

Endobiliary radiofrequency ablation for malignant biliary obstruction due to perihilar cholangiocarcinoma (RACCOON): study protocol for a randomised controlled trial

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Endobiliary radiofrequency ablation for malignant biliary obstruction due to perihilar cholangiocarcinoma (RACCOON): study protocol for a randomised controlled trial

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Trial registration: NCT05546372, first submitted 25 August 2022

Version/date: protocol version 2, 23 September 2025

Sponsor: Amsterdam UMC, telephone number: +31 20 444 4444

Role of sponsor: The study sponsor is responsible for the study design, data collection, data management, data analysis and interpretation, writing of the report, and the decision to submit the report for publication. The study funder approved the study design.

Endpoint adjudication committee: two independent gastroenterologists

Keywords: cholangiocarcinoma; malignant biliary obstruction; stent patency; endobiliary radiofrequency ablation; ERCP; clinical trial

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Abbreviations

AE	= Adverse Events
AF	= Alkaline Phosphatase
ALT	= Alanine Transaminase
AST	= Aspartate Aminotransferase
CCA	= Cholangiocarcinoma
CI	= Confidence Interval
CT	= Computed Tomography
DHCG	= Dutch Hepatocellular & Cholangiocarcinoma Group
DSMB	= Dutch Safety Monitoring Board
eCRF	= Electronic Case Report Form
EORTC QLQ	= European Organization for Research and Treatment Quality of Life Questionnaire
ERCP	= Endoscopic Retrograde Cholangiopancreatography
eRFA	= Endobiliary Radiofrequency Ablation
g-GT	= Gamma-Glutamyl Transpeptidase
IQR	= Interquartile Range
MDT	= Multidisciplinary Team
MRI/MRCP	= Magnetic Resonance Imaging / Magnetic Resonance Cholangiopancreatography
pCCA	= Perihilar Cholangiocarcinoma
PDT	= Photodynamic Therapy
PET	= Positron Emission Tomography
PTC	= Percutaneous Transhepatic Cholangiography
QALY	= Quality-Adjusted Life Year
QoL	= Quality of Life
uSEMS	= Uncovered Self-Expanding Metal Stent
WHO	= World Health Organization

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Author's contributions

This study was primarily designed by JF, ES and RPV. The manuscript was drafted by JF and ES under supervision of RPV. JYB, MB, JB, MJB, MCB, OD, PD, LvD, JE, PF, BGK, FvdH, JvH, CH, FH, PH, AI, JJ, GK, WL, WJL, CvdL, JWP, CP, SV, NV, RCV, JV, JdVG, TV, RvW, MB, IJZ, BZ critically reviewed

and contributed to the draft of the manuscript. All authors have approved of the final manuscript.
The guarantor of the article is RPV.

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Data availability

Data sharing with external researchers may be granted upon reasonable request, after publication, and approval from the principal investigator and ethics committee.

Declarations

Ethics approval and consent to participate

The Medical Research Ethics Committee Amsterdam UMC (Amsterdam, the Netherlands) approved the trial protocol (NL76591.029.22). Local IRBs of the participating centres approved the trial protocol before start of inclusion at the particular centre. All participants have provided written informed consent prior to trial inclusion.

Consent for publication

The participant information materials and informed consent forms are available from the corresponding author on request. No details, images, or videos relating to an individual person were used in this manuscript.

Competing interests

Jeska A. Fritzsche, Esmée Smit, Ji Young Bang, Mihaela Birligea, Marco J. Bruno, Johannes A. Bogaards, Joris I. Erdmann, Bas Groot Koerkamp, Frederik Hoogwater, Pieter Hindryckx, Akin Inderson, Jana Jarosova, Wim Laleman, Shyam Varadarajulu, Niels G. Venneman, Robert C. Verdonk, Joanne Verheij, Theodor Voiosu, Mattheus C.B. Wielenga and Babs A. Zonderhuis have no conflicts of interest or financial ties to disclose. Mark C. Burgmans received speaker's fees from Philips, Medtronic, Sirtex and Delcath Systems, research grants from KWF, Health Holland, EU-Innovative Health Initiative, MLDS and educational grants from Delcath Sytems and Medtronic. Otto M. van Delden received a speaker's fee from Cook Medical. Lydi M.J.W. van Driel received a speaker's fee from Boston Scientific. Paul Fockens performed as a consultant for Olympus and Cook Endoscopy. Frans van der Heide received speaker's fees from Takeda, Dr. Falk, Ipsen, Gilead and Mirum. Jeanine E. van Hooft received speaker's fees from Cook Medical, Boston Scientific, Fuji film and Falk and performed as consultant for Olympus. Geert

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Table 1. World Health Organization Trial Registration Data Set

Primary Registry and Trial Identifying Number	Clinicaltrials.gov NCT05546372
Date of registration in primary registry	25 August 2022
Secondary Identifying Numbers	NL-004816 (Dutch National Registry: CCMO Onderzoek met Mensen)
Source(s) of Monetary or Material Support	KWF Dutch Cancer Society project (grant number: 2022-3 DEV / 14676). Prion Medical (unrestricted grant).
Primary Sponsor	Amsterdam UMC
Contact for Public Queries	Esmée Smit Phone: +316 48 38 73 74 Email: e.smit1@amsterdamumc.nl
Contact for Scientific Queries	Dr. Rogier P. Voermans Phone: +316 25 47 41 91 Email: r.p.voermans@amsterdamumc.nl
Public Title	Endobiliary radiofrequency ablation for malignant biliary obstruction due to perihilar cholangiocarcinoma
Scientific Title	Endobiliary radiofrequency ablation for malignant biliary obstruction due to perihilar cholangiocarcinoma – a randomised controlled trial
Countries of Recruitment	Netherlands, Belgium, Romania, Czech, United States of America
Health Condition(s) or Problem(s) Studied	Perihilar cholangiocarcinoma
Intervention(s)	Arm 1: uSEMS + eRFA (intervention) group

	Randomly assigned participants to this group will receive eRFA prior to metal stent placement Arm 2: uSEMS (control) group Randomly assigned participants to this group will receive standard of care (metal stent placement)
Key Inclusion and Exclusion Criteria	Inclusion criteria: (1) patients with perihilar cholangiocarcinoma with indication for biliary drainage with uSEMS; (2) histological or cytological proof of CCA (adenocarcinoma); (3) advanced and irresectable disease; (4) age 18 years or above and (5) written informed consent. Exclusion criteria: (1) potentially eligible for resection or liver transplantation; (2) life-expectancy less than 3 months; (3) ERCP and PTC technically not feasible; (4) uncontrolled coagulopathy; (5) ongoing cholangitis or liver abscess; and (6) implantable pacemaker and/or cardioverter/defibrillator.
Study Type	Purpose: Treatment Allocation: Randomised controlled trial Masking: Open label Assignment: Parallel Type of endpoint: Efficacy
Date of First Enrolment	25-10-2022
Sample Size	122 patients
Primary outcome	Stent patency, defined as the period between uSEMS placement and recurrent biliary obstruction
Key secondary outcome(s)	Technical and functional success; procedure time; time to reintervention; total number of (non-elective) reinterventions; need for permanent percutaneous drainage; presumed causes of recurrent obstruction; stent patency following repeated eRFA; adverse events within 30 days; Quality of Life; overall survival (from diagnosis and intervention); and healthcare costs.
Ethics Review	Status: Approved Approval date: 24-9-2022 Contact: METC Amsterdam UMC
Individual Trial Participant Data sharing statement	The final de-identified trial dataset will be accessible to the study investigators. Data sharing with external researchers may be granted upon reasonable request, after publication, and approval from the principal investigator and ethics committee. Clinical data access requests to be sent to the principal investigator Dr. R.P. Voermans (r.p.voermans@amsterdamumc.nl)

Abstract

Background

The majority of patients with perihilar cholangiocarcinoma (pCCA) require palliative biliary drainage. While uncovered self-expanding metal stents (uSEMS) are currently the standard of care, they are prone to tumour ingrowth and recurrent biliary obstruction. Endobiliary radiofrequency ablation (eRFA) may prolong stent patency by targeting intraductal growth. However, existing evidence for eRFA for its use specifically in pCCA managed with uSEMS remains limited.

Methods

The RACCOON-trial is an international, multicentre, randomised controlled, parallel-group, superiority trial. Patients with pathologically proven, inoperable pCCA will be randomised (1:1) to the intervention group (eRFA + uSEMS) or to the control group (uSEMS alone). Key exclusion criteria include active cholangitis, liver abscess at the time of intervention, or a life expectancy <3 months. Randomisation is stratified by the intention to place one or multiple stents. The primary endpoint is stent patency, defined as the period between uSEMS placement and recurrent biliary obstruction. Secondary endpoints include technical and functional success, procedure time, time to reintervention, and the total number of (non-elective) reinterventions. Additionally, the study will evaluate the need for permanent percutaneous drainage, presumed causes of recurrent obstruction, stent patency following repeated eRFA, and adverse events within 30 days. Long-term outcomes include Quality of Life (QoL), overall survival (from diagnosis and intervention), and healthcare costs.

Discussion

The RACCOON-trial will evaluate whether adding eRFA to standard uSEMS placement improves stent patency for patients with inoperable pCCA. We hypothesize that eRFA will prolong the time to recurrent biliary obstruction, thereby improving QoL and reducing the burden of reinterventions during the palliative phase.

INTRODUCTION

Background and rationale

Cholangiocarcinoma (CCA) is a rare cancer, but its incidence is increasing globally. Approximately 0.3-6 per 100.000 people are diagnosed with perihilar CCA (pCCA) every year globally [1]. Treatment options are sparse and prognosis is poor with a 5-year survival rate as low as 5-10% [2]. Due to tumour growth in the bile ducts, almost all patients develop biliary obstruction in the course of their disease. This leads to symptoms such as jaundice, pruritis, cholangitis, and general malaise. Since most patients present with locally advanced or metastatic disease, or are too frail to undergo major liver surgery, 80-85% of patients are limited to palliative care. This management typically involves biliary stenting for adequate drainage and the administration of systemic therapy [3-6].

For patients with inoperable pCCA, effective biliary drainage is often hampered by complications such as stent occlusion and cholangitis. Uncovered self-expanding metal stents (uSEMS) are superior to plastic stents in terms of stent patency, number of reinterventions, and adverse events and are therefore the current standard of care [3, 4, 7-9]. Nonetheless, uSEMS are still prone to tumour ingrowth leading to limited stent patency and consequently a need for reinterventions. Since uSEMS cannot be removed, stent-in-stent placement is often needed in case of reintervention and repeated procedures become more challenging or insufficient when stents block segmental branches of the bile ducts [8-10]. This leads to a high burden of disease due to cholangitis, sepsis, reinterventions and re-admissions, delay or discontinuation of palliative chemotherapy, permanent external drainage catheters, and, if adequate drainage cannot be achieved, death [9, 10]. Therefore, improvement of stent patency seems of utmost importance to increase quality of life in patients with pCCA.

The use of additional local-ablative therapies such as photodynamic therapy (PDT) and endobiliary radiofrequency ablation (eRFA) may prolong stent patency [11-24]. While PDT has demonstrated efficacy regarding patency and survival, use in daily clinical practice is limited due to major side effects such as phototoxicity and high costs. Therefore, PDT is not mentioned in current international guidelines [3, 6, 19, 24, 25]. In contrast, eRFA has shown to have limited side effects and seems to be effective as well [17, 26, 27]. Theoretically, the benefits of endobiliary ablation are greater in tumours with an intraductal growth pattern (such as pCCA), rather than those causing extrinsic compression. Furthermore, eRFA may be particularly beneficial in addition to uSEMS, as these stents are susceptible to tumour ingrowth, unlike plastic or covered metal stents. However, currently eRFA has mostly been

studied when combined with plastic stents and in patients with tumours distal to the bifurcation [28-31].

The vast majority of patients with inoperable pCCA experience recurrent biliary obstruction with concomitant cholangitis requiring multiple reinterventions during the course of the disease. In the palliative phase of the disease, improved stent patency therefore is of utmost importance for quality of life.

Given that uSEMS are currently the standard of care, the aim of the current trial is to compare eRFA prior to uSEMS placement with uSEMS placement alone in patients with pCCA.

Objectives

The primary objective of the study is to evaluate whether eRFA prolongs stent patency of uSEMS in patients with a malignant biliary obstruction due to inoperable pCCA.

Trial design

This study is an international multicentre, open-label, parallel group randomised controlled superiority trial. Participants will be randomised to either eRFA followed by uSEMS placement (intervention arm) or uSEMS placement only (standard arm).

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

Study setting

The RACCOON-trial is being conducted in both academic and community teaching hospitals in the Netherlands, Belgium, Romania, Czech and the United States of America. An updated list of study sites can be obtained at clinicaltrials.gov (NCT05546372). The study is initiated by Amsterdam UMC in collaboration with the Dutch Hepatocellular & Cholangiocarcinoma Group (DHCG).

Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- 18 years or older.
- Capable of providing written and oral informed consent.
- Histological or cytological proof of CCA (adenocarcinoma).^a

- Perihilar biliary obstruction with an indication for biliary drainage with uSEMS, meaning patients are adequately drained with plastic stents or percutaneous drainage catheters.^b
- Advanced and irresectable disease according to multidisciplinary team, or patient considered unfit for surgery due to comorbidities, or patient wishes to refrain from surgery.

^aCytopathology with a classification of Papanicolaou Society of Cytopathology V or higher or a World Health Organization (WHO) 6 or higher is considered cytological proof [32, 33].

^bOnly patients with pCCA are eligible however in case of reasonable doubt between intrahepatic CCA with a perihilar biliary obstruction or mass-forming pCCA or in case of reasonable doubt between gallbladder cancer and pCCA, patients can be included. Adequate drainage is defined as bilirubin <40 µmol/L (<2.3 mg/dL) or bilirubin levels are decreasing and ≥50% decreased from the bilirubin prior to biliary drainage, or bilirubin levels are currently increasing but reached a level <40 µmol/L (<2.3 mg/dL) after biliary drainage of the intended segments.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients who potentially qualify for curative resection of pCCA.
- Patients who will be potentially eligible for liver transplantation.
- Life-expectancy less than 3 months.
- ERCP and PTC technically not feasible.
- Uncontrolled coagulopathy (PTT >1.5x prolonged or thrombocytes below 40*10⁹/L).
- Ongoing cholangitis or liver abscess. Patients are required to be off antibiotic treatment for cholangitis and/or liver abscess for at least 7 days.
- Any condition that is unstable or that could jeopardize the safety of the patient and their compliance in the study.
- Patients who are pregnant or breastfeeding.
- An implantable pacemaker and/or cardioverter/defibrillator.

Study procedures can be performed by gastroenterologists or interventional radiologists with experience in placement of uSEMS in patients with perihilar cholangiocarcinoma. Considering eRFA does not require greater technical expertise than stent placement, no additional requirements for physicians were defined. Approximately two interventional radiologists and gastroenterologists will be trained per centre.

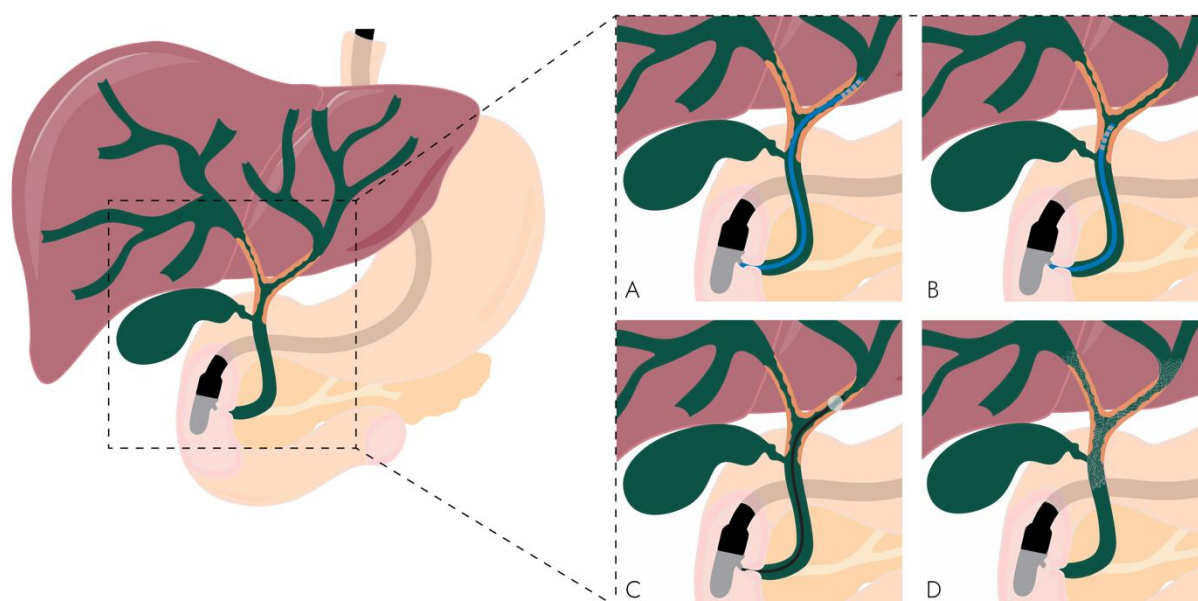
Interventions

RFA using the ELRA™ Endo Luminal Radiofrequency Ablation catheter and VIVA combo™ RF generator prior to the placement of an uSEMS (NiTi-S™ M-Stent) by TaeWoong Medical Co., Ltd., Seoul, Korea (Manufacturer: STARmed™ Co., Ltd., Gyeonggi-do, Korea) will be compared with an uSEMS placement only. In the intervention arm the tumour will be ablated at 7W for 120 seconds, at a target temperature of 75 degrees Celsius using the VIVA Combo™ generator's Impedance Monitoring System. The catheter will be kept in place after ablation until the tissue has cooled down to approximately 45 degrees Celsius, in order to avoid adhesion of the tissue to the electrodes. In general, a catheter with an 18 mm exposure length will be used, in case of a shorter stricture an 11 mm catheter can be used. The ablation will be subsequently repeated slightly overlapping the previous position until the complete stricture has been ablated. Necrotic tissue will be removed with an extraction balloon afterwards.

In both groups, bilateral side-by-side (8 mm) or unilateral (10 mm) uSEMS will be placed, with the length at the interventionist's discretion. In the intervention arm, stent placement is performed during the same procedure, immediately following eRFA. The intervention can be performed via ERCP or PTC, as depicted in Figure 1. Detailed pre- and post-procedural care is provided in the supplementary material.

Patients in both study arms will receive the current standard of care for inoperable pCCA. The only procedural difference between the groups is the addition of eRFA in the intervention arm. The study flowchart and schedule of events for both groups are depicted in Figure 2 and Table 1, respectively. The use of concomitant systemic therapy and/or radiotherapy is allowed in both groups.

Figure 1. Study procedure.



A) eRFA will be performed for 2 minutes with 7 Watt at target temperature of 75°C, B) eRFA will be sequentially repeated until complete ablation of the stenosis (if applicable, the stenosis in the other duct will subsequently be ablated), C) Necrotic tissue will be removed with an extraction balloon, D) uSEMS will be placed across the stenosis.

Reintervention for recurrent obstruction will be performed when clinically indicated, specifically upon the recurrence of symptoms (such as pruritus or cholangitis) or when necessary to initiate or continue systemic therapy. In the intervention group, repeat RFA (re-RFA) with or without additional stent placement is permitted; there is no maximum number of re-RFA treatments, provided they occur no more than once per month. The control group will receive standard care, including additional stent placement if required. As RFA is not part of standard care, it will not be administered to the control group in case of reintervention.

Outcomes

Primary outcome is stent patency e.g. the median time to biliary obstruction, defined as period between placement of uSEMS and recurrence of biliary obstruction. Recurrence of biliary obstruction is defined as recurrent jaundice, presence of biochemical evidence of cholestasis along with dilatation of the drained bile duct(s), or endoscopic or radiological findings suggesting stent occlusion. Recurrent jaundice is defined as conjugated bilirubin $\geq 40 \mu\text{mol/l}$ ($\geq 2.3 \text{ mg/dL}$) after previous adequate drainage. Biochemical evidence of cholestasis is defined as increased serum alkaline phosphatase, gamma-glutamyl transpeptidase, ALT, and AST > 1.5 times higher than the upper limit of normal value.

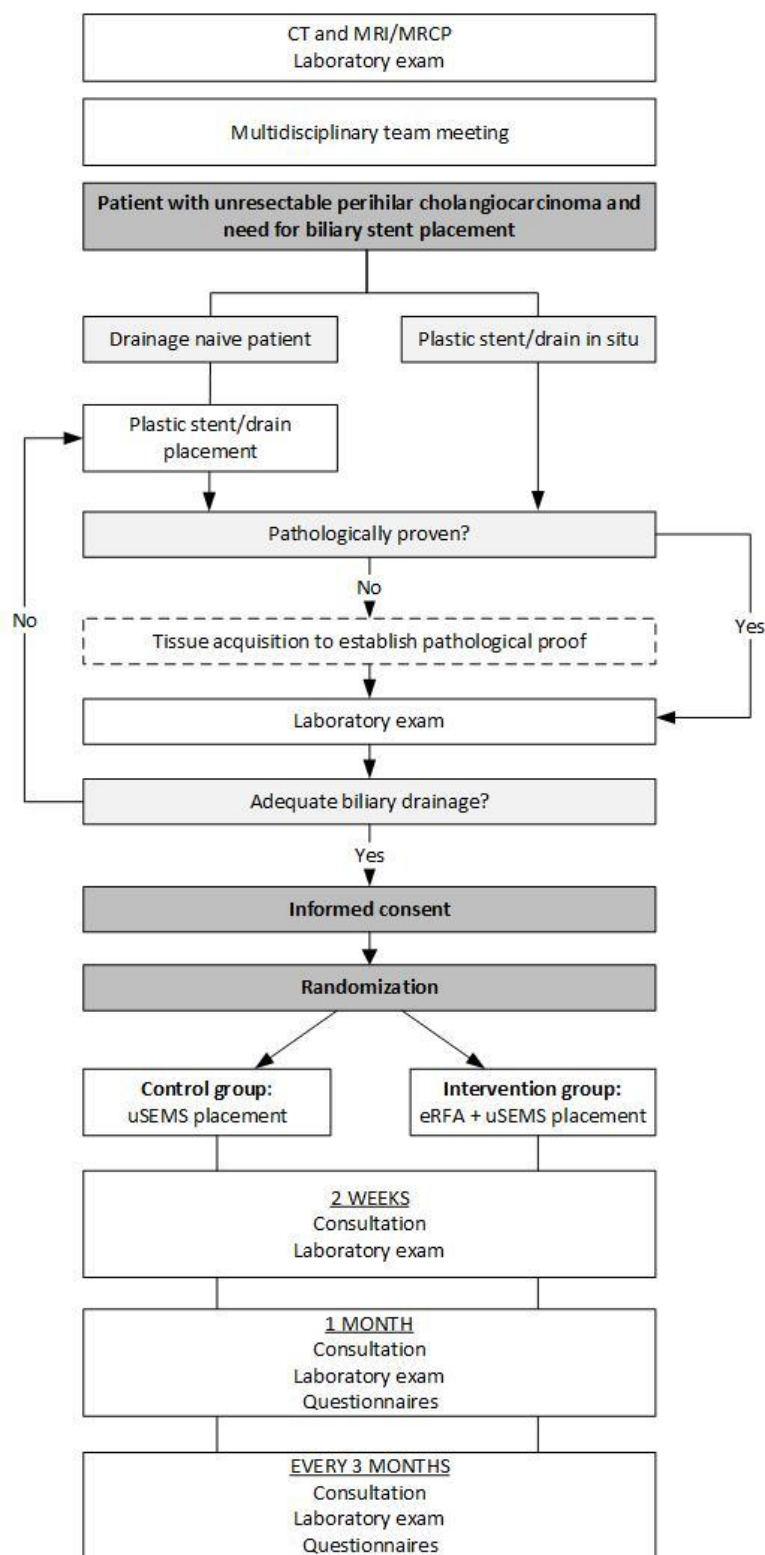
1 Secondary endpoints

2 Definitions of secondary endpoints are described in detail in additional file 3. Severity of adverse events
3 will be graded according to the AGREE-classification [34].

- 4 - Quality of life
- 5 - Technical success of initial ablation
- 6 - Technical success of stent placement
- 7 - Functional success
- 8 - Procedure time
- 9 - Presumed reason of recurrent biliary obstruction
- 10 - Need for permanent external percutaneous drainage catheters
- 11 - Time to reintervention
- 12 - Number of (non-elective) reinterventions
- 13 - Stent patency after repeated eRFA
- 14 - Adverse events within 30 days after the procedure
- 15 - Overall survival (since diagnosis and since procedure)
- 16 - Healthcare costs

17
18 Subset analyses are planned for one versus multiple metal stents at baseline and the use of
19 concomitant systemic therapy.

1 Figure 2. Study flowchart.



3
 4 Abbreviations: CT, computed tomography; eRFA, endobiliary radiofrequency ablation; MRI/MRCP,
 5 magnetic resonance imaging/magnetic resonance cholangiopancreatography; uSEMS, uncovered self-
 6 expanding metal stents.

7

1 Table 1. SPIRIT diagram: schedule of enrolment, interventions, and assessments.

	Study period									
	Eligibility assessment	Enrolment	Intervention	Post-allocation						
				Week		Month				
Timepoint	-t2	-t1	t0	2	4	3	6	9	12	Every 3 months
Enrolment:										
Eligibility screening	X									
Discussion in clinical MDT	X									
Informed consent		X								
Allocation		X								
Intervention:										
Stent placement +/- eRFA			X							
Assessments:										
Baseline variables		X								
Procedural variables			X							
Laboratory exam		X		X	X	X	X	X	X	X
QOL questionnaires		X			X	X	X	X	X	X
Telephonic assessment of AEs and symptoms				X	X	X	X	X	X	X

2 Abbreviations: AE, adverse events; eRFA, endobiliary radiofrequency ablation; MDT, multidisciplinary
3 team; QOL, quality of life

4
5 Sample size

6 The hypothesis is that combining eRFA with stent placement will increase stent patency, subsequently
7 improving quality of life. Sample size calculation was performed for a two-sided log-rank test with a
8 significance level (alpha) of 0.05 and 80% power. Based on a retrospective and subgroup analysis of a
9 small RCT that compared eRFA prior to placement of uSEMS performed by either ERCP or PTC in pCCA,
10 we expect median patency times of 7.94 months for the eRFA group and 4.35 months for the control
11 group. [18, 20]. Under the assumption of exponential survival, these median values correspond to
12 hazard rates of 0.087 and 0.159, respectively, resulting in a constant Hazard Ratio (HR) of 0.548. To
13 detect this difference, a total of 87 events (stent obstructions) are required. This approach tests for a
14 significant difference between the stent patency curves of both treatment arms. Dropout is defined as
15 patients who are censored because of death or loss to follow-up before reaching the primary endpoint.

Because of the relatively high risk of patients dying prior to experiencing recurrent biliary obstruction and to limit the risk of an underpowered study, the dropout rate will be assessed after enrolment of 60 patients and again, if deemed necessary, after enrolment of 85 and/or 110 patients and sample size adjusted accordingly.

Recruitment

Each patient is discussed in a multidisciplinary team meeting (MDT) in which their eligibility for study participation is determined. When study accrual is slow, additional international centres from the same or other countries will be involved in order to reach the target sample size.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation

Randomisation will be performed in a 1:1 ratio, stratified for the intended placement of one versus multiple stents using random block sizes of 2, 4, and 6. Castor EDC will be used to facilitate randomisation.

Blinding (masking)

Allocation is unblinded for both the investigator and the patient. An independent, masked adjudication committee, consisting of two gastroenterologists with focus on biliary endoscopy, will individually assess all suspected occurrences of the primary endpoint. Consensus meetings will be held to discuss discrepancies and reach a final determination.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection methods

Patients will be followed for at least 12 months, follow-up will end prematurely in case the patient prefers to stop follow-up.

Laboratory tests

At baseline, after 2 weeks, 1 month, and every 3 months after the intervention, laboratory tests will be obtained preferably including total bilirubin, direct bilirubin, alkaline phosphatase (AF), gamma-glutamyl transpeptidase (g-GT), alanine transaminase (ALT), aspartate aminotransferase (AST).

Quality of life

Standard quality of life assessment consists of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-30), the EORTC Quality of Life module for CCA and gallbladder cancer (EORTC QLQ-BIL21), and the EuroQol 5D (EQ-5D-5L). Questionnaires are filled out at baseline at inclusion, 1 month after the procedure, 3 months after the procedure and subsequently every 3 months until death. Participants will be reminded to fill out the questionnaires during the (telephonic) follow-up visit.

Imaging

At baseline (prior to first drainage procedure) computed tomography (CT) and/or magnetic resonance imaging (MRI)/ magnetic resonance cholangiopancreatography (MRCP) will be performed in every patient as is standard care. Additional (post-baseline) imaging such as ultrasound, CT, MRI/MRCP or positron emission tomography (PET)-CT will only be performed on indication. Prior to reintervention abdominal imaging, either CT or MRI/MRCP is preferably performed.

Data management

Data will be extracted by authorized research group personnel through electronic case report forms (eCRFs). These will be stored in Castor EDC. The eCRF will be checked for accuracy and completed where needed by the study coordinators. Castor EDC has an audit trail; changes and documentation within the eCRFs will be tracked. Questionnaires are sent by e-mail through Castor EDC or by mail to the patient's home address if preferred. Data validation will be performed, with multiple checks on the completeness and consistency of the data. The audit trail will be saved. A summary of demographic participant characteristics is depicted in Table 2.

Table 2. PRO EDI participant characteristics table

Characteristic	The people we would expect to see included
Age	More than half of the patients with pCCA is older than 70 years [35]. All patients older than 18 years will be included.
Sex	The disease affects both sexes, with a slight male preponderance [35]. Male and female participants will be included.
Gender	Only sex will be reported. No other sexes than male and female will be reported.

Race, ethnicity, and ancestry	The trial will aim for community levels of ethnic diversity, i.e. the same as the geographical area researched. Collection of race and ethnicity requires special ethical permission and is not part of routine data included in patient files.
Socioeconomic status	The trial will aim for broad participation across socioeconomic status. Explicit data on socioeconomic status will not be collected.
Location	Study participants will be recruited from the Netherlands, Belgium, Romania, Czech and the United States from both rural and urban areas. Explicit data on urban vs rural area will not be collected.

Statistical methods

Primary outcome

The primary endpoint, time to biliary obstruction, will be described as median time to recurrent biliary obstruction with 95% confidence interval (CI) and estimated using the Kaplan-Meier method. Comparison in survival curves between the randomisation arms will be made using the log-rank test. To adjust for relevant prognostic factors, a Cox-proportional hazards model will be generated. The model will include, at minimum, the following baseline covariates: number of stents (single vs. multiple), systemic therapy, and Bismuth-Corlette classification. Selection of additional prognostic factors will be guided by any observed imbalances in baseline characteristics between the study groups. As a sensitivity analysis, the adjusted hazard ratio will be calculated with 95% CI and compared to the results from the univariable Cox model. Patients will be censored at time of death (if prior to the primary endpoint) or at the end of the follow-up period. The end of follow-up is defined as the point when the last enrolled patient has either died or reached 12 months of follow-up. A sensitivity analysis will be performed in which all patients are censored at a maximum of 12 months, regardless of the total study duration. Frequency of recurrent biliary obstruction during 1-year follow-up will be shown and non-obstruction rates at 3, 6, 9 and 12 months will be estimated with corresponding 95%CI.

Secondary outcomes

For binary endpoints relative frequencies will be described as frequencies with percentages and 95% confidence intervals. Continuous variables as mean with standard deviation or median with interquartile range (IQR) in case of a non-normal distribution. Categorical variables will be compared by assessing the relative risk with corresponding 95%CI, continuous variables will be compared by

1 assessing the mean difference with corresponding 95%CI or median with IQR in case of a non-normal
2 distribution. Time to event data will be estimated using Kaplan-Meier analysis and relevant quantiles
3 will be compared using 95% CI. Survival time will be assessed from the date of intervention and from
4 the date of diagnosis until the date of death; additionally, a sensitivity analysis measuring survival from
5 the date of randomization will be performed. Count data will be analysed using Poisson regression
6 analysis.

7
8 Quality of Life outcomes will be assessed with (generalised) linear mixed model analyses with post-
9 baseline quality of life values as a dependent variable, a random intercept at the subject level, and fixed
10 effects for treatment arm, time and other prognostic factors. The interaction between treatment arm
11 and time will also be added to this model. The effect of eRFA will be tested by comparing the model
12 with and without the treatment term(s).

13
14 Should the study yield a positive result regarding the primary outcome, a cost-effectiveness analysis
15 will be performed. Since all participants are in the palliative phase of the disease, no major differences
16 in costs from a societal perspective are anticipated; therefore, we will focus exclusively on the hospital
17 perspective. The outcomes of these analyses will be the costs per patient without poor outcome
18 (defined as stent dysfunction) and the costs per quality-adjusted life year (QALY).

19
20 All main analyses will be performed by intention-to-treat. In case >10% missing data is present in the
21 primary endpoint; imputation analysis will also be shown.

22 Predefined subgroup analyses include: one versus multiple stents and use of systemic therapy.

METHODS: MONITORING

Data monitoring

An independent safety committee will monitor safety outcomes and the overall conduct of the study and provides the (Coordinating) PI with recommendations regarding continuing or stopping the study (for all subjects or subgroups of subjects). The DSMB will evaluate mortality and all possible trial related serious adverse events after the first 10 and subsequently every 25 enrolled patients. After enrolment of 60 patients, and again if deemed necessary at subsequent DSMB meetings, the dropout rate will be reassessed, and the sample size may be increased accordingly to avoid an underpowered study. No interim analysis for the primary endpoint will be performed.

Harms

All serious adverse events within 30 days after the initial procedure and/or reintervention will be reported to the sponsor without undue delay after obtaining knowledge of the event. Serious adverse events more than 30 days after the (re-)intervention are considered expected events within the natural course of cholangiocarcinoma and will not be reported.

Auditing

Study monitoring is organised in every country separately, monitoring will be done by an independent monitor. In general, one initiation visit, one regular monitoring visit and one close-out visit (remote or on-site) of each participating centre and the coordinating centre will be performed.

ETHICS AND DISSEMINATION

Research ethics approval

The study protocol was reviewed and approved by the medical ethical committee of Amsterdam UMC. Local medical ethical committees of the participating centres approved the trial protocol before start of inclusion at the particular centre.

Protocol amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. If the

1 amendments could have any influence on the decision of participants to participate in the trial, these
2 changes will be communicated to the participants as well.

3 4 Consent or assent

5 Patients who present at the outpatient clinic or are discussed in a MDT will be screened and invited for
6 study participation by their treating physician. If the patient is interested, full study information will be
7 provided by the coordinating investigator or one of the co-investigators during the outpatient clinic
8 appointment or by telephone/video consult. After the patient has had the opportunity to ask additional
9 questions and has had sufficient time to decide about participation, written informed consent will be
10 provided before randomisation. The trial does not involve collection of biological specimens.

11 12 Confidentiality

13 Laboratory results and reports from telephone/outpatient consults which are part of routine care will
14 be reported in the medical dossier. Research data that are coupled with other will be stored separately
15 from patient care by a subject identification code list. The code will not be based on the patient initials
16 or birthdate. The key to the code is safeguarded by the investigator. Only the research group personnel
17 and monitor will have access to the source data and to the database.

18 19 Access to data

20 The principal investigator and coordinating investigator will have access to the final trial dataset. Any
21 data required to support the protocol can be supplied on request.

22 23 Ancillary and post-trial care

24 The sponsor has a liability insurance which is in accordance with article 7 of the Dutch Medical Research
25 Involving Human Subjects Act (WMO). This insurance provides cover for damage to research subjects
26 through injury or death caused by the study in the Netherlands. The insurance applies to the damage
27 that becomes apparent during the study or within 4 years after the end of the study. In other countries
28 a comparable liability insurance is issued by the delegated sponsor.

29 30 Dissemination policy

31 The results of this trial will be submitted to a peer-reviewed medical journal regardless of the study
32 outcome. Moreover, results will be submitted for presentation at national and international
33 conferences and will be presented to the involved patient organizations. Authorship will be based on
34 international guidelines. Those involved with the study who do not fulfil these criteria will be listed as
35 “collaborator.” This study is registered in a publicly available prospective clinical trial registry before the

first patient was included. Access to participant-level data and the statistical code can be granted on request.

DISCUSSION

The RACCOON trial is designed to answer the question whether eRFA can improve the stent patency of uSEMS in patients with pCCA not eligible for surgery. This is the first published protocol describing an RCT focused on eRFA in combination with uSEMS in patients with pCCA.

Since the start of patient enrolment, two randomised controlled trials evaluating the effect of eRFA in combination with uSEMS in patients with pCCA have been published. Both of these trials did not meet their primary endpoint [36, 37]. Kang et al. used stent patency as the primary endpoint, but their cohort differs from our target population, of the 48 enrolled patients only ten presented with hilar strictures. The RCT by Jarosova et al. was the first to evaluate the effect of eRFA separately in CCA, and the majority were hilar strictures. However, survival was chosen as the primary endpoint. The study was stopped due to futility, which is unfortunate as after study termination it was underpowered to detect a potential benefit in stent patency [38]. To the best of our knowledge, two additional trials (NCT06175845, NCT07235007) have been registered since the start of our study.

In the RACCOON-trial we will only include patients with pCCA, or if there is reasonable doubt between intrahepatic and pCCA, who are eligible for uSEMS placement, to create a homogeneous group. Although the fact that eRFA and stent placement can be performed by either an endoscopic or percutaneous approach in the trial will introduce some heterogeneity, we do not believe that this will introduce significant bias and will increase the validity of this trial for clinical practice.

Considering the use of one versus multiple stents will most likely influence the time to biliary obstruction, patients will be stratified for this factor which will prevent a clinically relevant unbalanced representation of different Bismuth types between the two groups. However, it is difficult to distinguish the potential difference between these groups. Hence, the sample size is not separately calculated for both stratification groups (one versus multiple stents), but subset analysis for these strata are planned. Furthermore, it is suggested that systemic therapy in combination with eRFA could improve the time to biliary obstruction [39]. However, randomisation will not be stratified for systemic treatment, as the definitive treatment plan regarding systemic therapy is often not yet established at the time of stent placement. Instead, subset analyses will be performed to account for the impact of systemic therapy.

1
2 These planned subset analyses will possibly lead to observational data on a differential effect of these
3 factors. We do not stratify by centre, as this could negatively affect allocation concealment. In centres
4 with low recruitment numbers, unfilled randomisation blocks may occur, potentially leading to a lack
5 of balance between the two study arms [40].

6
7 In short, the RACCOON trial will specifically evaluate the effect of eRFA prior to uSEMS placement in
8 patients with inoperable pCCA, with the hypothesis to improve stent patency and consequently quality
9 of life in the palliative phase.

10 11 12 TRIAL STATUS

13
14 The first patient was included on 25-10-2022. Currently (16-03-2026) 104 patients have been enrolled
15 and the accrual rate proceeds as scheduled. The observed drop-out rate has been between 25-30%
16 and therefore the drop-out rate has been set at 28%, which means 122 patients need to be included.
17 Protocol version 2 is being used. The last patient is expected to be included in June 2026.

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