Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by unresectable cancer - evidence synthesis

Authors: Fiona Beyer, Stephen Rice, Giovany Orozco-Leal, Hannah O'Keefe, Madeleine Still, Nicole O'Connor, Professor Dawn Craig, Professor Stephen Pereira, Louise Carr, Dr John Leeds

Clinical advisory group: Professor Irfan Ahmed, Jayne Fairburn, Nickola Kilbride, Dr Manu Nayar, Dr Kofi Oppong

Prospero registration number: CRD42020170233

Funding: NIHR HTA reference number: NIHR129784

Start date: 01/03/2020

End date: 28/02/2021

This project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA reference number NIHR129784). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This protocol is reported according to the PRISMA-P guidelines [1]

Introduction

Rationale

The majority of malignant obstructions of the bile ducts are caused by a variety of cancers ranging from ampullary carcinoma, cholangiocarcinoma, adenocarcinoma of the pancreatic head and carcinoma of the gallbladder, which are inoperable in the majority of scenarios (e.g. less than 30% percent of cholangiocarcinomas and 20% of pancreatic carcinomas are resectable at the time of diagnosis).[2] Furthermore, evidence suggests an increase of incidence of gallbladder cancer and cholangiocarcinoma in the western world and globally.[3, 4]

Despite years of research, survival in this group of patients continues to be poor after chemotherapy and/or radiotherapy, hence, palliation of symptoms becomes a key aspect of therapy.[5] Current standard of care involves the insertion of a stent during endoscopic retrograde cholangiopancreatography (ERCP), which restores bile flow, alleviating symptoms associated with obstructive jaundice.[6] Metal stents are preferred over a plastic stents due to their longer duration of patency.[7] Despite this, metal stents remain patent for an average period of about 6 to 9 months after which repeat intervention may be necessary to restore outflow of bile.[8] These 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.[5] Some interventions which have been studied include photodynamic therapy (PDT) and intraductal radiotherapy; however there are many drawbacks to these treatments and they are usually delivered in multiple sessions.[9]

Radiofrequency ablation (RFA) for delivery in the bile duct has emerged as a promising modality in the last few years.[10] RFA produces coagulative necrosis of tissue and thus reduces tumour volume in the bile duct. This has been used both prior to placing biliary stent (primary RFA) and for management of blocked biliary stents (secondary RFA) in malignant bile duct obstruction.[10, 11] Although RFA is also used to treat hepatocellular cancer (HCC) or liver tumours that are unsuitable

for resection (including metastatic liver tumours, oesophageal tumours, and colorectal cancers),[12] these conditions are not included here as the main focus of this study is malignant biliary obstructions.

Overall survival in pancreatic and biliary cancers is poor and 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.[10, 11] 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. This could conceivably lead to improvements in quality of life during the last few months of life. 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 often take several weeks to recover from such an event. Additionally, because of the recurrent jaundice, patients are unable to receive chemotherapy, which may further adversely affect their outcome.[8]

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. These two probes have slightly different characteristics and therefore may not deliver the same outcomes for patients. Furthermore, there have been case reports of adverse events 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. This proposal will focus on both primary and secondary RFA to determine whether there is a difference in patient survival, adverse events, quality of life and cost effectiveness. Should the evidence base allow we will explore differences between the two probes, however it is likely that this will not be feasible.

Primary RFA: 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.[10] Two studies (including our previous work) have suggested that RFA prior to stent insertion may confer a doubling in overall survival.[10, 11] These studies however are small, single centre and not randomised, and therefore are not of sufficient quality to change clinical practice. Much of the data has arisen from retrospective analysis of clinical usage and primarily in patients with cholangiocarcinoma.[13] Review of the previous studies in this area with respect to size, trial design, control group selection, and outcomes reveals considerable heterogeneity and lack of high-quality study design. Only two of the studies are of prospective design[10, 14] and only four used a control group.[15-18] Some of the studies used historic controls[15-17] and one used the SEER database.[18] 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, adverse events, and effects upon quality of life. Pilot data from 2 UK centres (Aberdeen and the Hammersmith Hospitals) has shown that delivery of RFA during ERCP has a high technical success rate, low adverse event rate and suggests overall improvement in survival.[10, 11] The addition of RFA was also acceptable to patients during ERCP. How RFA leads to such effects are not fully understood. It is thought that RFA causes tissue necrosis and increases the diameter of biliary strictures, which may facilitate drainage and embedding of the stent.[14, 17] This mechanism alone does not explain the increased survival times seen in the current studies as most patients succumb with a patent stent. A further hypothesis is that RFA leads to antigen release, which in turn causes immune activation and antitumour responses. This has been shown in hepatocellular carcinoma and in rat models of metastatic colorectal cancer.[19] There are now several studies confirming the technical feasibility, safety, and efficacy of primary RFA but few of these studies are prospective and randomised.

Secondary RFA: 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.[20] Data from Newcastle has shown that RFA significantly increases the stricture diameter allowing for better flow.[21] However, similar to primary RFA, much of the data has been derived from small, single centre, retrospective studies with heterogeneous cohorts and often without suitable control groups. One study has examined secondary RFA purely in patients with occluded metal stents and matched to controls in which plastic stents were inserted across the occluded metal stent.[20] This study showed improved stent patency at 90 days and longer overall stent patency but did not comment on survival between the two groups.[20] Secondary RFA may improve stent patency and time to further intervention but overall survival has not been well studied. This is likely to be difficult compared to primary RFA as this group of patients have generally had their malignancy diagnosed for a longer period of time and may represent a more advanced tumour stage. There is also the question as to whether a further stent (and therefore additional time and cost) is required following secondary RFA as the rates of stent reinsertion in current studies appears to vary.

The current position of NICE with respect to this treatment modality (Interventional procedures guidance 464, published in 2013) is that the *"current evidence on the safety and efficacy of endoscopic bipolar radiofrequency ablation for treating biliary obstructions caused by cholangiocarcinoma or pancreatic adenocarcinoma is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. Further research, in the form of comparative or observational studies, should document details of patient selection and should report all adverse events. Outcomes should include survival, quality of life, biliary patency and the need for further procedures."*

Whilst there appears to be a suggestion from some studies that primary RFA may improve survival it is currently unclear whether this is cost effective or associated with an increased adverse event rate. Additionally, true impact upon quality of life is not known. For secondary RFA, there is a suggestion of improving stent patency duration but again cost effectiveness, adverse event 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 whether there is sufficient evidence for RFA in these circumstances or whether further research, and its directions, are required.

Aims and objectives

The aim of this research is to establish the expected value of undertaking additional research to determine the effectiveness and safety of endoscopic bipolar radiofrequency interventions for the treatment of malignant biliary obstruction.

The key objectives are:

- To undertake two systematic reviews: one assessing the clinical effectiveness and potential risks, and a second assessing the cost-effectiveness of endoscopic bipolar radiofrequency ablation 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

Two separate but linked systematic reviews will be conducted according to the general principles recommended in the Centre for Reviews and Dissemination guidance on the conduct of a systematic

review,[22] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines:[23]

1. a systematic review of clinical effectiveness and risks;
2. a systematic review of cost effectiveness of RFA, and the economic evaluation methods.

An economic model will be developed comparing standard care with the use of endoscopic bipolar radiofrequency ablation i) at the time of biliary stenting as per standard care, and ii) with a stent in-situ. The model will be used to estimate the cost-effectiveness of RFA, to quantify the main uncertainties facing decision makers, and to conduct a value of information analysis to quantify the value of undertaking further research to reduce these uncertainties. The decision model will be parameterised using the best available evidence, including a systematic review of the clinical effectiveness of endoscopic bipolar radiofrequency ablation for malignant biliary obstruction.

Systematic review

Eligibility criteria

Population: Patients with biliary obstruction caused by any form of unresectable malignancy who are ineligible for surgical resection. Malignancies can include cancer of the pancreas, bile duct, gall bladder, duodenum, and also ampullary and metastatic cancers. Studies considering those undergoing a first procedure, as well studies considering those with recurrent obstruction and a stent in-situ will be included. Studies will be included regardless of age, if patients have first diagnosis or previous history of cancer, if they are already undergoing treatment, or if they have underlying health issues (such as diabetes or asthma).

Studies that recruit patients with benign biliary obstruction only will be excluded. Studies with patients presenting both benign and malignant strictures will be considered for inclusion relative to the usefulness of the data provided. Studies that recruit patients with hepatocellular cancer or liver tumours will be excluded unless there is also biliary obstruction.

Types of interventions: endoscopic biliary radiofrequency ablation (RFA) where used to ablate malignant tissue that is obstructing the bile or pancreatic ducts, either in order to fit a stent (metal or plastic) or to clear obstructed stents; or stenting alone.

Studies that use RFA that is not endoscopic will be excluded.

Types of comparators: Insertion of a stent to clear the bile or pancreatic duct. Standard care where patients have an occluded stent. ‘Standard care’ is likely to be different between different countries and at different time points (e.g. ‘standard’ type of chemotherapy might be different now compared to 10 years ago even in the same hospital), so we will record what detail is available from the studies about what is provided as ‘standard care’.

Outcomes:

For the effectiveness review, primary outcomes are survival, quality of life, and procedure related adverse events (such as bleeding, perforation, liver infarction, infection, pancreatitis, cholangitis, biliary leakage). Reporting of any one of these outcomes will mean that a paper is eligible for the review. Additional outcomes of interest include technical success, relief of biliary obstruction, pain, nausea, resource use, number of further interventions, length of hospital stays and reintervention and readmission rates.

The inclusion of carer perspectives will also be accounted for. This will be done by collecting information on personal costs in terms of personal and physical health, well-being, and the financial impacts of the disease on patient carers.

It is likely that the outcomes of the cost-effectiveness review overlap with the clinical effectiveness review as the intervention is expected to have an impact on survival and health related quality of life by means of intervention-related adverse events or by reducing further interventions that may impair quality of life on a temporary or permanent basis. The cost-effectiveness review will focus on information in the measurements of patients' quality of life, the methods and instruments used to measure it, and the size and duration of these quality of life changes. Information on intervention costs will also be included as well as data on incremental cost effectiveness ratios if available.

Study design:

For the effectiveness review, scoping has uncovered a limited and heterogeneous literature, so we will consider all study designs to make the most use of available data. For information about risks, we will additionally include observational studies.

For the cost-effectiveness review, we will include full economic evaluations. A full economic evaluation is a study that evaluates the costs and outcomes of two or more interventions. Economic evaluations conducted alongside a clinical trial and economic models will be included.

Information sources

The following electronic databases will be searched from inception to May 2020:

1. Medline(R) and Epub Ahead of print, In-process & other non-indexed citations, daily and versions(R) (OVID)
2. Embase (OVID)
3. Cochrane Library (Wiley)
4. CINAHL (EBSCO)
5. Scopus
6. Database of Abstracts of reviews of effectiveness (DARE) (CRD)
7. HTA database (CRD)
8. NHS EED (CRD)

Other sources:

1. OpenGrey
2. Web of Science Conference proceedings index
3. Royal College of Surgeons
4. Health management information consortium (HMIC)
5. Cost-effectiveness analysis registry (CEA)
6. IDEAS (RePEc) database
7. Annual conference meetings
    - Digestive Disease Week (DDW)
    - United European Gastroenterology Week (UEGW)
    - International Digestive Endoscopy Network (IDEN)
    - British Society of Gastroenterology (BSG)
8. We will explore the potential of using patient registries

9. Trial registries: we know that a number of trials have been conducted in far Eastern countries. Therefore, trial registries from these countries will be searched in addition to the leading American and European trials registries.
    - ClinicalTrials.gov
    - European Clinical Trial registry (EudraCT)
    - International Standard Randomised Control Trials Number registry (ISRCTN)
    - International Conference on Harmonisation in Good Clinical Practice (ICH GP)
    - South Korean Clinical Research Information Service (CRiS)
    - NIPH Japan primary registry network
    - Thai Clinical Trails Registry (TCTR)

Search strategy

An experienced information specialist will design the search strategy in MEDLINE (appendix 1), in collaboration with the clinical team. Thesaurus headings and keywords will be used as appropriate and the search will be translated to other databases accordingly. The following concepts will be used within the search strategy:

Target condition:

Patients with unresectable malignant obstructions of the biliary tract who do not qualify for surgical resection will be considered for this review. This includes studies with patients undergoing primary stent insertion for biliary malignancies, or where *in-situ* stents have become occluded due to intraluminal tissue growth. Accepted malignancies will include pancreatic, bile duct, ampulla of vater, gall bladder, duodenum and metastatic growths.

Intervention:

Studies including endoscopic radiofrequency ablation (RFA) to reduce malignant obstructions at the time of biliary stent insertion (primary RFA) or in previously inserted biliary stents (secondary RFA) will be included.

Study designs/limitations:

All study designs will be considered for this review. No limitations will be placed on language or publication status. Date will be restricted to 2008, when radiofrequency ablation was first used for patients with unresectable biliary malignancies.

Study records

Data management

Endnote will be used to download and de-duplicate records from the bibliographic databases, and to manage the studies throughout the review. Rayyan will be used to screen records.

Selection process

Two reviewers will independently screen the titles and abstracts of the studies retrieved by the search. For studies deemed eligible, or studies where it is impossible to decide eligibility from the abstract, the full text will be retrieved, and two reviewers will independently assess for inclusion. Any disagreements will be resolved through discussion, or by reference to a third reviewer.

Data collection process

Data extraction will be undertaken by one reviewer and checked by a second, and discrepancies resolved by consultation with a third. Where studies are reported in multiple publications, we will

extract relevant data from all publications but consider as one study. Where data is missing or unclear, we will contact authors to request details or clarification.

Data items

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

- Citation information;
- Study design;
- Participant characteristics: 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: type of stent, RFA settings used, duration of ablation, type of probe used, detail of proposed mechanism of action;
- Comparator characteristics: type of stent, alternative treatment details; details of 'standard care' provision
- Outcomes: survival, relief of biliary obstruction, time to occlusion, adverse event details (quantitative or qualitative);
- Details of study methods to facilitate an assessment of risk of bias.

Primary outcomes are survival, quality of life and procedure-related adverse events.

For the cost-effectiveness review, the following data will be extracted from included studies:

- Bibliographic details (i.e. reference ID, author, year of publication)
- Date
- Study location (i.e. country/states/region)
- Type of economic evaluation (CCA,CEA,CUA,CBA)
- Study aims and objectives
- Study perspective
- Study design/methods (e.g. trial-based, model, time horizon)
- Patient population and setting
- Intervention(s)
- Summary of model (structure, analysis)
- Effectiveness data (study design)
- Clinical and health outcome measures
- Currency
- Basic costing method (e.g. top-down, bottom-up, national publications of unit costs)
- Price year
- Base case results, disaggregated for different perspectives if reported
    - Incremental Cost-Effectiveness Ratios (ICERs)
    - Net benefit
    - Costs and consequences
- Key uncertainty

Risk of bias in individual studies

Risk of bias will be conducted by two reviewers independently at a study level using the following tools according to study design, and any disagreements will be resolved in team discussions.

For the effectiveness review, RCTs will be assessed using the Cochrane RoB 2.0 tool, with an additional question relating to the similarity of the groups at baseline.

Non-randomised controlled studies will be assessed using criteria based on the ROBINS-I tool.

Uncontrolled studies will not be formally assessed using a tool but will be given less weight in the synthesis.

Risk of bias assessments will be used to inform sensitivity analyses, where studies at high risk of bias (and uncontrolled studies) will be removed from the analysis.

For the cost-effectiveness review, the Drummond BMJ checklist will be used to assess the quality of the included economic evaluations.

Data synthesis

In the first instance, we will present a summary of study characteristics, results, and risk of bias, in a series of structured tables to give a clear picture of the available evidence.

For the clinical effectiveness review, we will prioritise randomised controlled trials. For the effectiveness review, we anticipate where feasible that outcome data extracted from studies will be combined using appropriate meta-analytic methods: Mantel-Haenszel for odds ratios from dichotomous data, weighted mean difference (or standardised weighted mean difference if different metrics are used) for continuous outcomes, generic inverse variance method for time to event data. We will undertake, where feasible, a number of pair-wise meta-analyses. Heterogeneity between studies will be assessed by visual inspection of plots of the data, from the chi square test for heterogeneity, and the I^2 statistic. Possible reasons for heterogeneity will be explored, such as differences in the populations studied (e.g. comorbidities, concomitant treatments, cancer type and stage, age, gender), the detail of 'standard care' provided, or the way in which the outcomes were assessed. For the adverse event outcome, we will account for confounding from the 'baseline' adverse events that would be expected from the procedures (e.g. for having a stent inserted).

Meta-analyses will be conducted with and without adjustment for bias. Without adjustment for bias, consideration will be given to whether it is meaningful to combine studies of very different quality.

Separate analyses will be conducted for primary and secondary RFA.

Should there be enough data, subgroup analyses will be carried out according to the type of probe, the type of stent (metal or plastic) and the type of cancer.

Bias may affect the point estimate of an outcome, and the uncertainty associated with bias is not reflected in the standard errors of the effect estimates. The uncertainty associated with poor study quality needs to be captured in the economic analysis described below if the cost-effectiveness analysis and value of information analysis are to produce reasonable estimates. Accordingly, the risk of bias associated with each study providing an effectiveness estimate with a control arm will be elicited from the clinical advisory group. Each expert indicates a 67% range of bias associated with each type of bias. The results are then combined to adjust both the effect size and the standard error. The method of elicitation and the method of adjusting each study result for bias is that presented by Turner et al.[24]

The adjustment of study results for bias as described above will allow randomised and non-randomised studies to be combined in a meta-analysis. The non-randomised study will have less

weight in the analysis than the randomised study. This is operationalised in practice by adjusting the effect size and increasing the standard errors of the results for studies with a risk of bias. The inverse variance estimator for the pooled effect, the standard error and the between-study variance are stated in Turner et al.[24]

If there is insufficient data or it is inappropriate to pool studies due to differences between them in comparisons or reported outcomes, we will provide a narrative synthesis of the data, structured by outcome. The effectiveness estimates will feed into the economic model along with the data from economic studies.

For the cost-effectiveness review, a narrative synthesis will be undertaken for the cost-effectiveness review to describe the similarities and differences in study questions, methods and results.

Finally, we will synthesise the effectiveness and cost effectiveness data to provide an explanation of factors that impact on the success of RFA and list gaps that may benefit from further research. We will provide an assessment of the strength of evidence based on the robustness of the study designs and an assessment of the risk of bias in individual studies.

Economic model

Objectives

A de novo decision-analytic model will be developed to allow both an estimate of the cost-effectiveness of the alternative treatment options and the expected value of information/research.

Models will be developed for two cancer populations and two scenarios. The two cancer populations will be pancreatic cancer and bile duct cancer, which are the two most common cancers causing malignant biliary obstruction. The reason for developing separate models is that outcomes may differ for people with the different cancers. For each cancer, two scenarios will be modelled: i) at the time of biliary stenting as per standard care, and ii) with a stent in-situ. Model structures are likely to be similar, but parameters like survival are expected to be different. RFA will be compared with the standard of care in each scenario. In the UK metal stents are the current treatment standard.

Model structure

The model is likely to have a Markov model structure, as this is particularly suitable for modelling survival and time to event outcomes. The model structure will be developed by the research team based on the effectiveness and cost-effectiveness systematic reviews, in conjunction with the clinical expert advisors. The model will characterise the treatment pathway and the impact of the alternative treatment options on outcomes for the different scenarios. The structure will also be presented and agreed at the project advisory group meeting. The time horizon of the model will be the lifetime of the population.

The model will be developed in accordance with the NICE reference case (Methods for NICE Technology Appraisals). The perspective will be that of the National Health Service (NHS) and Personal Social Services. Both cost and outcomes will be discounted at 3.5%.

Effectiveness and complications

The effectiveness of RFA and the complications associated with RFA will be obtained from the aforementioned effectiveness systematic review. Methods for the meta-analysis of effectiveness data appropriate for the economic modelling were described in the Systematic Review section. Appropriate sensitivity analyses will be conducted.

Costs

The economic decision model will take the perspective of the NHS and the Personal Social Services. In addition to the review of cost-effectiveness studies, a focused review of cost studies in these populations will be conducted to identify resources and their costs associated with the intervention and outcomes. This information will be presented to the clinical advisory group to review the resource use applicable to the intervention and outcomes. Resources associated with the intervention will include changes in theatre time, staff time, equipment, medication and hospital stay.

Unit costs for these resource use estimates will be extracted from the literature or obtained through other relevant sources such as NHS reference costs and manufacturer price lists. Costs will be discounted at 3.5% per annum, where appropriate.

Quality of life

Health economic evaluations very often use quality-adjusted life years (QALYs) as the measure of benefit. The measure incorporates both life years and quality of life. The instruments used to estimate the health utility associated health outcomes can have their limitations in valuing the specific impact on patients. However, they do capture significant variations in quality of life and allow comparison of the cost-effectiveness of interventions in different diseases. For these reasons, QALYs are a requirement in the NICE reference case methods where possible. A composite measure of benefit is required to conduct value of information analysis.

A focused review of the literature will be conducted to identify health utility values and disease specific quality of life estimates for patients with stents with and without stent occlusion, and complications associated with the interventions. If necessary, mapping algorithms will be used to allow us to map from disease specific measures to utility outcomes.

Analyses and Results

The cost per quality-adjusted life-year (QALY) gained of RFA will be evaluated in the analyses. If there is clinical evidence of the effectiveness of RFA applicable to our populations and scenarios, and the studies have appropriate control groups, then uncertainty in the cost-utility of RFA will be evaluated through probabilistic sensitivity analysis. The uncertainty in the mean estimates of the parameters are modelled using probability distributions. Using Monte Carlo simulation, this parameter uncertainty is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, decision uncertainty. The uncertainty that an intervention is cost-effective is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY. Through bias elicitation, the effectiveness estimates will be adjusted and the uncertainty in the mean estimate will be changed accordingly. Without a minimum quality of clinical study design applicable to the population and scenario of interest, decision uncertainty cannot be evaluated through probabilistic sensitivity analysis. Only a range of plausible cost-effectiveness estimates can be obtained.

Where it is not possible to model the uncertainty in a parameter, and where there may be external validity queries surrounding a parameter estimate, sensitivity analysis will be conducted where the alternative values of the parameter are modelled and the effect on the model results is recorded.

If there is clinical evidence of the effectiveness of RFA applicable to our populations and scenarios, and the studies have appropriate control groups, then the expected value of perfect information (EVPI) will be estimated for the population expected to benefit from the intervention. This is the value of eliminating decision uncertainty. The expected value of partial perfect information (EVPPI) analysis will also be conducted for individual parameters where appropriate and feasible.

Ethical requirements:

Ethical approval is not required for this project. The study and it's protocol have been registered in the PROSPERO database and carried out according to PRISMA-P guideleines.

References

1 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4(1):1.

2 Goumas K, Poulou A. Endoscopic Palliative Management of the Malignancies of the Biliary Tract. In: Karaliotas CC, Broelsch CE, Habib NA, eds. *Liver and Biliary Tract Surgery: Embryological Anatomy to 3D-Imaging and Transplant Innovations*. Vienna: Springer Vienna 2006:289-96.

3 Karatzas G, Misiakos E. Callbladder Carcinoma. In: Karaliotas CC, Broelsch CE, Habib NA, eds. *Liver and Biliary Tract Surgery: Embryological Anatomy to 3D-Imaging and Transplant Innovations*. Vienna: Springer Vienna 2006:267-78.

4 Karatzas G, Misiakos E. Bile Duct Cancer. In: Karaliotas CC, Broelsch CE, Habib NA, eds. *Liver and Biliary Tract Surgery: Embryological Anatomy to 3D-Imaging and Transplant Innovations*. Vienna: Springer Vienna 2006:279-88.

5 Roque J, Ho S-H, Reddy N, Goh K-L. Endoscopic Ablation Therapy for Biliopancreatic Malignancies. Clinical Endoscopy. 2015;48(1):15-9.

6 Anderson MA, Appalaneni V, Ben-Menachem T, Decker GA, Early DS, Evans JA, et al. The role of endoscopy in the evaluation and treatment of patients with biliary neoplasia. Gastrointestinal Endoscopy. 2013;77(2):167-74.

7 Kaassis M, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcenserie R, et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointestinal Endoscopy. 2003;57(2):178-82.

8 Brien S, Hatfield AR, Craig PI, Williams SP. A three year follow up of self expanding metal stents in the endoscopic palliation of longterm survivors with malignant biliary obstruction. Gut. 1995;36(4):618.

9 Leggett CL, Gorospe EC, Murad MH, Montori VM, Baron TH, Wang KK. Photodynamic therapy for unresectable cholangiocarcinoma: A comparative effectiveness systematic review and meta-analyses. Photodiagnosis and Photodynamic Therapy. 2012;9(3):189-95.

10 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. Gastrointestinal Endoscopy. 2011;73(1):149-53.

11 De Nucci G, Redaelli D, Reati R, Morganti D, Mandelli ED, Manes G. P.05.45 Endoscopic radiofrequency ablation for extrahepatic malignant biliary obstruction: safety and efficacy of a single center experience. Digestive and Liver Disease. 2019;51:e202-e3.

12 Curley SA. Radiofrequency Ablation of Malignant Liver Tumors. The Oncologist. 2001;6(1):14-23.

13 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. Scientific Reports. 2019;9(1):13685.

14 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. Journal of Oncology. 2013;2013:910897.
15 Kallis Y, Phillips N, Steel A, Kaltsidis H, Vlavianos P, Habib N, et al. Analysis of Endoscopic Radiofrequency Ablation of Biliary Malignant Strictures in Pancreatic Cancer Suggests Potential Survival Benefit. Digestive Diseases and Sciences. 2015;60(11):3449-55.
16 Strand DS, Cosgrove ND, Patrie JT, Cox DG, Bauer TW, Adams RB, et al. ERCP-directed radiofrequency ablation and photodynamic therapy are associated with comparable survival in the treatment of unresectable cholangiocarcinoma. Gastrointestinal Endoscopy. 2014;80(5):794-804.
17 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? Digestive Diseases and Sciences. 2014;59(12):3099-102.
18 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. Digestive Diseases and Sciences. 2015;60(7):2164-9.
19 Bastianpillai C, Petrides N, Shah T, Guillaumier S, Ahmed HU, Arya M. Harnessing the immunomodulatory effect of thermal and non-thermal ablative therapies for cancer treatment. Tumor Biology. 2015;36(12):9137-46.
20 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. Gastrointestinal Endoscopy. 2015;81(5, Supplement):AB195.
21 Nayar M, Oppong K, Bekkali N, Leeds J. Novel temperature-controlled RFA probe for treatment of blocked metal biliary stents in patients with pancreaticobiliary cancers: initial experience. 2018;6(5):E513-E7.
22 CRD's guidance for undertaking reviews in health care. University of York: Centre for Reviews and Dissemination 2008.
23 Moher DPL, Alessandro MD, DrPH; Tetzlaff, Jennifer BSc; Altman, Douglas G. DSc; the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Annals of Internal Medicine. 2009;151(4):264-9.
24 Turner RM, Spiegelhalter DJ, Smith GCS, Thompson SG. Bias Modelling in Evidence Synthesis. Journal of the Royal Statistical Society Series A (Statistics in Society). 2009;172(1):21-47.

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	duodenal obstruction/
17	common bile duct neoplasms/
18	cholangiocarcinom*.ti,ab,kw,kf.
19	((bile or biliar* or endobiliar* or bile duct or pacrea* or choliangio* or gallbladder or duodenal) adj4 (obstruct* or occlu* or cancer* or carcinom* or adenocarcinom* or tumo?r* or malignan* or lump* or mass or masses or sarcom* or metasta* or stricture*)).ti,ab.
20	exp Biliary tract diseases/
21	"stent*".ti,ab.
22	exp Stents/
23	((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 metasta* or stricture*)).ti,ab.
24	or/9-23
25	8 and 24
26	(EndoHBP or ELRA).ti,ab,kw,kf.
27	25 or 26
28	exp Animals/ not exp Human/
29	27 not 28
30	limit 29 to yr="2008-Current"