ClinicalTrials.gov. *Quality of Life After Radiofrequency Ablation of Pancreatic Cancer*. URL: https://ClinicalTrials.gov/show/NCT02637596 (accessed 23 September 2022) 4. ClinicalTrials.gov. *Efficacy and Safety of Radiofrequency Ablation in Pancreatic Neuroendocrine and Cystic Tumor*. URL: https://ClinicalTrials.gov/show/NCT02330497 (accessed 23 September 2022) 5. ClinicalTrials.gov. *Safety Study of Radiofrequency Ablation of Locally Advanced Pancreatic Cancer*. URL: https://ClinicalTrials.gov/show/NCT01628458 (accessed 23 September 2022) 6. ClinicalTrials.gov. *Comparison of Endoscopic Radiofrequency Ablation Versus Photodynamic Therapy for Inoperable Cholangiocarcinoma*. URL: https://ClinicalTrials.gov/show/NCT01739465 (accessed 23 September 2022) 7. ClinicalTrials.gov. *Efficacy and Safety of Endobiliary Radiofrequency Ablation by Using a Novel RF Catheter (ELRA®) on Maintaining the Patency of Endobiliary Metal Drainage in Patients With Malignant Biliary Strictures: A Double-arm Comparable Study*. URL: https://ClinicalTrials.gov/show/NCT02646514 (accessed 23 September 2022) 8. ClinicalTrials.gov. *A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-controlled Study of AG-120 in Previously-treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation*. 2017. URL: https://clinicaltrials.gov/ct2/show/NCT02989857 (accessed November 2021) 9. Agrawal S, Khehra R, Thakkar S, Ganesan S, Kulkarni A. Multiple surgical clips found in duodenum after balloon dilation. *Am J Gastroenterol* 2013;**108**:S308 10. Akinfeyev V, Orehov V, Dudarau V. Massive liver destruction followed by a biloma formation after radiofrequency ablation for multiple HCC. *Cardiovasc and Intervent Radiol* 2012;**35**:S255 11. Andrasina T, Bernard V, Panek J, Hlavsa J, Boudny J, Valek V. Endoluminal ablation for malignant biliary duct stenosis. *Cardiovasc and Intervent Radiol* 2014;**37**:S267 12. Andrasina T, Hlavsa J, Valek V, Kala Z, Neubauer J. Possibilities of radiofrequency ablation of the pancreatic tumors – first experiences. *Ceska Radiologie* 2008;**62**:361–5 13. Andrasina T, Valek V, Panek J, Hlavsa J. Use of endoluminal radiofrequency ablation to recanalize occluded metallic biliary stent. *Cardiovasc and Intervent Radiol* 2010;**33**:213 14. Andren S, berg A, Ansorge C, Gilg S. Pancreatic carcinoma: therapeutic future prospects. *Viszeralmedizin* 2010;**26**:116–21 15. Anonymous. Abstracts of the 9th Congress of the European-African HPBA, E-AHPBA. *HPB* 2011;**13** 16. Anonymous. CIRSE 2012. *Cardiovasc and Intervent Radiol* 2012;**35**

continued

TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	17. Anonymous. Oral. *J Gastroenterol Hepatol (Australia)* 2015;**30**:1–27 18. Anonymous. JGES-Asian International Joint Symposium – with the 17th JGES-KSGE. *Dig Endosc* 2018;**30** 19. Augustine MM, Pawlik TM. Palliation of advanced gastrointestinal malignancies using minimally invasive strategies. *Prog Palliat Care* 2009;**17**:250–60 20. Ayaz E, Aşık M. Endobiliary radiofrequency ablation and percutaneous biliary stent placement for choledocal invasion of renal cell carcinoma. *Turk J Gastroenterol* 2019;**30**:854–7. https://doi.org/10.5152/tjg.2019.18745 21. Ballem N, Berber E, Pitt T, Siperstein A. Laparoscopic radiofrequency ablation of unresectable hepatocellular carcinoma: long-term follow-up. *HPB* 2008;**10**:315–20. https://doi.org/10.1080/13651820802247102 22. Baron TH. Endoscopic management of biliary disorders: diagnostic and therapeutic. *Surg Clin North Am* 2014;**94**:395–411. https://doi.org/10.1016/j.suc.2013.12.005 23. Bartos A, Breazu C, Sparchez Z, Tantau M, Iancu C, Bartos D. Radiofrequency ablation of locally advanced pancreatic tumors. The surgical approach. *Journal of gastrointestinal and liver diseases*: JGLD 2018;**27**:102-4. 24. Baudin E, Caron P, Lombard-Bohas C, Tabarin A, Mitry E, Reznick Y, *et al.* Malignant insulinoma: recommendations for characterisation and treatment. *Ann Endocrinol* 2013;**74**:523–33. https://doi.org/10.1016/j.ando.2013.07.001 25. Begu-Le Corroller A, Valero R, Moutardier V, Henry JF, Le Treut YP, Gueydan M, *et al.* Aggressive multimodal therapy of sporadic malignant insulinoma can improve survival: a retrospective 35-year study of 12 patients. *Diabetes Metab* 2008;**34**:343–8 26. Benson M, Pfau P. Pain relief and the celiac plexus: can burning exceed injecting? *Gastrointest Endosc* 2019;**89**:67–8 27. Berelavichus SV, Kriger AG, Dugarova RS, Kaldarov AR. Treatment of Insulinomas with minimally invasive physical procedure. Literature review. *SN Compr Clin Med* 2019;**1**:104–12 28. Bezzi M. Tips and tricks for challenging cases. *Cardiovasc and Intervent Radiol* 2012;**35**:S21–2 29. Bhuva N,Wasan H, Spalding D, Stamp G, Harrison M. Intraductal tubulopapillary neoplasm of the pancreas as a radiation induced malignancy. *BMJ Case Rep* 2011;**2011**:bcr0920114777. https://doi.org/10.1136/ bcr.09.2011.4777 30. Bohlsen D, Kalmar P, Schreiber F, Portugaller RH. Percutaneous transhepatic biliary drainage and endoscopic retrograde cholangiography in biloma – a rendezvous procedure. *Endoscopy* 2013;**45**:E292–3. https://doi.org/10.1055/s-0033-1344573 31. Brugge WR. EUS. *Gastrointest Endosc* 2013;**78**:414–20 32. Butros SR, Shenoy-Bhangle A, Mueller PR, Arellano RS. Radiofrequency ablation of intrahepatic cholangiocarcinoma: feasibility, local tumor control, and long-term outcome. *Clin Imaging* 2014;**38**:490–4 33. Cananzi FCM, Jayanth A, Lorenzi B, Belgaumkar A, Mochlinski K, Sharma A, *et al.* 'chronic' metastatic pancreatic acinar cell carcinoma. *Pancreatology* 2013;**13**:549–52 34. Cantore M, Girelli R, Mambrini A, Frigerio I, Boz G, Salvia R, *et al.* Combined modality treatment for patients with locally advanced pancreatic adenocarcinoma. *Br J Surg* 2012;**99**:1083–8. https://doi.org/10.1002/bjs.8789 35. Cantore M, Girelli R, Mambrini A, Frigerio I, Boz G, Simoncini E, *et al.* A triple approach strategy for patients with locally advanced pancreatic adenocarcinoma. *J Clin Oncol* 2011;**29** 36. Catalano MF, Aslam N, Taha R, Guda NM, Geenen JE. Endoscopic ampullectomy of adenoma of the major duodenal papilla (MPD): long-term outcome. *Gastrointest Endosc* 2011;**73**:AB270 37. Cavallini M, La Torre M, Citone M, Rossi M, Rebonato A, Nava AK, *et al.* A novel approach in surgical palliation for unresectable pancreatic cancer with untreatable chronic pain: radiofrequency ablation of pancreatic mass and celiac plexus. *Am Surg* 2010;**76**:108–9 38. Chanez B. Caillol F. Ratone J. *P0267 - Endoscopic Radiofrequency Ablation as Focal Therapy for Pancreatic Metastasis from Renal Cell Carcinoma: A Monocentric Experience (Abstract No. 465).* UECG; 2019

TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
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The paper focuses on an ineligible comparator (*n* = 5)	1. Gao DJ, Hu B, Ye X, Wu J,Wang TT, Xia MX, *et al.* Radiofrequency ablation has comparable overall survival to photodynamic therapy in the treatment of cholangiocarcinoma and ampullary carcinoma. *Gastrointest Endosc* 2018;**87**:AB72 2. Gao J, Zhang Q, Zhang J, Kong J,Wang S, Ding X, *et al.* Radiofrequency ablation of the main lesion of hepatocellular carcinoma and bile duct tumor thrombus as a radical therapeutic alternative: two case reports. *Medicine* 2015;**94**:e1122. https://doi.org/10.1097/MD.0000000000001122 3. Kim EJ, Cho JH, Lee YN, Jeong S, Cheon YK, Park SW, *et al.* Efficacy of endobiliary radiofrequency ablation for malignant distal biliary obstruction: Multicenter experience of temperature controlled radiofrequency ablation. *Gastrointest Endosc* 2018;**87**:AB598 4. Schmidt A, Bloechinger M, Weber A, Siveke J, von Delius S, Prinz C, *et al.* Short-term effects and adverse events of endoscopically applied radiofrequency ablation appear to be comparable with photodynamic therapy in hilar cholangiocarcinoma. *United European Gastroenterol J* 2016;**4**:570–9. https://doi.org/10.1177/2050640615621235 5. Str, SD, Cosgrove N, Patrie JT, Cox DG, Sauer BG, *et al.* ERCP-directed radiofrequency ablation and photodynamic therapy are associated with comparable survival in the treatment of unresectable cholangiocarcinoma. *Gastrointest Endosc* 2013;**77**:AB140–AB1
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The paper is an exact duplicate (*n* = 109)	1. A Randomized Trial of Endoscopic Biliary Co-axial Stent Placement Plus/Minus Use of Radiofrequency Ablation (RFA) for Clearance of Occluded Self Expandable Metal Stents (SEMS) in Patients With Distal Biliary Obstruction From Unresectable Biliary-pancreatic Malignancies. 2015 2. A Randomized Trial of Endoscopic Biliary Co-axial Stent Placement Plus/Minus Use of Radiofrequency Ablation (RFA) for Clearance of Occluded Self Expandable Metal Stents (SEMS) in Patients With Distal Biliary Obstruction From Unresectable Biliary-pancreatic Malignancies. 2015 3. Ataei A, Reiss G, Garcia A. Endoscopic radiofrequency ablation as palliative treatment of cholangiocarcinoma. *J Invest Med* 2020;**68**:504 4. Atar M, Kadayifci A, Forcione DG, Casey B, Kelsey PB, Brugge WR. Efficacy of radiofrequency ablation (RFA) for the management of occluded biliary metal stents. *Gastrointest Endosc* 2015;**81**:AB195 5. Atar M, Kadayifci A, Forcione DG, Casey B, Kelsey PB, Brugge WR. Efficacy of radiofrequency ablation (RFA) for the management of occluded biliary metal stents. *Gastrointest Endosc* 2015;**81**:AB195 6. Atar M, Kadayifci A, Forcione DG, Casey B, Kelsey PB, Brugge WR. Efficacy of radiofrequency ablation (RFA) for the management of occluded biliary metal stents. *Gastrointest Endosc* 2015;**81**:AB195 7. Atar M, Kadayifci A, Forcione DG, Casey B, Kelsey PB, Brugge WR. Efficacy of radiofrequency ablation (RFA) for the management of occluded biliary metal stents. *Gastrointest Endosc* 2015;**81**:AB195 8. Choi HJ, Cho JH, Jeong S, Cheon YK, Moon JH, Kim Y, *et al.* Safety and efficacy of endobiliary radiofrequency ablation by using a novel RF catheter (ELRA®) in patients with distal malignant biliary strictures: a single-arm feasibility study. *Gastrointest Endosc* 2017;**85**:AB639–AB40 9. Choi HJ, Cho JH, Jeong S, Cheon YK, Moon JH, Kim Y, *et al.* Tu1466 Safety and efficacy of endobiliary radiofrequency ablation by using a novel RF Catheter (ELRA®) in patients with distal malignant biliary strictures: a single-arm feasibility study ... Digestive Disease Week (DDW) 2017 American Society for Gastrointestinal Endoscopy (ASGE) program and abstracts, Chicago, Illinois, 6–9 May 2017. *Gastrointest Endosc* 2017;**85**:AB639-AB40 10. Choi HJ, Cho JH, Jeong S, Cheon YK, Moon JH, Kim Y, *et al.* Tu1466 Safety and efficacy of endobiliary radiofrequency ablation by using a novel RF catheter (ELRA®) in patients with distal malignant biliary strictures: a single-arm feasibility study ... Digestive Disease Week (DDW) 2017 American Society for Gastrointestinal Endoscopy (ASGE) program and abstracts, Chicago, Illinois, 6–9 May 2017. *Gastrointest Endosc* 2017;**85**:AB633-AB4

TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	11. Choi HJ, Cho JH, Jeong S, Cheon YK, Moon JH, Kim YS, *et al.* Safety and efficacy of endobiliary radiofrequency ablation by using a novel rf catheter (ELRA) in patients with distal malignant biliary strictures: a single-arm feasibility study. *Gastrointest Endosc* 2017;**85**:AB633–AB4 12. Choi HJ, Cho JH, Jeong S, Cheon YK, Moon JH, Kim YS, *et al.* Safety and efficacy of endobiliary radiofrequency ablation by using a novel rf catheter (ELRA) in patients with distal malignant biliary strictures: a single-arm feasibility study. *Gastrointest Endosc* 2017;**85**:AB639–AB40 13. ClinicalTrials.gov. *Radiofrequency Ablation for Malignant Biliary Obstruction*. URL: https://ClinicalTrials.gov/show/NCT01758341 (accessed 27 September 2022) 14. ClinicalTrials.gov. *Radiofrequency Probe for Management of Unresectable Bile Duct and Pancreatic Cancer*. URL: https://ClinicalTrials.gov/show/NCT02042859 (accessed 27 September 2022) 15. ClinicalTrials.gov. *Radiofrequency Ablation for Biliopancreatic Malignancy*. URL: https://ClinicalTrials.gov/show/NCT02468076 (accessed 27 September 2022) 16. ClinicalTrials.gov. *RFA RCT for Pancreatic or Bile Duct Cancer*. URL: https://ClinicalTrials.gov/show/NCT02166190 (accessed 27 September 2022) 17. ClinicalTrials.gov. *RFA for Malignant Biliary Obstruction*. URL: https://ClinicalTrials.gov/show/NCT03166436 18. ClinicalTrials.gov. *Role of Endoscopic RFA in Prolonging the Patency of Metal Stents in Patients With Malignant Obstructive Jaundice*. URL: https://ClinicalTrials.gov/show/ NCT01275768 (accessed 27 September 2022) 19. ClinicalTrials.gov. *Role of Endoscopic RFA in Prolonging the Patency of Metal Stents in Patients With Malignant Obstructive Jaundice*. URL: https://ClinicalTrials.gov/show/NCT01275768 (accessed 27 September 2022) 20. ClinicalTrials.gov. *Role of Endoscopic RFA in Prolonging the Patency of Metal Stents in Patients With Malignant Obstructive Jaundice*. URL: https://ClinicalTrials.gov/show/NCT01275768 (accessed 27 September 2022) 21. ClinicalTrials.gov. *Endoscopic Biliary Radiofrequency Ablation of Malignant Distal Common Bile Duct Strictures*. URL: https://ClinicalTrials.gov/show/NCT01721174 (accessed 27 September 2022) 22. ClinicalTrials.gov. *Comparison of Endoscopic Radiofrequency Ablation Versus Photodynamic Therapy for Inoperable Cholangiocarcinoma*. URL: https://ClinicalTrials.gov/show/NCT01739465 (accessed 27 September 2022) 23. ClinicalTrials.gov. *Endoscopic Biliary Radiofrequency Ablation of Malignant Distal Common Bile Duct Strictures*. URL: https://ClinicalTrials.gov/show/NCT01721174 (accessed 27 September 2022) 24. ClinicalTrials.gov. *Endobiliary RFA for Unresectable Malignant Biliary Strictures*. URL: https://ClinicalTrials.gov/show/NCT01844245 (accessed 27 September 2022) 25. ClinicalTrials.gov. *Endobiliary RFA for Unresectable Malignant Biliary Strictures*. URL: https://ClinicalTrials.gov/show/NCT01844245 (accessed 27 September 2022) 26. ClinicalTrials.gov. *RFA RCT for Pancreatic or Bile Duct Cancer*. URL: https://ClinicalTrials.gov/show/NCT02166190 (accessed 27 September 2022) 27. ClinicalTrials.gov. *RFA RCT for Pancreatic or Bile Duct Cancer*. URL: https://ClinicalTrials.gov/show/NCT02166190 (accessed 27 September 2022) 28. ClinicalTrials.gov. *Endoscopic Biliary Co-axial Stent Placement Plus/Minus Use of Radiofrequency Ablation (RFA) for Clearance of Occluded Self Expandable Metal Stents (SEMS) in Patients With Distal Biliary Obstruction From Unresectable Biliary-pancreatic Malignancies.* URL: https://ClinicalTrials.gov/show/NCT02340728 (accessed 27 September 2022) 29. ClinicalTrials.gov. *Endoscopic Biliary RFA of Malignant Bile Duct Obstruction*. URL: https://ClinicalTrials.gov/show/NCT02582541 (accessed 27 September 2022) 30. ClinicalTrials.gov. *Endoscopic Biliary RFA of Malignant Bile Duct Obstruction*. URL: https://ClinicalTrials.gov/show/NCT02582541 (accessed 27 September 2022) 31. ClinicalTrials.gov. *Endobiliary Radiofrequency Ablation With S-1 for Unresectable Cholangiocarcinoma*. URL: https://ClinicalTrials.gov/show/NCT02592538 (accessed 27 September 2022) 32. ClinicalTrials.gov. *Endoscopic Biliary Co-axial Stent Placement Plus/Minus Use of Radiofrequency Ablation (RFA) for Clearance of Occluded Self Expandable Metal Stents (SEMS) in Patients With Distal Biliary Obstruction From Unresectable Biliary-pancreatic Malignancies*. URL: https://ClinicalTrials.gov/show/NCT02340728 (accessed 27 September 2022)

continued

TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	33. ClinicalTrials.gov. *Efficacy and Safety of Endobiliary Radiofrequency Ablation by Using a Novel RF Catheter (ELRA®) on Maintaining the Patency of Endobiliary Metal Drainage in Patients With Malignant Biliary Strictures: a Double-arm Comparable Study*. URL: https://ClinicalTrials.gov/show/NCT02646514 (accessed 27 September 2022) 34. ClinicalTrials.gov. *Efficacy and Safety of Endobiliary Radiofrequency Ablation by Using a Novel RF Catheter (ELRA®) on Maintaining the Patency of Endobiliary Metal Drainage in Patients With Malignant Biliary Strictures: a Double-arm Comparable Study*. URL: https://ClinicalTrials.gov/show/NCT02646514 (accessed 27 September 2022) 35. ClinicalTrials.gov. *Cholangioscopic Assessment of Occluded Biliary Stent and Role of Biliary Radiofrequency Ablation*. URL: https://ClinicalTrials.gov/show/NCT03133026 (accessed 27 September 2022) 36. ClinicalTrials.gov. *RFA for Malignant Biliary Obstruction*. URL: https:// ClinicalTrials.gov/show/NCT03166436 (accessed 27 September 2022) 37. ClinicalTrials.gov. *RFA for Malignant Biliary Obstruction*. URL: https:// ClinicalTrials.gov/show/NCT03166436 (accessed 27 September 2022) 38. ClinicalTrials.gov. *Cholangioscopic Assessment of Occluded Biliary Stent and Role of Biliary Radiofrequency Ablation*. URL: https://ClinicalTrials.gov/show/NCT03133026 (accessed 27 September 2022) 39. UMIN-CTR Clinical Trial. *Endoscopic Biliary Radiofrequency Ablation with Multiple Metal Stents in Patients with Unresectable Malignant Hilar Biliary Stenosis: A Multicenter Prospective Observation Study*. 2017. URL: https://center6.umin.ac.jp/cgi-open-bin/ ctr_e/ctr_view.cgi?recptno=R000030078 (accessed 16 November 2022) 40. Dolak W, Schreiber F, Schwaighofer H, Gschwantler M, Plieschnegger W, Ziachehabi A, *et al.* Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications. *Surg Endosc* 2014;**28**:854–60. https://doi.org/10.1007/s00464-013-3232-9 41. Dutta AK, Basavaraju U, Sales L, Leeds JS. Radiofrequency ablation for management of malignant biliary obstruction. *Gut* 2015;**64**:A216–A7 42. Dutta AK, Basavaraju U, Sales L, Leeds JS. Radiofrequency ablation for management of malignant biliary obstruction: a single-center experience and review of the literature. *Expert Rev Gastroenterol Hepatol* 2017;**11**:779–84. https://doi.org/10.1080/17474124.2017.1314784 43. Ermerak G, Wu N, Abi HD, Edwards P, Bassan M. Endoscopic biliary radiofrequency ablation for the palliative management of malignant biliary obstruction: a prospective case series. *J Gastroenterol Hepatol* 2018;**33**:4 44. UMIN-CTR Clinical Trial. *Prospective Evaluation of Radiofrequency Ablation for Stent Occlusion After Bilateral Metal Stent Placement in Patients With Malignant Hilar Biliary Obstructions*. 2020. URL: https://center6.umin.ac.jp/cgi-open-bin/ ctr_e/ctr_view.cgi?recptno=R000045784 (accessed 16 November 2022) 45. Gunasingam N, Craig PI. Cholangioscopy-directed radiofrequency ablation of complex biliary cholangiocarcinoma. *Video GIE* 2019;**4**:211–13 46. Hashimoto S, Tanoue S, Iwashita Y, Kamikihara Y, Tsuneyoshi K, Nakamura Y, *et al. Short-Term Outcomes of Endoscopic Radiofrequency Ablation for Unresectable Malignant Hilar Biliary Obstruction*.Vienna: United European Gastroenterology; 2019 47. Han SY, Kim DU, Baek DH, Kim GH, Song GA. OE-0590 (PE-0036) the feasibility of temperature controlled endobiliary radiofrequency ablation in patients with advanced hilar cholangiocarcinoma. *J Gastroenterol Hepatol* 2018;**33**:238 48. UMIN-CTR Clinical Trial. *Exploratory Survey of the Safety and Efficacy of Endoscopic Radiofrequency Ablation for Malignant Biliary Stricture*. 2018. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000036026 (accessed 16 November 2022) 49. Hashimoto S, Tanoue S, Iwashita Y, Kamikihara Y, Tsuneyoshi K, Nakamura Y, *et al.* Short-term outcomes of endoscopic radiofrequency ablation for unresectable malignant hilarbiliary obstruction. *United European Gastroenterol J* 2019;**7**:297 50. World Health Organization International Clinical Trials Registry Platform Search Portal. *Treatment of Endobiliary Radiofrequency Ablation for the Treatment of Malignant Extrahepatic Biliary Stricture*. 2018. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=KCT0003373 (accessed 16 November 2022)

TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	51. Hu B. ERCP-guided radiofrequency ablation as the primary therapy for inoperable ampullary carcinomas. *J Gastroenterol Hepatol* 2018;**33**:121 52. Hu B, Gao DJ,Wu J, Pan YM,Wang TT, Yang XM, *et al.* Intraductal radiofrequency ablation for the resolution of refractory benign biliary stricture. *Gastrointest Endosc* 2013;**77**:AB320 53. Hu B, Gao DJ,Wu J, Sun B. Endobiliary radiofrequency ablation as the principal therapy for papillary carcinomas unsuitable for surgery. *Gastrointest Endosc* 2018;**87**:AB595–AB6 54. Hu B, Gao DJ,Wu J,Wang TT, Yang XM, Ye X. Intraductal radiofrequency ablation for refractory benign biliary stricture: pilot feasibility study. *Dig Endosc* 2014;**26**:581–5. https://doi.org/10.1111/den.12225 55. Hu B, Gao DJ, Zhang X, Zhang YC. Endobiliary radiofrequency ablation improve overall survival of cholangiocarcinoma: a multi-center randomized control study. *Gastrointest Endosc* 2016;**83**:AB126 56. Hu B, Gao D-j, Zhang X, Zhang Y-c. 121 Endobiliary radiofrequency ablation improve overall survival of cholangiocarcinoma: a multi-center randomized control study ... 2016 DDW (Digestive Disease Week) ASGE (American Society for Gastrointestinal Endoscopy) program and abstracts 21 May 2016–24 May 2016, San Diego, California. *Gastrointest Endosc* 2016;**83**:AB126 57. Hucl T, Macinga P, Gogova D, Fronek J, Spicak J. Radiofrequency ablation plus stenting vs. stenting alone in the treatment of pancreatic cancer and cholangiocarcinoma. *Pancreas* 2018;**47**:1394 58. UMIN-CTR Clinical Trial. Endobiliary Radiofrequency Ablation Using A New Catheter for Malignant Biliary Strictures: *A Prospective Multicenter Study*. 2017. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000029721 (accessed 16 November 2022) 59. World Health Organization International Clinical Trials Registry Platform Search Portal. *Comparison of Endoscopic Radiofrequency Ablation Versus Stenting Alone for the Treatment of Unresectable Malignant Biliary Obstruction*. 2020. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=KCT0004623 (accessed 16 November 2022) 60. Jianfeng Yang N, Zhou Y, Jin H, Gu W, Zhang X. Tu1404 Endoscopic biliary radiofrequency ablation prolong the survival of patients with unrespectable extrahepatic cholangiocarcinoma ... Digestive Disease Week (DDW) 2017 American Society for Gastrointestinal Endoscopy (ASGE) program and abstracts, Chicago, Illinois, 6–9 May 2017. *Gastrointest Endosc* 2017;**85**:AB605 61. Kallis YN, Phillips N, Steel A, Baldwin CH, Nicholls J, Jiao LR, *et al.* First report of the long term efficacy of a novel endoscopic radiofrequency ablation technique for malignant biliary obstruction. *Hepatology* 2011;**54**:1365A–6A 62. Kim DU, Baek DH, Kim CW, Song GA. Su1611 Temperature-controlled intraductal radiofrequency ablation for hilar cholangiocarcinoma: pilot feasibility study. *Gastrointest Endosc* 2015;**81**:AB350 63. Kim DU, Baek DH, Kim CW, Song GA. Temperature-controlled intraductal radiofrequency ablation for hilar cholangiocarcinoma: pilot feasibility study. *Gastrointest Endosc* 2015;**81**:AB350 64. Kruger AJ, Krishna SG. An unexpected outcome following radiofrequency ablation of a malignant biliary stricture. *Am J Gastroenterol* 2017;**112**:S1126 65. Kruger AJ, Krishna SG. Unexpected outcome following radiofrequency ablation of a malignant biliary stricture. *Turk J Gastroenterol* 2018;**29**:230–2 66. Lorenzo D, Barret M, Bordacahar B, Leblanc S, Chaussade S, Cattan P, Prat F. Intraductal radiofrequency ablation of an intraductal papillary mucinous neoplasia of the main pancreatic duct. *Endoscopy* 2018;**50**:176–7. https://doi.org/ 10.1055/s-0043-121459 67. Lou JY, Su W, Wei SM, Huang FB, Chen W,Wang J, *et al.* [Clinical features, diagnosis and treatment of intraductal papillary neoplasm of the bile duct.] *Zhonghua Wai Ke Za Zhi* 2018;**56**:350–4. https://doi.org/10.3760/cma.j.issn.0529-5815.2018.05.006 68. Ludvik N, Kumar M, Fahmawi Y, Mizrahi M. Fire in the hole! Role of radiofrequency ablation for biliary stent occlusion: prolonging the stent patency. *Am J Gastroenterol* 2019;**114**:S767 69. Lui KL, Li KK. Intraductal radiofrequency ablation of tumour ingrowth into an uncovered metal stent used for inoperable cholangiocarcinoma. *Hong Kong Med J* 2013;**19**:539–41. https://doi.org/10.12809/hkmj133867

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TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	70. Mansilla-Vivar R, Argüello-Viúdez L, Sánchez-Montes C, Alonso-Lázaro N, Pons-Beltrán V. Endoluminal radiofrequency ablation with SpyGlass™ in the management of cholangiocarcinoma. *Rev Esp Enferm Dig* 2019;**111**:803–5 71. Mok SRS, Khara HS, Johal AS, Confer BD, Diehl DL. Cholangioscopic appearance after radiofrequency ablation of cholangiocarcinoma. *VideoGIE* 2017;**2**:279–83 72. Monga A, Gupta R, Ramchandani M, Rao GV, Santosh D, Reddy DN. Endoscopic radiofrequency ablation of cholangiocarcinoma: new palliative treatment modality (with videos). *Gastrointest Endosc* 2011;**74**:935–7. https://doi.org/10.1016/j.gie.2010.10.018 73. Monga A, Wee EWL, Gupta R, Ramch, ani M, Reddy DN. Endoscopic radiofrequency ablation of unresectable malignant obstructive jaundice. *Ann Acad Med Singap* 2011;**40**:S132 74. Morales MJ, De La Mora-Levy JG, Ortega Espinosa CR, Alonso-Larraga JO, Ramirez-Solis ME, Del Monte JS, *et al.* Endoscopic radio-frequency ablation of biliary strictures unleashed: a case series in a variety of clinical scenarios. *Gastrointest Endosc* 2017;**85**:AB640 75. Mukund A, Arora A, Rajesh S, Bothra P, Patidar Y. Endobiliary radiofrequency ablation for reopening of occluded biliary stents: a promising technique. *J Vasc Interv Radiol* 2013;**24**:142–4. https://doi.org/10.1016/j.jvir.2012.09.018 76. Mukund A, Rajesh S, Arora A, a D. Endobiliary RFA and balloon sweep to restore the patency of occluded metallic biliary stents-a feasibility study. *J Vasc Interv Radiol* 2014;**25**:S75 77. Musquer N, Ménager Tabourel E, Luet D, Caroli-Bosc FX, Métivier Cesbron E. Recanalization of obstructed metallic uncovered biliary stent using endobiliary radiofrequency ablation. *Gastrointest Endosc* 2016;**83**:256–7. https://doi.org/10.1016/j.gie.2015.07.010 78. Ogura T, Onda S, Sano T, Takagi W, Okuda A, Miyano A, *et al.* Evaluation of the safety of endoscopic radiofrequency ablation for malignant biliary stricture using a digital peroral cholangioscope (with videos). *Gastroenterological Endosc* 2018;**60**:270–6 79. Ogura T, Ueno S, Nishioka N, Yamada M, Higuchi K. Success of stent-in-stent deployment after intraductal radiofrequency ablation for hepatic hilar obstruction. *Endoscopy* 2020;**52**:E206–E207. https://doi.org/10.1055/ a-1067-4213 80. Powers P, Adler DG. Radiofrequency ablation for biliary disease. *Pract Gastroenterol* 2018;**42**:17–29 81. Rao B, Garg M, Gulati A, Singh S, Thakkar S. 1048 Successful use of radiofrequency ablation for the management of a recurrent ampullary adenoma with intraductal extension ... Digestive Disease Week (DDW) 2017 American Society for Gastrointestinal Endoscopy (ASGE) program and abstracts, Chicago, Illinois, 6–9 May 2017. *Gastrointest Endosc* 2017;**85**:AB128 82. Ribeiro AL. Tu1426 Endobiliary radiofrequency ablation for palliation of malignant biliary stricture ... Digestive Disease Week (DDW) 2017 American Society for Gastrointestinal Endoscopy (ASGE) program and abstracts, Chicago, Illinois, 6–9 May 2017. *Gastrointest Endosc* 2017;**85**:AB616 83. Rustagi T, Irani S, Reddy ND, Abu Dayyeh BK, Baron TH, Gostout C, *et al.* Sa2015 Endoscopic radiofrequency ablation for intraductal extension of ampullary neoplasms ... 2016 DDW (Digestive Disease Week) ASGE (American Society for Gastrointestinal Endoscopy) program and abstracts 21 May 2016–24 May 2016, San Diego, California. *Gastrointest Endosc* 2016;**83**:AB298 84. Rustagi T, Irani S, Reddy ND, Abu Dayyeh BK, Baron TH, Gostout C, *et al.* Sa2015 Endoscopic radiofrequency ablation for intraductal extension of ampullary neoplasms ... 2016 DDW (Digestive Disease Week) ASGE (American Society for Gastrointestinal Endoscopy) program and abstracts 21 May 2016-24 May 2016, San Diego, California. *Gastrointest Endosc* 2016;**83**:AB298 85. Sampath K, Hyder SM, Gardner T, Gordon SR. Tu1526 The effect of endoscopic radiofrequency ablation on survival in patients with unresectable peri-hilar cholangiocarcinoma. *Gastrointest Endosc* 2016;**83**:AB595 86. Sharaiha RZ, Widmer JL, Sarkaria S, Natov N, Gaidhane M, Kahaleh M. Comparison of self expanding metal stenting with radiofrequency ablation versus stenting alone in the treatment of malignant biliary strictures: is there an added benefit? *Gastrointest Endosc* 2013;**77**:AB300–AB1

TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	87. Steel A, Postgate AJ, Vlavianos P, Khors, i SE, Habib N, *et al.* The use of a novel endoscopically placed radiofrequency probe for the management of malignant bile duct obstruction. *Gastrointest Endosc* 2010;**71**:AB321 88. Suarez AL, Coté GA, Elmunzer BJ. Adjunctive radiofrequency ablation for the endoscopic treatment of ampullary lesions with intraductal extension (with video). *Endosc* Int Open 2016;**4**:E748–51. https://doi.org/10.1055/ s-0042-107665 89. Tal A, Trojan J, Albert JG. Intraductal radiofrequency ablation: new palliative treatment modality for cholangiocarcinoma. *Gastroenterologe* 2013;**8**:235–40 90. Tian Q,Wang G, Zhang Y, Jin Y, Cui Z, Sun X, Shen Z. Endoscopic radiofrequency ablation combined with fully covered self-expandable metal stent for inoperable periampullary carcinoma in a liver transplant patient: a case report. *Medicine* 2017;**96**:e5790. https://doi.org/10.1097/ MD.0000000000005790 91. Tian Q,Wang G, Zhang Y, Jin Y, Cui Z, Sun X, Shen Z. Endoscopic radiofrequency ablation combined with fully covered self-expandable metal stent for inoperable periampullary carcinoma in a liver transplant patient: a case report. *Medicine* 2017;**96**:e5790. https://doi.org/10.1097/ MD.0000000000005790 92. Tian Q,Wang G, Zhang Y, Jin Y, Cui Z, Sun X, Shen Z. Endoscopic radiofrequency ablation combined with fully covered self-expandable metal stent for inoperable periampullary carcinoma in a liver transplant patient: a case report. *Medicine* 2017;**96**:e5790. https://doi.org/10.1097/ MD.0000000000005790 93. Topazian M, Levy MJ, Patel S, Charlton MR, Baron TH. Hepatic artery pseudoaneurysm formation following intraductal biliary radiofrequency ablation. *Endoscopy* 2013;**45**:E161–2. https://doi.org/10.1055/s-0032-1326644 94. Tringali A, Bove V, Valerii G, i R, Perri V, Boskoski I, *et al.* Radiofrequency ablation (RFA) for intrabiliary extension of adenoma of the papilla of vater: preliminary results. *United European Gastroenterol J* 2018;**6**:A606–A7 95. Tringali A, Bove V, Valerii G, i R, Perri V, Boskoski I, *et al.* Radiofrequency ablation (RFA) for intrabiliary extension of adenoma of the papilla of vater: preliminary results. *United European Gastroenterol J* 2018;**6**:A606–A7 96. Tyberg A, Zerbo S, Sharaiha RZ, Kahaleh M. Digital cholangioscopy: assessing the impact of radiofrequency ablation. *Endoscopy* 2015;**47**:E544. https://doi.org/10.1055/s-0034-1393144 97. Thai Clinical Trials Registry. *Endobiliary Radiofrequency Ablation in Recurrence and Unresectable Cholangiocarcinoma (EBRFA_THAI)*. 2019. URL: https://www.thaiclinicaltrials.org/show/TCTR20190704002# (accessed 16 November 2022) 98. Uppal DS, Northup PG, Argo CK, Pelletier SJ, Maluf DG, Rahma OE, *et al.* Endoscopically-delivered neoadjuvant photodynamic therapy and radiofrequency ablation in patients with unresectable cholangiocarcinoma awaiting liver transplantation: a pilot experience. *Gastroenterology* 2015;**148**:S1029 99. Wu J, Gao DJ, Hu B. Endoscopic radiofrequency ablation for management of occluded metal stents in malignant distal biliary obstruction. *Gastrointest Endosc* 2017;**85**:AB95 100. Wu J, Gao D-j, Hu B. 680 Endoscopic radiofrequency ablation for management of occluded metal stents in malignant distal biliary obstruction ... Digestive Disease Week (DDW) 2017 American Society for Gastrointestinal Endoscopy (ASGE) program and abstracts, Chicago, Illinois, 6–9 May 2017. *Gastrointest Endosc* 2017;**85**:AB95 101. Wu J, Pan YM,Wang TT, Gao DJ, Hu B. Biliary drainage combined with intraductal radiofrequency ablation for treatment of malignant biliary obstruction. *Acad J Second Mil Med Univ* 2013;**34**:257–60 102. Wu L, Tsilimigras DI, Farooq A, Hyer JM, Merath K, Paredes AZ, *et al.* Potential survival benefit of radiofrequency ablation for small solitary intrahepatic cholangiocarcinoma in nonsurgically managed patients: a population-based analysis. *J Surg Oncol* 2019;**120**:1358–64. https://doi.org/10.1002/jso.25736 103. Yang J. Clinical effect and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma, a prospective study. *United European Gastroenterol J* 2017:A124–A5

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TABLE 17 Clinical effectiveness review: excluded articles (*continued*)

Reason for exclusion	Reference
	104. Yang J. Clinical effect and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma, a prospective study. *United European Gastroenterol* J 2017:A124–A5 105. Yang J, Han S, Zhang X, Shah RJ. 1115 The efficacy and safety of endoscopic papillectomy combined with endobiliary radiofrequency ablation for ampullary neoplasms with intraductal biliary extension ... Digestive Disease Week, May 18–21, 2019, San Diego, CA. *Gastrointest Endosc* 2019;**89**:AB138 106. Yang J, Zhang X, Lou Q, Lv W, Jin H. Efficacy and safety of endobiliary radiofrequency ablation in treatment of nonresectable extrahepatic cholangiocarcinoma. *J Gastroenterol Hepatol* 2016;**31**:221 107. Yoon WJ, Brugge WR. Radiofrequency ablation of malignant biliary obstruction. *Gastrointest Endosc* 2012;**75**:AB116 108. Zheng X, Bo ZY,Wan W,Wu YC,Wang TT, Wu J, *et al*. Endoscopic radiofrequency ablation may be preferable in the management of malignant biliary obstruction: a systematic review and meta-analysis. *J Dig Dis* 2016;**17**:716–24. https://doi.org/10.1111/1751-2980.12429 109. Zheng X, Bo ZY,Wan W,Wu YC,Wang TT, Wu J, *et al*. Endoscopic radiofrequency ablation may be preferable in the management of malignant biliary obstruction: a systematic review and meta-analysis. *J Dig Dis* 2016;**17**:716–24. https://doi.org/10.1111/1751-2980.12429
The paper was an animal study (*n* = 1)	1. Inoue T, Ito K, Yoneda M. Novel balloon catheter-based endobiliary radiofrequency ablation system: ex-vivo experimental study. *Dig Endosc* 2020;**32**:974–8. https://doi.org/10.1111/den.13622

Appendix 4 Included studies list: clinical effectiveness review

TABLE 18 Clinical effectiveness review: included articles grouped according to study

Study	Article type	Reference
Gao 2020	Paper	Gao DJ, Yang JF, Ma SR, Wu J,Wang TT, Jin HB, *et al.* Endoscopic radiofrequency ablation plus plastic stent placement versus stent placement alone for unresectable extrahepatic biliary cancer: a multicenter randomized controlled trial. *Gastrointest Endosc* 2021;**94**:91–100.e2
Yang 2018	Paper	Yang J,Wang J, Zhou H, Zhou Y,Wang Y, Jin H, *et al.* Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. *Endoscopy* 2018;**50**:751–60. https://doi.org/10.1055/s-0043-124870
	Trial registry	ClinicalTrials.gov. *Endobiliary Radiofrequency Ablation With S-1 for Unresectable Cholangiocarcinoma*. URL: https://ClinicalTrials.gov/show/NCT02592538 (accessed 27 September 2022)
Hu 2016	Abstract	Hu B, Gao DJ, Zhang X, Zhang YC. Endobiliary radiofrequency ablation improve overall survival of cholangiocarcinoma: a multi-center randomized control study. *Gastrointest Endosc* 2016;**83**:AB126
	Abstract	Hu B, Gao D-j, Zhang X, Zhang Y-c. 121 Endobiliary radiofrequency ablation improve overall survival of cholangiocarcinoma: a multi-center randomized control study ... 2016 DDW (Digestive DiseaseWeek) ASGE (American Society for Gastrointestinal Endoscopy) program and abstracts 21 May 2016–24 May 2016, San Diego, California. *Gastrointest Endosc* 2016;**83**:AB126
	Trial registry	ClinicalTrials.gov. *Endobiliary RFA for Unresectable Malignant Biliary Strictures*. URL: https://ClinicalTrials.gov/show/NCT01844245 (accessed 27 September 2022)
Hucl 2018	Abstract	Hucl T, Macinga P, Gogova D, Fronek J, Spicak J. Radiofrequency ablation plus stenting vs. stenting alone in the treatment of pancreatic cancer and cholangiocarcinoma. *Pancreas* 2018;**47**:1394
	Trial registry	ClinicalTrials.gov. *RFA for Malignant Biliary Obstruction*. URL: https://ClinicalTrials. gov/show/NCT03166436 (accessed 27 September 2022)
Teoh 2018	Abstract	Teoh AY, Cheung SY, Chong C, Lee KF, Ng EK, Lai PB, *et al.* Endoscopic biliary radiofrequency ablation for malignant distal common bile duct strictures does not improve survival. A randomized controlled trial. *Gastrointest Endosc* 2018;**87**:AB104–AB5
	Trial registry	ClinicalTrials.gov. *Endoscopic Biliary Radiofrequency Ablation of Malignant Distal Common Bile Duct Strictures*. URL: https://ClinicalTrials.gov/show/NCT01721174 (accessed 27 September 2022)
Yang 2017	Abstract	Yang J, Zhou Y, Jin H, Gu W, Zhang X. Endoscopic biliary radiofrequency ablation prolong the survival of patients with unrespectable extrahepatic cholangiocarcinoma. *Gastrointest Endosc* 2017;**85**:AB605
	Abstract	Yang J. Clinical effect and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma, a prospective study. *United European Gastroenterol J* 2017:A124–A5

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TABLE 18 Clinical effectiveness review: included articles grouped according to study (*continued*)

Study	Article type	Reference
Bokemeyer 2019	Paper	Bokemeyer A, Matern P, Bettenworth D, Cordes F, Nowacki TM, Heinzow H, *et al.* Endoscopic radiofrequency ablation prolongs survival of patients with unresectable hilar cholangiocellular carcinoma – a case–control study. *Sci Rep* 2019;**9**:13685. https://doi.org/10.1038/s41598-019-50132-0
	Abstract	Bokemeyer A, Matern P, Bettenworth D, Cordes F, Nowacki T, Heinzow H, *et al.* Endoscopic radiofrequency ablation prolongs survival in patients with advanced hilar cholangiocellular carcinomas. *Endoscopy* 2019;**51**:S36
Kallis 2015	Paper	Kallis Y, Phillips N, Steel A, Kaltsidis H, Vlavianos P, Habib N, Westaby D. Analysis of endoscopic radiofrequency ablation of biliary malignant strictures in pancreatic cancer suggests potential survival benefit. *Dig Dis Sci* 2015;**60**:3449–55. https://doi.org/10.1007/s10620-015-3731-8
Sharaiha 2014	Paper	Sharaiha RZ, Natov N, Glockenberg KS, Widmer J, Gaidhane M, Kahaleh M. Comparison of metal stenting with radiofrequency ablation versus stenting alone for treating malignant biliary strictures: is there an added benefit? *Dig Dis Sci* 2014;**59**:3099–102
	Abstract	Sharaiha RZ, Widmer J, Natov N, Gaidhane M, Kahaleh M. Comparison of self expanding metal stenting with radiofrequency ablation versus stenting alone in the treatment of malignant biliary strictures: is there an added benefit? *United European Gastroenterol J* 2013;**1**:A456
	Trial registry	ClinicalTrials.gov. *Radio Frequency Ablation in the Management of Pancreatico-biliary Disorders: A Multicenter Registry*. URL: https://ClinicalTrials.gov/show/NCT01439698 (accessed 27 September 2022)
Dutta 2017	Paper	Dutta AK, Basavaraju U, Sales L, Leeds JS. Radiofrequency ablation for management of malignant biliary obstruction: a single-center experience and review of the literature. *Expert Rev Gastroenterol Hepatol* 2017;**11**:779–84. https://doi.org/10.1080/17474124.2017.1314784
	Abstract	Dutta AK, Basavaraju U, Sales L, Leeds JS. Radiofrequency ablation for management of malignant biliary obstruction. *Gut* 2015;**64**:A216–A7
Kadayifci 2016	Paper	Kadayifci A, Atar M, Forcione DG, Casey BW, Kelsey PB, Brugge WR. Radiofrequency ablation for the management of occluded biliary metal stents. *Endoscopy* 2016;**48**:1096–101. https://doi.org/10.1055/s-0042-115938
	Abstract	Atar M, Kadayifci A, Forcione DG, Casey B, Kelsey PB, Brugge WR. 1061 Efficacy of radiofrequency ablation (RFA) for the management of occluded biliary metal stents. *Gastrointest Endosc* 2015;**81**:AB195
Andalib 2017	Abstract	Andalib I, Tyberg A, Siddiqui A, Novikov AA, Gaidhane M, Kedia P, *et al.* Comparison of endoscopically applied radiofrequency ablation with stenting versus stenting alone in patients with unresectable malignant biliary obstruction: can we improve our biliary drainage? *Gastrointest Endosc* 2017;**85**:AB611–AB2
Buerlein 2019	Abstract	Buerlein R, Strand DS, Patrie JT, Sauer BG, Shami VM, Scheiman JM, *et al.* 544 ERCP-directed biliary ablation prolongs survival in patients with unresectable perihilar cholangiocarcinoma compared to stenting alone. *Gastrointest Endosc* 2019;**89**:AB91–AB2
Kallis 2011	Abstract	Kallis Y, Phillips N, Steel A, Baldwin C, Nicholls J, Jiao L, *et al.* First report of the long-term efficacy of a novel endoscopic radiofrequency ablation technique for malignant biliary obstruction. *Gut* 2011;**60**:A9
Nair 2020	Abstract	Nair P, Rao H, Koshy A, Venu RP. Safety and efficacy of intraluminal RFA for inoperable cholangiocarcinoma – a prospective cohort study. *J Gastroenterol Hepatol* 2019;**34**:622. https://doi.org/10.1111/jgh.14865

TABLE 18 Clinical effectiveness review: included articles grouped according to study (*continued*)

Study	Article type	Reference
Sampath 2016	Abstract	Sampath K, Hyder SM, Gardner T, Gordon SR. The effect of endoscopic radiofrequency ablation on survival in patients with unresectable peri-hilar cholangiocarcinoma. *Gastrointest Endosc* 2016;**83**:AB595
Schwarzer 2016	Abstract	Schwarzer R, Hametner S, Ziachehabi A, Gerstl S, Fugger R, Schofl R, *et al.* Therapeutic options in patients with malignant biliary obstruction-a retrospective single center analyze. *Z Gastroenterologie* 2016;**54**
Wu 2017	Abstract	Wu J, Gao DJ, Hu B. Endoscopic radiofrequency ablation for management of occluded metal stents in malignant distal biliary obstruction. *Gastrointest Endosc* 2017;**85**:AB95
Alis 2013	Paper	Alis H, Sengoz C, Gonenc M, Kalayci MU, Kocatas A. Endobiliary radiofrequency ablation for malignant biliary obstruction. *Hepatobiliary Pancreat Dis Int* 2013;**12**:423–7
Dolak 2014	Paper	Dolak W, Schreiber F, Schwaighofer H, Gschwantler M, Plieschnegger W, Ziachehabi A, *et al.* Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications. *Surg Endosc* 2014;**28**:854–60. https://doi.org/10.1007/s00464-013-3232-9
	Trial registry	ClinicalTrials.gov. *Radiofrequency Ablation for Malignant Biliary Obstruction*. URL: https://ClinicalTrials.gov/show/NCT01758341 (accessed 27 September 2022)
Figueroa-Barojas 2013	Paper	Figueroa-Barojas P, Bakhru MR, Habib NA, Ellen K, Millman J, Jamal-Kabani A, *et al.* Safety and efficacy of radiofrequency ablation in the management of unresectable bile duct and pancreatic cancer: a novel palliation technique. *J Oncol* 2013;**2013**:910897. https://doi.org/10.1155/2013/910897
	Abstract	Figueroa-Barojas P, Bakhru MR, Habib N, Ellen K, Gaidhane M, Kahaleh M. Safety and efficacy of radiofrequency ablation in the management of unresectable bile duct and pancreatic cancer: a novel palliation technique. *Gastrointest Endosc* 2011;**73**:AB127
	Trial registry	ClinicalTrials.gov. *Endoscopic Bipolar Radiofrequency Probe (ENDOHPB) in the Management of Unresectable Bile Duct and Pancreatic Cancer*. In: https://ClinicalTrials.gov/show/NCT01303159 (accessed 27 September 2022)
Han 2020	Paper	Han SY, Kim DU, Kang DH, Baek DH, Lee TH, Cho JH. Usefulness of intraductal RFA in patients with malignant biliary obstruction. *Medicine* 2020;**99**:e21724. https://doi.org/10.1097/MD.0000000000021724
Lee 2019	Paper	Lee YN, Jeong S, Choi HJ, Cho JH, Cheon YK, Park SW, *et al.* The safety of newly developed automatic temperature-controlled endobiliary radiofrequency ablation system for malignant biliary strictures: a prospective multicenter study. *J Gastroenterol Hepatol* 2019;**34**:1454–9. https://doi.org/ 10.1111/jgh.14657
Ogura 2017	Paper	Ogura T, Onda S, Sano T, Takagi W, Okuda A, Miyano A, *et al.* Evaluation of the safety of endoscopic radiofrequency ablation for malignant biliary stricture using a digital peroral cholangioscope (with videos). *Dig Endosc* 2017;**29**:712–17. https://doi.org/10.1111/den.12837
Sharaiha 2015	Paper	Sharaiha RZ, Sethi A, Weaver KR, Gonda TA, Shah RJ, Fukami N, *et al.* Impact of radiofrequency ablation on malignant biliary strictures: results of a collaborative registry. *Dig Dis Sci* 2015;**60**:2164–9. https://doi.org/10.1007/s10620-015-3558-3
Steel 2011	Paper	Steel AW, Postgate AJ, Khorsandi S, Nicholls J, Jiao L, Vlavianos P, *et al.* Endoscopically applied radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction. *Gastrointest Endosc* 2011;**73**:149–53. https://doi.org/10.1016/j.gie.2010.09.031
	Abstract	Steel A, Postgate A, Vlavianos P, Khorsandi S, Habib N, Westaby D. PTU-021 The use of a novel endoscopically placed radiofrequency probe for the management of malignant bile duct obstruction. *Gut* 2010;**59**:A56–A57

continued

TABLE 18 Clinical effectiveness review: included articles grouped according to study (*continued*)

Study	Article type	Reference
Tal 2014	Paper	Tal AO, Vermehren J, Friedrich-Rust M, Bojunga J, Sarrazin C, Zeuzem S, *et al.* Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction. *World J Gastrointest Endosc* 2014;**6**:13–19. https://doi.org/10.4253/wjge.v6.i1.13
	Abstract	Tal AO, Rust FM, Trojan J, Sarrazin C, Zeuzem S, Albert JG. Endoscopic treatment of malignant biliary stricture by intraductal radio-frequency ablation (RFA)-safety concerns from a pilot study. *Gastrointest Endosc* 2013;**77**:AB305
Battish 2016	Abstract	Battish R, Lewis ME, Dehel BA, Niesley ME, Vashi P. Efficacy and safety of endoscopic retrograde cholango-pancreatography (ERCP) guided biliary radiofrequency ablation (RFA). *Gastrointest Endosc* 2016;**83**:AB612
De Nucci 2019	Abstract	De Nucci G, Domenico M, elli E, Redaelli D, Reati R, Morganti D, *et al.* Endoscopic radiofrequency ablation for extrahepatic malignant biliary obstruction: safety and efficacy of a single center experience. *Endoscopy* 2019;**51**:S154–S5
Ermerak 2018	Abstract	Ermerak G, Wu N, Abi HD, Edwards P, Bassan M. Endoscopic biliary radiofrequency ablation for the palliative management of malignant biliary obstruction: a prospective case series. *J Gastroenterol Hepatol* 2018;**33**:4
Han 2019	Abstract	Han S, Kim DU, Lee MW, Lee SH, Baek DH, Lee BE, *et al.* The feasibility of temperature-controlled endobiliary radiofrequency ablation in patients with advanced hilar cholangiocarcinoma. *Gastrointest Endosc* 2019;**89**:AB219
Hashimoto 2019	Abstract	Hashimoto S, Tanoue S, Iwashita Y, Kamikihara Y, Tsuneyoshi K, Nakamura Y, *et al. Short-Term Outcomes of Endoscopic Radiofrequency Ablation for Unresectable Malignant Hilar Biliary Obstruction*. Vienna: United European Gastroenterology; 2019
Kahaleh 2014	Abstract	Kahaleh M, Sharaiha RZ, Sethi A, Gonda TA, Shah RJ, Fukami N, *et al.* Radiofrequency ablation for palliation of malignant biliary strictures: an American collaborative experience. *Gastrointest Endosc* 2014;**79**:AB232
Kallis 2012	Abstract	Kallis Y, Phillips N, Steel A, Dickinson R, Nicholls J, Jiao L, *et al.* Radiofrequency ablation for biliary metal stent occlusion: Evolution of a novel endoscopic technique and proof of concept. *Gastrointest Endosc* 2012;**75**:AB377–AB8
Ribeiro 2017	Abstract	Ribeiro AL. Endobiliary radiofrequency ablation for palliation of malignant biliary stricture. *Gastrointest Endosc* 2017;**85**:AB616
Samuel 2020	Abstract	Samuel GO, Asagbra EE, Samuel OB, Arhinful J, Mudireddy P. Safety and efficacy of radiofrequency ablation in the palliative management of malignant biliary strictures. *Am J Gastroenterol* 2020;**115**:S491
Saraswat 2018	Abstract	Saraswat VA, Nayak H, Mohindra S, Ey G, Butala SP, Bhadauria AS. Early experience with endobiliary radiofrequency ablation (Endo-RFA) in unresectable malignant hilar biliary obstruction. *Indian J Gastroenterol* 2018;**37**:A98
Ueno 2019	Abstract	Ueno S, Ogura T, Okuda A, Nishioka N, Imoto A, Masuda D, *et al.* Evaluation of the safety of endoscopic radiofrequency ablation for malignant biliary stricture using a digital peroral cholangioscope. *Gastrointest Endosc* 2019;**89**:AB228
Marti Romero 2019	Paper	Martí Romero L, Martínez Escapa V, Castelló Miralles I, Estellés Arnau J, Querol Ribelles JM. Intraductal ablation by radiofrequency for inoperable biliopancreatic neoplasms with jaundice: experience at a regional hospital. *Rev Esp Enferm Dig* 2019;**111**:485–7. https://doi.org/10.17235/reed.2019.5720/ 2018
Mukund 2013	Paper	Mukund A, Arora A, Rajesh S, Bothra P, Patidar Y. Endobiliary radiofrequency ablation for reopening of occluded biliary stents: a promising technique. *J Vasc Interv Radiol* 2013;**24**:142–4. https://doi.org/10.1016/j.jvir.2012.09.018

TABLE 18 Clinical effectiveness review: included articles grouped according to study (*continued*)

Study	Article type	Reference
Nayar 2018	Paper	Nayar MK, Oppong KW, Bekkali NLH, Leeds JS. Novel temperature-controlled RFA probe for treatment of blocked metal biliary stents in patients with pancreaticobiliary cancers: initial experience. *Endosc Int Open* 2018;**6**:E513–E517. https://doi.org/10.1055/s-0044-102097
	Abstract	Nayar M, Oppong K, Bekkali N, Leeds J. Preliminary results of a novel temperature controlled endo luminal radio-frequency ablation (ELRA) electrode for treatment of blocked biliary stents in patients with inoperable pancreaticobiliary cancers. *Gut* 2017;**66**:A210
Lewis 2012	Abstract	Lewis J, Mehendiratta V, Korenblit J, Siddiqui AA, Kowalski TE, Loren DE. Safety of an endoscopic bipolar radiofrequency probe in the management of malignant biliary strictures: a single center experience. *Gastrointest Endosc* 2012;**75**:AB388
Morales 2017	Abstract	Morales MJ, De La Mora-Levy JG, Ortega Espinosa CR, Alonso-Larraga JO, Ramirez-Solis ME, Del Monte JS, *et al.* Endoscopic radio-frequency ablation of biliary strictures unleashed: a case series in a variety of clinical scenarios. *Gastrointest Endosc* 2017;**85**:AB640
Mukund 2014	Abstract	Mukund A, Rajesh S, Arora A, Panda D. Endobiliary RFA and balloon sweep to restore the patency of occluded metallic biliary stents-a feasibility study. *J Vasc Interv Radiol* 2014;**25**:S75
Watson 2012	Abstract	Watson J, Habr F. Safety and efficacy of endoscopic radiofrequency ablation in non-resectable cholangiocarcinoma: a case series. *Am J Gastroenterol* 2012;**107**:S78
Bastos 2018	Paper	Bastos VR, Safatle-Ribeiro AV, Baba ER, da Costa Martins B, Maluf-Filho F. The impact of probe-based confocal endomicroscopy on the management of indeterminate bile duct strictures. *VideoGIE* 2018;**3**:26–7. https://doi.org/10.1016/j.vgie.2017.10.003
Gunasingam 2019	Paper	Gunasingam N, Craig PI. Cholangioscopy-directed radiofrequency ablation of complex biliary cholangiocarcinoma. *VideoGIE* 2019;**4**:211–13
Han 2018	Paper	Han SY, Song GA, Kim DU, Baek DH, Lee MW, Kim GH. Bile duct patency maintained after intraductal radiofrequency ablation in a case of hepatocellular cholangiocarcinoma with bile duct invasion. *Clin Endosc* 2018;**51**:201–5. https://doi.org/10.5946/ce.2017.097
Inoue 2020	Abstract	Inoue T, Kitano R, Ibusuki M, Kobayashi Y, Ito K, Yoneda M. Simultaneous triple stent-by-stent deployment following endobiliary radiofrequency ablation for malignant hilar biliary obstruction. *Endoscopy* 2021;**53**:E162–E163
Kruger 2018	Paper	Kruger AJ, Krishna SG. Unexpected outcome following radiofrequency ablation of a malignant biliary stricture. *Turk J Gastroenterol* 2018;**29**:230–2
	Abstract	Kruger AJ, Krishna SG. An unexpected outcome following radiofrequency ablation of a malignant biliary stricture. *Am J Gastroenterol* 2017;**112**:S1126
Laquiere 2016	Paper	Laquière A, Boustière C, Leblanc S, Penaranda G, Désilets E, Prat F. Safety and feasibility of endoscopic biliary radiofrequency ablation treatment of extrahepatic cholangiocarcinoma. *Surg Endosc* 2016;**30**:1242–8. https://doi.org/ 10.1007/s00464-015-4322-7
Lee 2020	Paper	Lee YW, Kim HJ, Lee SY, Heo J, Jung MK. Palliative measures with ethanol gallbladder ablation and endobiliary radiofrequency ablation followed by endoscopic biliary stent placement in an advanced case of common bile duct cancer: a case report. *Korean J Gastroenterol* 2020;**75**:50–5. https://doi.org/10.4166/kjg.2020.75.1.50
Lorenzo 2018	Paper	Lorenzo D, Barret M, Bordacahar B, Leblanc S, Chaussade S, Cattan P, Prat F. Intraductal radiofrequency ablation of an intraductal papillary mucinous neoplasia of the main pancreatic duct. *Endoscopy* 2018;**50**:176–7. https://doi.org/10.1055/ s-0043-121459

continued

TABLE 18 Clinical effectiveness review: included articles grouped according to study (*continued*)

Study	Article type	Reference
Lui 2013	Paper	Lui KL, Li KK. Intraductal radiofrequency ablation of tumour ingrowth into an uncovered metal stent used for inoperable cholangiocarcinoma. *Hong Kong Med J* 2013;**19**:539–41. https://doi.org/10.12809/hkmj133867
Mansilla-Vivar 2019	Paper	Mansilla-Vivar R, Arguello-Viudez L, Sanchez-Montes C, Alonso-Lazaro N, Pons-Beltran V. Endoluminal radiofrequency ablation with SpyGlass™ in the management of cholangiocarcinoma. *Rev Esp Enferm Dig* 2019;**111**:803–5
	Abstract	Mansilla-Vivar R, Alonso-Lazaro N, Arguello-Viudez L, Ponce-Romero M, Bustamante-Balen M, Sanchez-Montes C, *et al.* Endoluminal radiofrequency ablation with spyglass in the management of cholangiocarcinoma. *Endoscopy* 2019;**51**:S235
Mok 2017	Paper	Mok SRS, Khara HS, Johal AS, Confer BD, Diehl DL. Cholangioscopic appearance after radiofrequency ablation of cholangiocarcinoma. *VideoGIE* 2017;**2**:279–83
Monga 2011	Paper	Monga A, Gupta R, Ramchandani M, Rao GV, Santosh D, Reddy DN. Endoscopic radiofrequency ablation of cholangiocarcinoma: new palliative treatment modality (with videos). *Gastrointest Endosc* 2011;**74**:935–7. https://doi.org/10.1016/j.gie.2010.10.018
	Abstract	Monga A, Wee EWL, Gupta R, Ramch, ani M, Reddy DN. Endoscopic radio-frequency ablation of unresectable malignant obstructive jaundice. *Ann Acad MedSingap* 2011;**40**:S132
	Trial registry	ClinicalTrials.gov. *Role of Endoscopic RFA in Prolonging the Patency of Metal Stents in Patients With Malignant Obstructive Jaundice*. URL: https://ClinicalTrials.gov/show/NCT01275768 (accessed 27 September 2022)
Linz 2016	Abstract	Linz CM, Modi RM, Krishna SG. A dual-modality approach of endobiliary radiofrequency ablation and self-expandable metal stent placement to control malignant hemobilia. *Endoscopy* 2017;**49**:E21–E2
Ludvik 2019	Abstract	Ludvik N, Kumar M, Fahmawi Y, Mizrahi M. Fire in the hole! Role of radiofre-quency ablation for biliary stent occlusion: prolonging the stent patency. *Am J Gastroenterol* 2019;**114**:S767
Morais 2019	Abstract	Morais R, Vilas-Boas F, Antunes J, Pereira P, Macedo G. Endoscopic radiofre-quency ablation for palliative treatment of hilar cholangiocarcinoma. *Endoscopy* 2019;**51**:S87
Musquer 2016	Abstract	Musquer N, Ménager Tabourel E, Luet D, Caroli-Bosc FX, Métivier Cesbron E. Recanalization of obstructed metallic uncovered biliary stent using endobiliary radiofrequency ablation. *Gastrointest Endosc* 2016;**83**:256–7. https://doi.org/10.1016/j.gie.2015.07.010
Saumoy 2017	Abstract	Saumoy M, Dawod E, Xu MM, Kahaleh M. Two-step endoscopic radiofrequency ablation for metastatic cholangiocarcinoma. *Endoscopy* 2017;**49**:E210–E211. https://doi.org/10.1055/s-0043-111714
Schlosser 2019	Abstract	Schlosser SH, Casty A, Netzer P. Endobiliary radiofrequency ablation (ELRA) for malignant billiary obstruction over 24 months follow-up. *Swiss Med Wkly* 2019;**149**:11S
Sonpal 2012	Abstract	Sonpal N, Saitta P, Haber G. Maintaining stent patency with radiofrequency ablation and interim plastic stent placement for Klatskin tumors. *Am J Gastroenterol* 2012;**107**:S337
Tian 2017	Abstract	Tian Q,Wang G, Zhang Y, Jin Y, Cui Z, Sun X, Shen Z. Endoscopic radiofre-quency ablation combined with fully covered self-expandable metal stent for inoperable periampullary carcinoma in a liver transplant patient: a case report. *Medicine* 2017;**96**:e5790. https://doi.org/10.1097/MD. 0000000000005790
Tyberg 2015	Abstract	Tyberg A, Zerbo S, Sharaiha RZ, Kahaleh M. Digital cholangioscopy: assessing the impact of radiofrequency ablation. *Endoscopy* 2015;**47**:E544. https://doi.org/ 10.1055/s-0034-1393144

TABLE 18 Clinical effectiveness review: included articles grouped according to study (*continued*)

Study	Article type	Reference
Yoon 2012	Abstract	Yoon WJ, Brugge WR. Radiofrequency ablation of malignant biliary obstruction. *Gastrointest Endosc* 2012;**75**:AB116
	Trial registry	ClinicalTrials.gov. *Endoscopic Therapy of Malignant Bile Duct Strictures*. URL: https://ClinicalTrials.gov/show/NCT01543607 (accessed 27 September 2022)
Ogura 2019	Paper	Ogura T, Ueno S, Nishioka N, Yamada M, Higuchi K. Success of stent-in-stent deployment after intraductal radiofrequency ablation for hepatic hilar obstruction. *Endoscopy* 2020;**52**:E206–E207
ClinicalTrials.gov	Trial registry	ClinicalTrials.gov. *Cholangioscopic Assessment of Occluded Biliary Stent and Role of Biliary Radiofrequency Ablation*. URL: https://ClinicalTrials.gov/show/NCT03133026 (accessed 27 September 2022)
ClinicalTrials.gov	Trial registry	ClinicalTrials.gov. *Intra-luminal Radiofrequency Ablation for Inoperable Malignant Biliary Stenosis*. URL: https://ClinicalTrials.gov/show/NCT02841800 (accessed 27 September 2022)
ClinicalTrials.gov	Trial registry	ClinicalTrials.gov. *Endoscopic Biliary RFA of Malignant Bile Duct Obstruction*. URL: https://ClinicalTrials.gov/show/NCT02582541 (accessed 27 September 2022)
ClinicalTrials.gov	Trial registry	ClinicalTrials.gov. *Radiofrequency Ablation for Biliopancreatic Malignancy*. URL: https://ClinicalTrials.gov/show/NCT02468076 (accessed 27 September 2022)
ClinicalTrials.gov	Trial registry	ClinicalTrials.gov. *Endoscopic Biliary Co-axial Stent Placement Plus/Minus Use of Radiofrequency Ablation (RFA) for Clearance of Occluded Self Expandable Metal Stents (SEMS) in Patients With Distal Biliary Obstruction From Unresectable Biliary-pancreatic Malignancies*. In: https://ClinicalTrials.gov/show/ NCT02340728 (accessed 27 September 2022)
ClinicalTrials.gov	Trial registry	ClinicalTrials.gov. *RFA RCT for Pancreatic or Bile Duct Cancer*. URL: https://ClinicalTrials.gov/show/NCT02166190 (accessed 27 September 2022)
ClinicalTrials.gov	Trial registry	ClinicalTrials.gov. *Radiofrequency Probe for Management of Unresectable Bile Duct and Pancreatic Cancer*. URL: https://ClinicalTrials.gov/show/ NCT02042859 (accessed 27 September 2022)
Kct0003373	Trial registry	World Health Organization International Clinical Trials Registry Platform Search Portal. *Treatment of Endobiliary Radiofreqeuncy Ablation for the Treatment of Malignant Extrahepatic Biliary Stricture*. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=KCT0003373 (accessed 16 November 2022)
Kct0004623	Trial registry	World Health Organization International Clinical Trials Registry Platform Search Portal. *Comparison of Endoscopic Radiofrequency Ablation Versus Stenting Alone for the Treatment of Unresectable Malignant Biliary Obstruction*. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=KCT0004623 (accessed 16 November 2022)
Kct0003275	Trial registry	World Health Organization International Clinical Trials Registry Platform Search Portal. *Efficacy of Additional Radiofrequency Ablation in Malignant Hilar Biliary Obstruction. 2018*. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=KCT0003275 (accessed 16 November 2022)
TCTR20190704004002	Trial registry	Thai Clinical Trials Registry. Endobiliary *Radiofrequency Ablation in Recurrence and Unresectable Cholangiocarcinoma*. URL: www.thaiclinicaltrials.org/show/TCTR20190704002 (accessed November 2021)
Jprn, U	Trial registry	N Kato. *Exploratory Survey of the Safety and Efficacy of Endoscopic Radiofrequency Ablation for Malignant Biliary Stricture*. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000036026 (accessed November 2021)
Jprn, U	Trial registry	S Hashimoto. *Endoscopic Biliary Radiofrequency Ablation with Multiple Metal Stents in Patients with Unresectable Malignant Hilar Biliary Stenosis: A Multicenter Prospective Observation Study*. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030078 (accessed November 2021)

continued

TABLE 18 Clinical effectiveness review: included articles grouped according to study (*continued*)

Study	Article type	Reference
Jprn, U	Trial registry	K Ogura. *Multicenter Prospective Study of Feasibility and Safety of Radio Frequency Ablation for Malignant Biliary Stricture Under ERCP Guidance*. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030476 (accessed November 2021)
Jprn, U	Trial registry	HY Choi. *Endobiliary Radiofrequency Ablation Using a New Catheter for Malignant Biliary Strictures: a Prospective Multicenter Study*. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000029721 (accessed November 2021)
Gastroenterology TOSCMCDo	Trial registry	UMIN-CTR Clinical Trial. *Efficacy and Safety of the Endoscopic Radiofrequency Ablation for Unresectable Cholangiocarcinoma: The Pilot Study*. 2017. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000040330 (accessed 16 November 2022)
Gastroenterology TOSCMCDo	Trial registry	M Inoue. *Endoscopic Radiofrequency Ablation Combined with Bilateral Metal Stent Placement for Malignant Hilar Biliary Obstruction*. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000037989 (accessed November 2021)
Gastroenterology TOSCMCDo	Trial registry	T Inoue. *Prospective Evaluation of Radiofrequency Ablation for Stent Occlusion After Bilateral Metal Stent Placement in Patients with Malignant Hilar Biliary Obstructions*. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045784 (accessed November 2021)
Gastroenterology TOSCMCDo	Trial registry	T Inoue. *Prospective Evaluation of Radiofrequency Ablation Combined with a Novel Uncovered Metal Stent Placement for distal Malignant Biliary Obstruction*. URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045117 (accessed November 2021)

Appendix 5 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for cost-effectiveness review

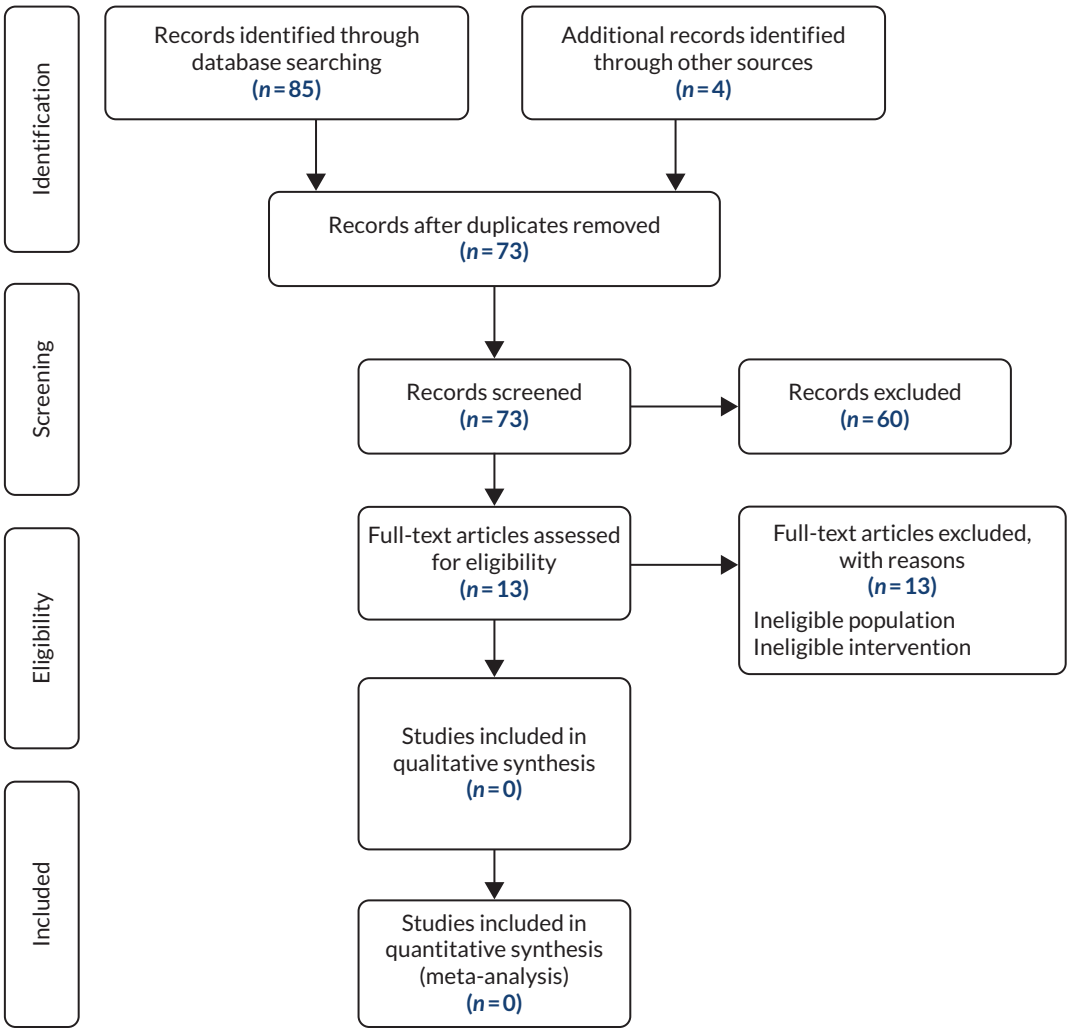

FIGURE 18 A PRISMA flow diagram for cost-effectiveness review.[116] Reproduced with permission from Moher *et al.*[116] This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The figure above includes minor additions and formatting changes to the original figure.

Appendix 6 Excluded studies list: cost-effectiveness review

No articles were excluded based on language alone. All articles were screened at title/abstract level, regardless of language. Google Translate was used to assess an article if the title/abstract was not available in English. Full-text articles of potentially eligible articles that were not in the English language were translated by individuals fluent in those languages. Studies were excluded where international interlibrary loans were required because of The British Library's limitations during the COVID-19 pandemic.

The full references for all excluded articles are provided in *Table X*. Articles were excluded for one of the following reasons (in order of hierarchical importance):

1. The paper focuses on an ineligible patient population (*n* = 1).
2. The paper did not focus on endoscopic RFA plus stenting (*n* = 3).
3. The paper describes an ineligible study design (*n* = 9).

TABLE 19 Cost-effectiveness review: excluded articles

Reason for exclusion	Reference
The paper focuses on an ineligible patient population (*n* = 1)	1. Valente R, Urban O, Del Chiaro M, Capurso G, Blomberg J, Löhr JM, Arnelo U. ERCP-directed radiofrequency ablation of ampullary adenomas: a knife-sparing alternative in patients unfit for surgery. *Endoscopy* 2015;**47**:E515–6. https://doi.org/10.1055/s-0034-1392866
The paper did not focus on endoscopic RFA plus stenting (*n* = 3)	1. Acu B, Kurtulus Ozturk E. Feasibility and safety of percutaneous transhepatic endobiliary radiofrequency ablation as an adjunct to biliary stenting in malignant biliary obstruction. *Diagn Interv Imaging* 2018;**99**:237–45 2. Buell JF, Thomas MT, Rudich S, Marvin M, Nagubandi R, Ravindra KV, *et al.* Experience with more than 500 minimally invasive hepatic procedures. *Ann Surg* 2008;**248**:475–86. https://doi.org/10.1097/SLA.0b013e318185e647 3. Pérez-Cuadrado-Robles E, Piessevaux H, Moreels TG, Yeung R, Aouattah T, Komuta M, *et al.* Combined excision and ablation of ampullary tumors with biliary or pancreatic intraductal extension is effective even in malignant neoplasms. *United European Gastroenterol J* 2019;**7**:369–76. https://doi.org/10.1177/2050640618817215
The paper describes an ineligible study design (*n* = 9)	1. Paper alert. *Eur J Gastroenterol Hepatol* 2008;**20**:i–iv 2. Becq A, Camus M, Rahmi G, de Parades V, Marteau P, Dray X. Emerging indications of endoscopic radiofrequency ablation. *United European Gastroenterol J* 2015;**3**:313–24. https://doi.org/10.1177/2050640615571159 3. Canakis A, Law R, Baron T. An updated review on ablative treatment of pancreatic cystic lesions. *Gastrointest Endosc* 2020;**91**:520–6 4. Coronel E, Waxman I. State-of-the-art endoscopic *procedures for pancreatic cancer. Future Oncol* 2016;**12**:2037–47 5. Dev B, Priyadarshini P, Chadga H, Anupama C, Santosham R, Vishnu S. How I do it: radiofrequency ablation. *Indian J Radiol Imaging* 2008;**18**:166–70 6. Kabnick L, Almeida J. Summaries of recent phlebological abstracts. *Phlebology* 2016;**31**:69–72 7. McCarty TR, Rustagi T. New indications for endoscopic radiofrequency ablation. *Clin Gastroenterol Hepatol* 2018;**16**:1007–17 8. Navaneethan U, Moon JH, Itoi T. Biliary interventions using single-operator cholangioscopy. *Dig Endosc* 2019;**31**:517–26. https://doi.org/10.1111/den.13361 9. Nicholson T, Adam A. The availability of interventional radiology: an issue of patient safety. *Clin Risk* 2009;**15**:43–6

Appendix 7 Bias estimates

Turner *et al.*[96] report low, medium and high bias estimates on the log-odds ratio scale, and these estimates relate to 2.7%, 28% and 84% increases in the SE, respectively. Estimates for the log-HR scale and the mean difference scale were derived by find the same per cent increase in the SE assuming additive bias. Although Turner *et al.*[96] estimated the bias estimates assuming rare events, SEs from included studies for stent patency and HR of mortality were used to determine the bias estimates. The bias estimates used are reported in *Table 20*.

Bias checklists

The bias checklists can be found in Turner *et al.*[96]

Bias scales

Examples of bias scales are *presented in Figures 19* and *20*.[96]

Selection bias

Independent of effect scale

For bias that the assessor has indicated that the bias does NOT depend on the magnitude of the intervention effect, mark the degree of bias on the 'independent of effect' scale (*Figure 19*) and do this by dragging the crosses to a point on the line. Answer the following question: 'even if there were no intervention effect in this study, what apparent effect (ignoring sampling variation) might be induced by this bias?'.

Dependent on effect scale

For bias that the assessor has indicated that the bias DOES depend on the magnitude of the intervention effect, mark the degree of bias on the dependent on effect scale (*Figure 20*). The assessor answers the question 'What proportional change to the intervention effect (represented by the log-HR, ignoring sampling variation) might this bias induce?'.

Bias adjustment

The bias-adjusted mean and SE estimates for the individual studies were calculated using the formulae reported in section 6 of Turner *et al.*[96]

TABLE 20 Bias-adjustment ranges for low, medium and high bias

% increase of SE	log-odds ratio	log-HR	Mean difference
2.7	0.9, 0.9	0.92, 0.92	0.075, 0.075
28	0.7, 0.7	0.76, 0.76	0.255, 0.255
84	0.5, 0.5	0.59, 0.59	0.5, 0.5

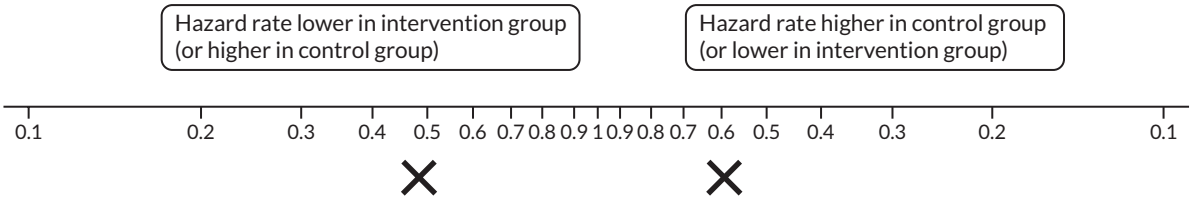

FIGURE 19 Adjustment scale independent of the effect scale. None (1); low (0.92–1); medium (0.76–0.92); high (< 0.76). Adapted from Turner *et al.*[96] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 2.5) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited.

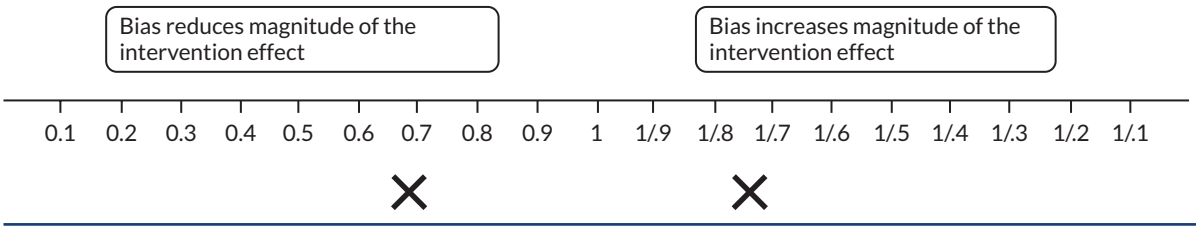

FIGURE 20 Adjustment scale dependent on the effect scale. None (1); low (0.9–1.0); medium (0.7–0.9); high (< 0.7). Adapted from Turner *et al.*[96] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 2.5) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited.

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