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FINAL DEGREE PROJECT

INTRADUCTAL RADIOFREQUENCY ABLATION FOR UNRESECTABLE MALIGNANT DISTAL BILIARY OBSTRUCTION

A RANDOMISED CONTROLLED CLINICAL TRIAL

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Voldria agrair en primer lloc al meu tutor clínic, Dr. Carlos Huertas, per tota l'ajuda, motivació i temps dedicat a l'elaboració d'aquest treball.

Al servei de Digestiu de l'Hospital Universitari Doctor Josep Trueta, per acollir-me durant aquests dos mesos i fer-me sentir part de l'equip

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1 ABSTRACT

BACKGROUND: pancreatic cancer and cholangiocarcinoma are malignant tumors with an increasing incidence and generally a poor prognosis. They are the main causes of malignant biliary obstruction. Patients typically remain asymptomatic until the disease is significantly advanced with no possibilities of surgical resection. Endoscopic placement of biliary stents to relieve jaundice is the main palliative treatment, no local treatment is currently available. Endoscopic biliary radiofrequency ablation reduces the tumoral burden and has been reported to prolong stent patency, which may be beneficial in improving patient survival. Moreover, it has shown to have an adequate safety profile in previous studies. Nevertheless, available evidence is still insufficient as most of the data come from retrospective series, with a limited number of patients and uncontrolled studies.

OBJECTIVES: the aim of this study is to assess whether the application of radiofrequency combined with stent placement in unresectable malignant distal biliary obstructions increases survival rate in comparison to stent placement alone. When it comes to secondary objectives, quality of life during the follow-up period will be assessed, as well as stent patency and number of hospitalizations.

DESIGN AND SETTING: this study is designed as a multicentric, randomized, controlled, single-blind, interventional clinical trial, performed in *Hospital Universitari Doctor Josep Trueta* and *Hospital Universitari Germans Trias i Pujol*.

PARTICIPANTS: adult patients with a histological confirmed pancreatic cancer or cholangiocarcinoma, presenting with an unresectable malignant distal biliary obstruction.

METHODS: 118 patients will be recruited consecutively in *Hospital Universitari Doctor Josep Trueta* and *Hospital Universitari Germans Trias i Pujol.* Patients will be randomly assigned into two treatment groups: radiofrequency ablation plus stent placement (intervention group) or stent placement alone (control group). Participants will be followed during a two-year period in order to assess survival rates, stent patency, number of hospitalizations and quality of life.

KEYWORDS: *malignant biliary obstructions, endoscopic radiofrequency, intraductal radiofrequency ablation, pancreatic cancer, cholangiocarcinoma, stent patency, overall survival.*

2 ABBREVIATIONS

ASA	American Society of Anesthesiologists
ASGE	American Society for Gastrointestinal Endoscopy
BMI	Body mass index
BS	Biliary stricture
CA 19.9	Carbohydrate antigen
CA125	Carbohydrate antigen 125
CBD	Common biliary duct
CCA	Cholangiocarcinoma
CEA	Carcinoembryonic antigen
CEIC	Comitè Ètic d'Investigació Clínica
CHD	Common hepatic duct
CT	Computerized tomography
dCCA	Distal cholangiocarcinoma
ECOG	Eastern cooperative oncology group
ELRA	Endoluminal radiofrequency ablation
ERCP	Endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
EUS	Endoscopic ultrasonography
FCSEMS	Fully covered self-expandable metal stent
HPB	Hepatico-pancreato-biliary
HUGTP	Hospital Universitari Germans Trias i Pujol
HUJT	Hospital Universitari Doctor Josep Trueta
iCCA	Intrahepatic cholangiocarcinoma
ICD-O3	International Classification of Diseases for Oncology Third Edition
LHD	Left hepatic duct
MBO	Malignant biliary obstruction

MDBO	Malignant distal biliary obstruction
MRCP	Magnetic resonance cholangiopancreatography
NCCN	National comprehensive cancer network
OS	Overall survival
PC	Pancreatic cancer
pCCA	Perihilar cholangiocarcinoma
PCSEMS	Partially covered self-expandable metal stent
PS	Plastic stents
QoL	Quality of life
RFA	Radiofrequency
RHD	Right hepatic duct
SEMS	Self-expandable metal stents
USEMS	Uncovered self-expandable metal stent

3 INTRODUCTION

3.1 BILIARY TRACT ANATOMY

The biliary tract is divided into intra and extra-hepatic bile ducts.

The intrahepatic drainage system starts when bile canaliculi unite and form the segmental bile ducts that drain the different hepatic segments. Segmental bile ducts from hepatic segments 2, 3, 4a and 4b unite to form the left hepatic duct (LHD) while ducts from segments 5, 6, 7 and 8 form the right hepatic duct (RHD). The left and right hepatic ducts unite and form the common hepatic duct (CHD). The bile ducts that come from segment 1 (caudate lobe) drain into the angle where the left and right hepatic ducts meet (1).

The CHD ends when the cystic duct joins on its right margin. Its average diameter is 4.0 mm, and its length goes from 1.0 cm to 7.5 cm. Then, the common biliary duct (CBD) is formed. The CBD is about 7-8 cm, and its average diameter is 7-8 mm. It is divided into supraduodenal, retroduodenal, intrapancreatic and intraduodenal segments. The supraduodenal part travels in the free edge of the lesser omentum. Then, the retroduodenal segment runs behind the superior duodenum part and goes downwards and to the right, behind the head of the pancreas, forming the retropancreatic segment. Finally, the CBD and the pancreatic duct unite to pierce the descending duodenum and form the ampulla of Vater. The Oddi sphincter is a set of circular muscle fibers that surround the ampulla and the last part of the CBD and the pancreatic duct (Figure 1) (2).

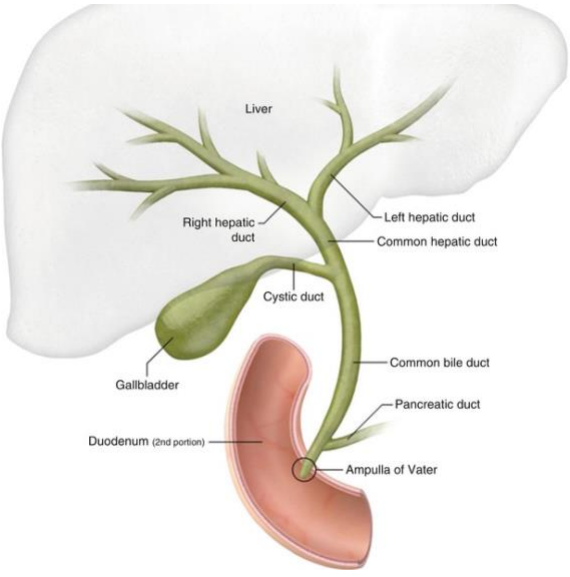

Figure 1. ***Biliary tract anatomy*** *(3)*

3.2 MALIGNANT BILIARY OBSTRUCTION

A Biliary stricture (BS) is an area of luminal stenosis in the extrahepatic or intrahepatic biliary system. Depending on the etiology and the chronicity of the disease, patients with BS can present with acute or subacute obstructive symptoms. BS are classified into two groups, malignant and benign BS (4). The main cause of BS in the western world is a malignant disease, representing 70% of them (5).

Malignant biliary tract obstruction (MBO) is a consequence of stenosis and blockage of the bile ducts due to local tumor invasion or compression (6). MBO are classified into hilar or distal depending on the level of the stricture. The most frequent cancers that can present with a BS are pancreatic cancer (PC) and cholangiocarcinoma (CCA). However, ampullary tumors, metastatic lesions from other solid organs, extrinsic compression from gallbladder cancer or periportal lymph nodes can also cause BS (4).

*Table 1: **Etiology of biliary tract obstructions**. Adapted from (7)*

MALIGNANT (70%)	BENIGN (30%)
Cholangiocarcinoma	**Iatrogenic:** Post-endoscopic sphincterotomy, post-hepatobiliary surgery.
Pancreatic cancer, ampullary or duodenal malignancies	**Inflammatory:** Primary and secondary sclerosing cholangitis, acute or chronic pancreatitis.
Carcinoma in the gallbladder	**Ischemic**: Hepatic artery stenosis or thrombosis.
Lymphoma and metastatic lymphadenopathy	**Infectious:** Recurrent pyogenic cholangitis, human immunodeficiency virus, cholangiopathy, tuberculosis, sarcoidosis, parasitic, choledocholithiasis.
Intrahepatic metastasis	**Autoimmune**: Immunoglobulin G4 cholangitis.
	Miscellaneous: Portal biliopathy, trauma, papillary stenosis.

3.2.1 CLINICAL PRESENTATION OF MALIGNANT BILIARY OBSTRUCTION

MBO is a frequent clinical entity and a common cause of jaundice. Patients with malignancies causing MBO usually remain asymptomatic until late stages of the disease. Symptoms of obstructive jaundice cause an important impairment in a patient's quality of life and can promote liver dysfunction unless intervention to decompress the biliary tract is performed (8). MBO presents with the following symptoms:

- **Jaundice**: tends to be the first presenting symptom. Manifested by skin yellowness or scleral icterus. Other accompanying symptoms include choluria, acholia, pruritus, nausea and right upper quadrant discomfort.
- **Nonspecific symptoms suggesting malignancy**: weight loss, anorexia, fatigue, generalized dyspepsia, dull abdominal pain, new-onset diabetes, early satiety and others.
- **Cholangitis:** clinical syndrome presented with fever, jaundice and abdominal pain (Charcot triad).

The laboratory work-up shows a cholestatic pattern. Serum bilirubin (mainly direct), alkaline phosphatase and gamma-glutamyl transpeptidase are elevated. About tumor markers, they are usually nonspecific. CA 19-9 is the main biomarker in pancreatic cancer, but can be elevated in other gastrointestinal malignancies such as cholangiocarcinoma, hepatocellular cancer, esophageal cancer, gastric cancer, colorectal cancer, and it is also elevated in benign processes like acute cholangitis or pancreatitis (8).

3.2.2 DIAGNOSIS OF MALIGNANT BILIARY OBSTRUCTION

The main diagnostic techniques for MBO are the following (9):

- **Abdominal ultrasound**: first imaging modality performed in obstructive jaundice. It identifies biliary dilatation and, in some cases, the cause of it. It is essential in determining the next suitable image modality for further evaluation.

- **Magnetic resonance cholangiopancreatography (MRCP)**: essential in the evaluation of MBO. It has a high sensitivity (96-99%) for identifying the stricture and its anatomical location but low specificity in differentiating benign from malignant ones (85%).

- **Computerized tomography (CT)**: provides staging information. No tissue diagnosis is obtained by imaging, but it is important to have the anatomic details to plan ERCP-related interventions or preoperative staging before surgery.

- **Endoscopic retrograde cholangiopancreatography (ERCP)**: a better visualization of the bile ducts is achieved, allows tissue diagnosis and provides palliative treatment of MBO by placing a biliary stent.

- **Endoscopic ultrasonography (EUS) and fine needle aspiration:** plays an important role in the initial evaluation of pancreatobiliary lesions, complementing ERCP. Allows tissue sampling, tumor staging, and to exclude benign causes of biliary obstruction.

3.2.3 MANAGEMENT OF MALIGNANT BILIARY OBSTRUCTION

The treatment depends on the localization, severity and resectability of the stricture. Most of the patients present an unresectable MBO. Only 30% of them are resectable at the time of the diagnosis. Because of it, the main treatment in these patients is palliation, relieving the biliary obstruction endoscopically. The goal of the palliative treatment is to treat or prevent biliary obstruction and to reduce the related symptoms such as jaundice, cholangitis and pruritus, improving their quality of life (6).

The least invasive and more cost-effective technique to provide biliary decompression is stent placement. At first, it was done with plastic stents (PS), but they were substituted by self-expandable metal stents (SEMS) because it has been seen they have a larger patency[1], less need for reintervention, increased survival and cost-effectiveness (5).

[1] Stent patency: time between the stent placement and its obstruction.

There are different types of SEMS (Figure 2):

- **Fully covered (FCSEMS**): covered by a thin plastic which avoids the tumor ingrowth through the stent. They are removable but also more likely to migrate and obstruct the cystic or pancreatic duct.
- **Partially covered (PCSEMS**): proximal and distal flanges are uncovered, being less likely to migrate. They can develop a biofilm deposition in the covered area and epithelial hyperplasia in the uncovered area (10).
- **Uncovered (USEMS):** there is no material covering the stent and for this reason they have higher rates of tumor ingrowth. They are nonremovable and unlikely to migrate (10,11).

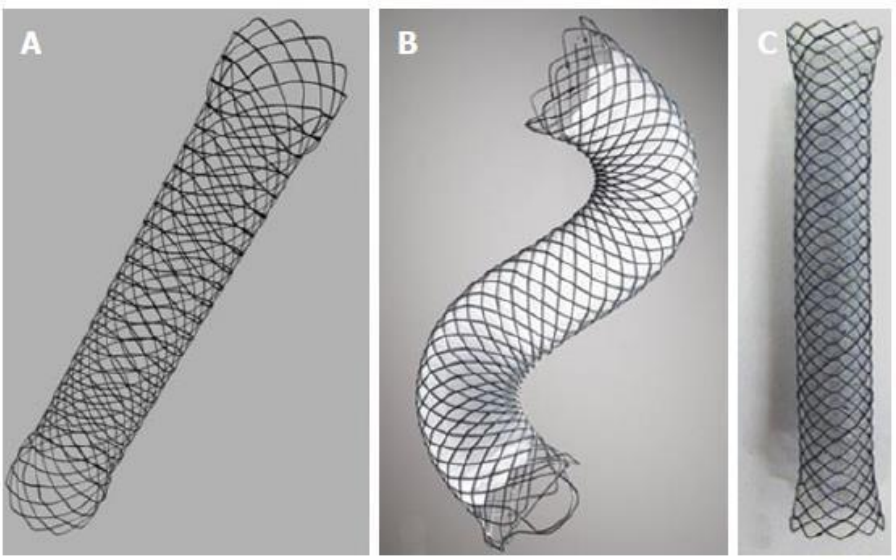

*Figure 2. **Different types of SEMS**: A) uncovered stent B) partial covered stent C) fully covered stent (12)*

SEMS placement can relieve biliary obstruction but not for long. SEMS patency is limited to 6-8 months. Tumor ingrowth, epithelial hyperplasia, biofilm deposition, biliary sludge and granulation tissue cause stent occlusion. Because of that, some authors developed the idea to apply radiofrequency (RFA) before SEMS placement to treat unresectable MBO, aiming to lengthen stent patency (5,10).

3.2.4 MAIN ETIOLOGIES OF MALIGNANT BILIARY OBSTRUCTION

Pancreatic cancer (PC) and cholangiocarcinoma (CCA) are the most frequent causes of MBO.

3.2.4.1 Pancreatic cancer

The incidence of PC in Spain has increased progressively during the last six decades. REDECAN estimates 9252 new cases in 2022 in Spain. In 2020, PC was the third cause of death in Spain, behind lung and colorectal cancer (13). In Girona, according to a study performed in the Medical Oncology Department of *Hospital Universitari Doctor Josep Trueta*, the incidence rate for PC was 11.43 cases per 100.000 inhabitants/year (14). It has a poor prognosis, the five-year survival rate is under 10% (10,13). Its risk increases with age, and rarely occurs under the age of 40. Life expectancy is increasing, and together with the improved diagnosis could be the main reasons for the higher incidence, particularly in high-income countries (15).

Some described risk factors for PC are cigarrete smoking, alcohol, obesity, new-onset diabetes or long-standing diabetes, chronic pancreatitis and family history of PC (15).

90% of PC are ductal adenocarcinomas, representing malignancy of the exocrine pancreas. Neuroendocrine tumors represent a minority of them (16).

Most patients with PC do not present symptoms until the disease is significantly advanced. Symptoms are often nonspecific, and for that reason, at the time of diagnosis PC is locally advanced or has metastatic disease, being 80-85% of them unresectable. The main reasons for its poor prognosis are the vague symptomatology and the proximity of important blood vessels (16). Most common symptoms are weight loss, anorexia, fatigue and abdominal or back pain. About 60-70% of PC are located in the head of the pancreas and therefore, more likely to associate biliary obstructive symptoms as jaundice and pruritus (16). When PC is in the body or tail of the gland, epigastric or back pain is more usual. Less common symptoms are steatorrhea, gastric outlet obstruction or acute pancreatitis (17).

Serum biomarkers can help with the diagnosis. CA 19.9 (carbohydrate antigen 19.9) is a well-known biomarker, increased in advanced PC, but it can also be elevated in non-tumoral biliary obstructions. Other non-specific serum biomarkers such as CEA (carcinoembryonic antigen) and CA125 (carbohydrate antigen 125) can be elevated (18).

Abdominal ultrasound is usually the first technique to be performed when biliary obstructive symptoms are present. It allows you to see duct dilatation and sometimes to identify the tumor. CT with intravenous contrast, using a dual phase pancreatic protocol, is the most recommended technique for the initial diagnosis. It evaluates resectability and staging. USE is used to see the presence of regional lymph nodes, nearby vessels and allows fine needle aspiration for tissue confirmation. If the biliary tract is obstructed, ERCP can be performed in order to decompress it by placing a stent (18).

Pancreatic tumors are classified depending on its resectability in a three-category staging system, which guides treatment decisions. NCCN (national comprehensive cancer network) guidelines describe a tumor as resectable when there are no arterial/venous involvement and no distant spray (ANNEX I) (17).

In resectable tumors, the treatment consists in partial surgical removal of the pancreatic affected region followed by chemotherapy. In borderline tumors, neoadjuvant chemotherapy is administered before the surgery.

Palliative treatment is the only option for unresectable tumors. In this group, the treatment includes adequate pain management, chemotherapy (folfirinox or gemcitabine) and relief of BO with a stent, which reduces the risk of cholangitis and enables the administration of chemotherapy (17,18).

3.2.4.2 Cholangiocarcinoma

CAA is an heterogenous group of tumors arising from the epithelium of the bile ducts. It is the second most frequent type of liver cancer after hepatocellular carcinoma. Its incidence has increased during the last decade and has a remarkable high prevalence in Asia. In Girona, the incidence rate for CCA is about 7,32 cases per 100.000 inhabitants/year (19). CAA typically presents in the seventh decade of life and affects men more frequently (20,21).

They can be classified depending on the site of origin into (Figure 3):

- **Intrahepatic cholangiocarcinoma (iCCA):** arises in the intrahepatic biliary ducts. It represents 10-20% of all CCA (21).
- **Perihilar cholangiocarcinoma (pCCA):** arises in the extrahepatic ducts involving biliary ducts confluence in the hilum. 50-60% of all CCA are perihilar (21).
- **Distal cholangiocarcinoma (dCCA):** arises in the mid or lower half of CBD, frequently in the head of the pancreas. It represents between 20-30% of all CCA. DCCA clinical presentation and management is similar to PC, nevertheless pathophysiology is distinctly different (22).

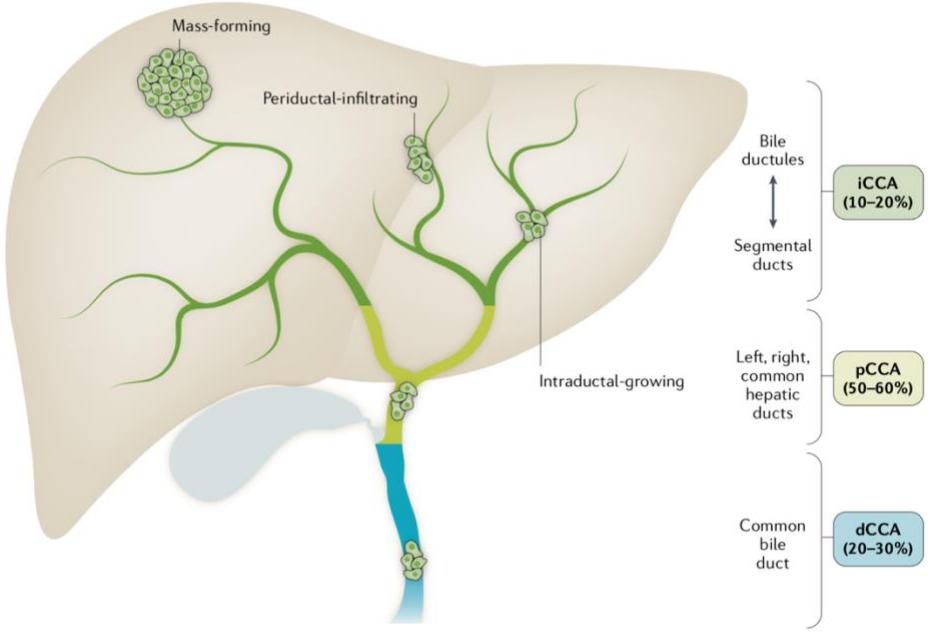

Figure 3. ***Anatomical classification of cholangiocarcinoma*** *(23)*

CCA subtypes have numerous differences in etiology, risk factors, prognosis, and its management. Despite the differences, they generally have a poor prognosis and surgical resection is the best chance for these patients, but most times is not possible because of the late stage at diagnosis. The median overall survival in resectable and unresectable tumors is 51.2 and 11.7 months respectively (23).

Most of the patients diagnosed with CCA do not have identifiable risk factors, but it is known that chronic biliary inflammation can lead to CCA. Main risk factors for CCA are presented in the following table:

Table 2. ***Main risk factors for CCA****. Adapted from (20)*

Intrahepatic CCA (iCCA)	Extrahepatic CCA (pCCA, dCCA)
- *Cirrhosis* - *HBV / HCV* - *Alcohol* - *Chronic pancreatitis* - *Non-alcoholic fatty liver disease (NAFLD)* - *Diabetic and obesity* - *Smoking* - *Chemical exposure (e.g., thorotrast)*	- *Primary sclerosing cholangitis (PSC)* - *Choledochal cysts* - *Cholelithiasis/choledocholithiasis* - *Chronic pancreatitis* - *Diabetes and obesity* - *Smoking* - *Liver fluke infection (Opisthorchis viverrini and Clonorchis sinensis). In southeast of Asia* - *Chemical exposure (e.g.,1,2-dichloropropane)*

ICCA often is an incidental diagnosis. Symptoms tend to be non-specific such as fullness, fatigue, malaise, anorexia and weight loss. Jaundice is not common and if it appears, usually means an advanced disease. PCCA and dCCA typically present with jaundice, pruritus, choluria and acholia. Non-specific symptoms, as in iCCA, are usually present (20,21).

Patients usually have increased liver function tests. In extrahepatic CCA, a cholestatic pattern is typically present. Tumor markers as CA 19-9 can be elevated especially in unresectable patients, but it is not always correlated with CCA (21).

In iCCA, CT or MRI are the first imaging modalities, but imaging is not enough for the diagnosis. Usually, percutaneous image guided biopsy is required for the definitive diagnosis. In pCCA and dCCA, transabdominal echography is the initial technique to assess the biliary tree. CT and MRCP are performed to see the location and extension of the biliary and vascular involvement (staging), and the presence of intrahepatic locoregional or distant metastasis. EUS and ERCP provides a better visualization of the biliary tree, tumor depth and its relation with adjacent vascular structures. Fine needle aspiration biopsies can be performed (21,22).

The following algorithm shows the treatment options depending on the tumor localization and its resectability. Resectability is based on metastatic affection and liver function (Figure 4) (24).

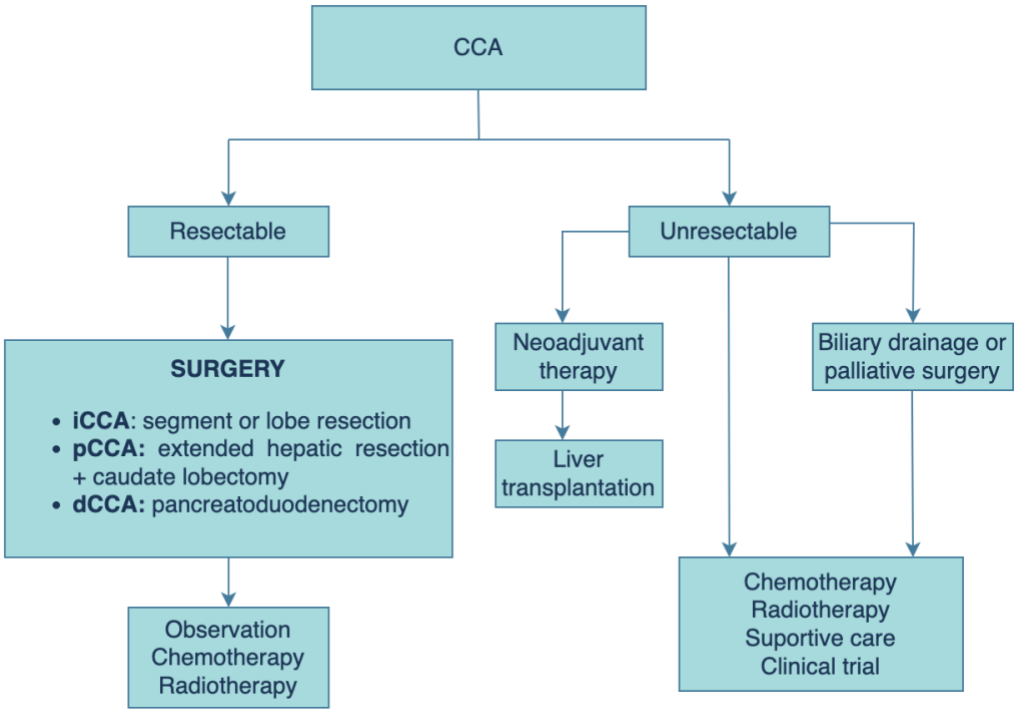

*Figure 4.**Treatment algorithm for cholangiocarcinoma**. Adapted from (24)*

3.3 ENDOSCOPIC RADIOFREQUENCY ABLATION

3.3.1 GENERAL CONCEPTS ABOUT RADIOFREQUENCY

Radiofrequency (RFA) is a local ablation technique. It increases the target tissue temperature to cause irreversible cellular injury. RFA induces cell death via hyperthermic injury, and the result is a coagulative necrosis.

There is a high-frequency alternating current that oscillates between the active and the reference electrodes (grounding path) or between two active electrodes in bipolar systems. This ionic oscillation causes friction and heats the tissue (6).

The target temperature to induce coagulative necrosis is between 60-100ºC. Tissues that are closer to the electrode receive more dose than the cells from the peripheral zone, but they still get into thermal distress. Temperatures higher than 100ºC result in charring, vaporization and carbonization reducing the RFA effectiveness (decreases the electrical conductivity).

Necrotic cells lose their plasma membrane integrity and release intracellular antigens that can be recognized by the host immune system leading to a systemic immune response (6).

There are different ways to perform RFA. It can be done percutaneously by laparotomy, laparoscopy, endoscopy, or endoscopic ultrasound (6).

RFA has numerous indications in gastrointestinal disorders for both benign and malignant lesions. It has been used in many solid organ malignancies, especially in hepatocellular carcinoma and in hepatic metastatic lesions (25). It is also used for the eradication of premalignant lesions such as Barrett's esophagus. Some benign indications are mucosal ablation to control hemorrhage in gastric antral vascular ectasia (GAVE) and chronic radiation proctitis (26).

Over the past ten years two endoluminal biliary catheters have been approved for clinical use, and RFA into the biliary ducts is being done (6). With this procedure it is possible to apply a local treatment to unresectable biliary tumors. This could have an impact on survival in patients with

MBO. Endoluminal biliary RFA is also useful for occluded stents, ampullary adenoma and benign biliary strictures.

3.3.2 ENDOSCOPIC BILIARY RADIOFREQUENCY ABLATION

3.3.2.1 Technique

The endoscopic biliary radiofrequency is performed during the conventional ERCP.

Using a duodenoscopy, we get to the papilla and common bile duct cannulation is performed. Afterwards, contrast is introduced to perform a cholangiography. The contrast allows to determine the dimension of the stricture, its length, diameter and localization. Then, the dimensions of the ablation are determined. Afterwards, a sphincterotomy is performed and the RFA catheter is introduced over a wire to the level of the stricture, under fluoroscopic guidance. The catheter has x-ray visible marks to place it properly. Sometimes, balloon dilatation is required before introducing the RFA catheter. Once the RFA is done, if there are necrotic debris, they can be removed with a balloon sweep (6). Eventually, a metal or plastic stent is placed (Figure 5).

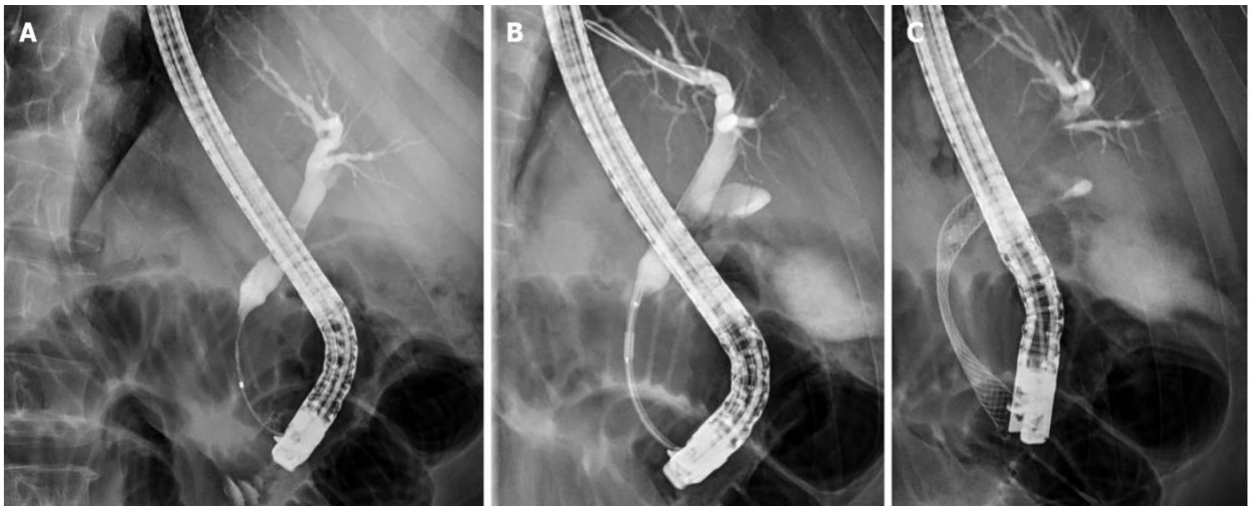

Figure 5. ***Radiofrequency ablation of pancreatic cancer*** *A) Distal common bile stricture B) Radiofrequency ablation of the bile duct stricture C) Self-expandable metal stents drainage post RFA (6)*

3.3.2.2 Radiofrequency ablation devices

During the last 10 years, two endoluminal biliary catheters have become commercially available. The most used is Habib endoHPB™ (hepatico-pancreato-biliary) bipolar radiofrequency catheter (Boston Scientific, Massachusetts, United states). The other one is ELRA (endoluminal radiofrequency ablation, Taewoong medical, South Korea) (6).

- **Habib™ endoHPB bipolar radiofrequency catheter** (Figure 6) (27)

  Is the first RFA catheter indicated in Europe for malignant or benign tissue ablation in the pancreatic and the biliary tract.

  The catheter is passed down the duodenoscope with a working channel and then is introduced over a wire to the level of the stricture (Figure 7). Can be connected to an ERBE electrosurgical generator (surgical technology group, Hampshire, United Kingdom) or RITA-1500X generator (Angiodynamics, Latham, NY, United States) (6).

  RFA is performed using a power of 7W for ampulla and above biliary bifurcation, and 10W below biliary bifurcation, for 90 seconds. After that, the electrode must be kept at the ablation point for 60 seconds so that the probe cools before being moved (25).

Figure 6. ***HabibTM endoHPB bipolar radiofrequency catheter*** *(27)*

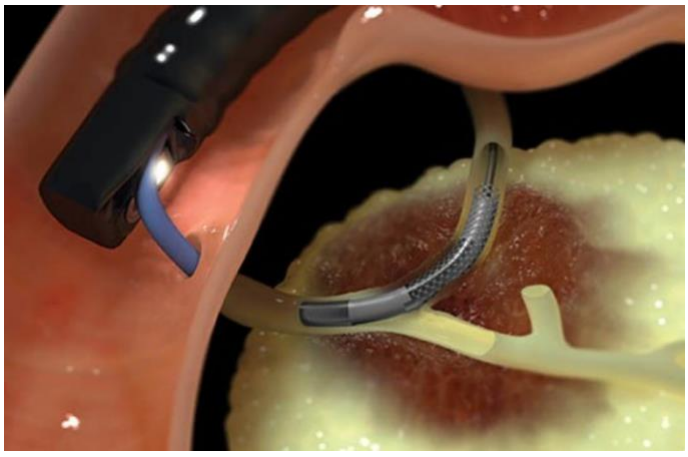

Figure 7. ***Biliary stent placement along with the Habib catheter*** *(27)*

Table 3. ***Habib HPB specifications*** *(27)*

Device specification	Intended benefits
180 cm useable length, 2.7mm diameter	*Enables biliary access through a 3.2mm working channel duodenoscope*
Two 8mm stainless steel ring electrodes separated by 8 mm of free space and a 5mm distal leading tip	*Produces an ablation zone 25mm ± 3mm long by 9mm ± 2 mm wide*
Compatible with commonly available RF generators and endoscopes with a working channel of 3.2 mm or greater	*Does not require the purchase of dedicated capital equipment*
Bipolar RF device	*Use of adapter cable enable bipolar RF ablation and avoids the need for electrode grounding pads.*

Habib™ endoHPB bipolar radiofrequency catheter cannot be used on patients with cardiac pacemakers or other active implants (27).

3.3.2.3 Indications

Several indications of endoscopic biliary radiofrequency have been described (5). Some of them remain uncertain and need more studies to clarify data.

- **Malignant biliary strictures:** the main cause of BS in western countries is the presence of a malignant disease. The most frequent ones are caused by PC and CCA. Other malignant diseases that can cause MBO are gallbladder cancers, malignant hilar lymphadenopathy and hepatocellular carcinoma.

- **Benign biliary strictures:** can be from different etiologies such as postoperative bile duct injury, chronic bile duct inflammation or chronic pancreatitis. These strictures tend to be shorter; some authors say that a different probe with a shorter electrode should be used in order to focus de RF current on the stenosis.

- **Treatment of occluded stents:** RFA probe can be used to ablate tissue in-growth in occluded stents (SEMS) instead of stent-in-stent insertion technique.

- **Ampullary adenomas:** another possible application is the ablation of endobiliary residual tissue after papillectomy. Short duration of RFA (30s) and a lower power (10W) should be used in order to minimize the risk of having pancreatitis.

3.3.2.4 Complications

Most complications are known to be associated with the ERCP technique (26).

- **Complications related to ERCP**:
    - **Acute pancreatitis:**

      Is the most frequent complication after ERCP due to manipulation of the biliary tract. Its incidence goes from 1,6 to 15%. Most of them are mild or moderate. The diagnosis is based on the revised Atlanta international consensus (RAC), defining acute pancreatitis when ≥2 of the following criteria are present: characteristic abdominal pain, amylase or lipase ≥3 times the normal limit, characteristic findings on imaging (28).

    - **Hemorrhage:**

      The rate of post sphincterotomy bleeding after ERCP is about 0.3-2%. Mild hemorrhage is defined by clinical evidence of bleeding or hemoglobin drop <3g/dl, with no need for transfusion. Moderate hemorrhage requires transfusion (<4 units), and severe hemorrhage requires transfusion (>5 units) or surgical/angiographic intervention (28,29).

    - **Cholangitis:**

      Post ERCP cholangitis has an incidence of 0,5 to 3%. Clinical presentation includes fever, jaundice, abdominal pain and in severe cases hypotension and altered mental status. The most common bacteria are gram-negative organisms (28).

- **Perforation:**

  Occurs in <1% of the cases. Can be either bowel wall perforations caused by the scope pass or biliary and pancreatic ducts perforations, caused by guidewires or stents. Bowel perforations are an emergency. It is essential to suspect them if there is a severe abdominal pain, leukocytosis, fever and tachycardia. Surgical consultation is necessary. Guidewire perforations of the bile or pancreatic ducts can be managed endoscopically by placing a stent. (28,29).

- **Complications related to biliary RFA ablation**

There is evidence in literature that endoscopic biliary RFA has an acceptable safety profile and because of it, RFA technique for treating MBO is expanding (26).

Potentially, thermal injury could lead to severe adverse events of adjacent vessels and walls of the bile duct and there is still concern about that. However, to date, most of the studies have not reported thermal injury related complications such as bile duct perforation, gastrointestinal perforation, severe bleeding or liver infarction (30). Exceptionally, haemobilia and liver infarction have been reported in RFA procedure for hilar tumors that are close to the hilar vessels (31).

Abdominal pain seems to be higher in patients who undergo RFA in comparison to those who just have stent placement according to a meta-analysis of mostly observational studies (32).

Theoretically, RFA could predispose stent migration by reopening the malignant stricture, but literature does not report any increased rate of stent migration. More studies are needed to provide more data (26).

To apply biliary RFA, a bipolar catheter is used. Therefore, there is no risk of skin burns as no reference electrode is required.

4 JUSTIFICATION

Pancreatic cancer and cholangiocarcinoma are malignant tumors with an increasing incidence and generally a poor prognosis. They are the main causes of MBO. The only opportunity for long-term survival is a surgical resection with negative margins. However, patients generally remain asymptomatic until the disease is significantly advanced and the only option is a palliative treatment to relieve the biliary obstruction, no local treatment is currently available. Furthermore, only a modest increase in survival has been achieved during the last decades (14).

Nowadays, palliation treatment consists in SEMS placement. After 6-8 months the stent becomes occluded as the tumor continues to grow, leading to obstructive symptomatology. Related complications of stent obstruction as cholangitis have a direct impact on survival. For this reason, some authors developed the idea to treat unresectable MBO with RFA before placing SEMS. Biliary RFA would reduce tumoral burden, lengthen stent patency and increase overall survival as a result (5).

RFA has been used in numerous gastrointestinal disorders with high technical and clinical efficacy. There is evidence in literature about endoscopic RFA having an adequate safety profile (26).

There are few studies saying that intraductal RFA plus stent placement increases stent patency and survival, but most of them come from retrospective series with limited number of patients and often uncontrolled studies. The studies published are highly heterogeneous about etiology, stage of disease and treatment given. Randomized studies with better characterized and stratified populations are needed to accept biliary RFA as a routine clinical practice (6).

There are only a few clinical trials published about intraductal RFA, most of them evaluating its efficacy for hilar cholangiocarcinoma, which has numerous differences with distal cholangiocarcinoma and pancreatic cancer. With our study, we want to focus on unresectable

distal malignant biliary obstructions, mainly produced by pancreatic cancer and distal cholangiocarcinoma. Both malignancies are clinically similar in presentation and management.

The aim of this clinical trial is to evaluate if RFA plus biliary stenting increases survival rate in comparison to stent placement alone. Also stent patency, number of hospitalizations, and quality of life will be assessed.

Patients will be stratified in order to avoid confusing variables such as initial ECOG, presence of metastasis, histological diagnosis (CP/CCA), local lymph nodes, chemotherapy and other covariables. Moreover, they will randomly undergo RFA plus stent or stent alone.

We aim to provide more evidence about the use of RFA in MDBO. If results are favorable, RFA could become a routine clinical practice in the management of unresectable MDBO.

5 HYPOTHESES

5.1 MAIN HYPOTHESIS

Endoscopic biliary radiofrequency ablation combined with stent placement in unresectable distal malignant biliary obstruction increases **survival rate** in comparison to biliary stent placement alone.

5.2 SECONDARY HYPOTHESES

1. The **stent patency** will be higher in patients who receive RFA combined with stent placement in comparison to those who just undergo stent placement.
2. Individuals receiving RFA will have **fewer hospitalizations** due to complications of biliary obstruction in comparison to the non RFA group.
3. Using RFA plus stent placement to treat malignant biliary obstruction supposes a **better quality of life** in comparison to biliary stent placement alone.

6 OBJECTIVES

6.1 MAIN OBJECTIVE

The main objective of this project is to assess whether the application of RFA combined with stent placement in unresectable distal malignant biliary obstruction increases **survival rate** in comparison to stent placement alone.

6.2 SECONDARY OBJECTIVES

1. To evaluate the **stent patency** in both groups and see if there is an increased stent patency in the RFA plus stent group.
2. To assess if the individuals treated with RFA before the stent placement have **less hospitalizations due** to complications of biliary obstruction in comparison to the non RFA group.
3. To assess if using RFA plus stent placement to treat malignant biliary obstructions supposes a **better quality of life** in comparison to biliary stent placement alone.

7 MATERIAL AND METHODS

7.1 STUDY DESIGN

This study will be carried out as a multicentric, randomized, controlled, single blind, interventional clinical trial.

7.2 STUDY SETTING

This protocol is designed to be a multicentric study in which two Catalan hospitals will participate, both part of the national public health system:

- *Hospital Universitari Doctor Josep Trueta (HUJT),* Girona: 800.000 inhabitants of reference.
- *Hospital Universitari Germans Trias i Pujol (HUGTP),* Badalona: 800.000 inhabitants of reference.

The reference center of this clinical trial will be *HUJT.* One researcher will be assigned as the representant and coordinator of *HUGTP* to obtain good communication and coordination between both centers.

7.3 STUDY POPULATION

The study population will include patients with a MDBO caused by pancreatic cancer or distal cholangiocarcinoma, who have *HUJT* and *HUGTP* as a reference center.

There will not be previous data collection, we will include only new diagnosis of unresectable MDBO who have not been treated previously with stent placement. All patients must meet all the inclusion criteria and non-exclusion criteria.

7.3.1 INCLUSION CRITERIA

- Patients aged 18 years or older.
- Pathologically confirmed MBO (pancreatic cancer or distal cholangiocarcinoma).

- Non-resectable disease based on a multidisciplinary team decision (distant metastasis, locally advanced disease, patient related factors) confirmed by CT, MRCP, EUS or surgical.
- Laboratory and clinical signs of biliary obstruction (serum bilirubin level greater than 5 mg/dL, clinical jaundice and/or cholangitis).
- Accepted and signed informed consent (ANNEX III).

7.3.2 EXCLUSION CRITERIA

- Unstable patient to undergo an ERCP procedure.
- Implantable pacemaker, implantable cardioverter/defibrillator, or another active implant.
- Eastern Cooperative Oncology Group (ECOG) performance status ≥3 (ANNEX VII).
- Life expectancy < 3month.
    - Patients presenting encephalopathy, clinically relevant ascitis, spontaneous bacterial peritonitis or renal failure.
    - Presence of main portal vein thrombosis.
    - Active sepsis.
    - Multiple hepatic metastases with significant blockage of liver segment
- Pregnant or lactating women.
- Major surgery within the last 30 days.
- Prior SEMS placement.

7.3.3 WITHDRAWAL CRITERIA

- Patients who request to withdraw (ANNEX IV). Participants can leave the research study at any time by communicating it to the research team.
- Patient lost to follow up**.** Participants will be considered lost to follow up when they do not attend scheduled visits after trying to contact them multiple times.
- Severe complications during the follow up that don’t let the patient continue in the study.
- Dead of the patient not related to clinical tumor progression.

All data obtained during the study before the withdrawal will be used for the results of the clinical trial.

7.4 SAMPLING

7.4.1 SAMPLE SELECTION

A consecutive non-probabilistic sampling method will be carried out. Patients with a recent diagnosis of MDBO who have *HUJT* and *HUGTP* as a reference center and meet inclusion and exclusion criteria will be offered to participate in the study.

7.4.2 SAMPLE SIZE

In a bilateral test, with an alpha equal to 5%, statistical power equal to 80% and assuming that the intervention effectivity goes from moderate to high, 49 individuals will be needed in each group. However, assuming a drop-out rate of 20%, the number of subjects required in each group will be 59.

The intervention effectivity is based on a previous clinical trial that assessed efficacy and safety of RFA for extrahepatic CCA (25).

Computations were carried out with Prof. Dr. Marc Saez' software based on the package 'pwr' of the free statistical environment R (version 4.2.1).

7.4.3 ESTIMATED TIME OF RECRUITMENT

As calculated before, 118 individuals are needed to carry out the clinical trial.

According to a study performed in HUJT medical oncology department which evaluated the incidence and survival rates of PC in Girona, the incidence rate for PC was 11.43 cases per 100.000 inhabitants/year (14). Knowing that HUJT reference population is about 800.000 and that 70-80% of PC are unresectable, most of them presenting with MBO, we assume there are 64 dMBO caused by PC in a year.

Regarding CCA, the incidence rate was 7.38 cases per 1000.000 inhabitants/year (19). Distal CCA represent only 25% of them, for this reason, we assume there are 4 unresectable dMBO caused by CCA in a year.

Summing up, we have 68 cases of dMBO in HUJT reference population. In order achieve the estimated sample size and not prolonging the study too much we will need to perform a multicentric study.

HUGTP has the same reference population as HUJT and, with these data, we can assume a similar incidence of dMBO, achieving the estimated sample size.

Estimated time of recruitment to achieve the sample size (118) will be about 1 year.

7.4.4 RANDOMIZATION

Patients attending with MDBO will be randomized in a 1:1 ratio into the following groups:

- **Intervention group**: these patients will receive RFA before the SEMS placement.
- **Control group:** patients will be treated only with a SEMS.

Randomization will be generated by a software and, in order to maintain confidentiality, an identification number will be automatically assigned to each patient.

7.4.5 MASKING TECHNIQUES

It is not feasible to perform a double blinded trial as the gastroenterologist must know whether to apply RFA or not. For this reason, a single blind trial will be performed. Patients will be blinded since ERCP with stent placement will be the same in both groups, being RFA the only difference with no significant adverse effects described. Therefore, patients will not be able to distinguish which treatment has been applied.

A gastroenterologist who has not been present throughout the ERCP procedure will be responsible for patient follow-up. The independent statistic who will analyze the results will also be blinded.

7.5 VARIABLES AND MEASUREMENTS

7.5.1 INDEPENDENT VARIABLE

The intervention will be RFA application prior to stent placement in unresectable MDBO.

This is a qualitative dichotomous variable. We will consider the patients undergoing RFA plus stent placement and the patients undergoing stent placement alone.

7.5.2 DEPENDENT VARIABLE

- **MAIN OUTCOME**
  - **Survival rate:** defined by the percentage of patients that will be alive at a certain time since the RFA plus stent placement or stent placement alone. Survival rates will be evaluated more than once due to the short life expectancy of these patients: 3 months, 6 months, 12 months, 18 months and 24 months.

- **SECONDARY OUTCOMES**
  - **Stent patency:** number of months from the procedure to stent occlusion estimated by biochemical parameters (total bilirubin, alkaline phosphatase) or ultrasound abdomen. It will be evaluated from stent insertion date. This is a quantitative continuous variable measured in months.

  - **Number of hospitalizations:** number of hospitalizations since the date of the procedure. Any hospital admissions, procedures related to the trial indication or complications of the intervention that the patient undergoes during the follow-up trial period. This is a quantitative discrete variable.

  - **Quality of life**: this is a quantitative discrete variable measured by the EORTC QLQ-C30 questionnaire (ANNEX XII), created by the European organization for research and treatment for cancer (EORTC) to assess the quality of life (QoL) of oncologic patients in clinical trials (33).

This questionnaire contains 30 questions and evaluates quality of life over 10 subscales.

- **Functional subscales:** physical function, role function, cognitive function, and emotional function.
- **Symptom subscales**: pain, fatigue, nausea.
- **Other subscales**: global health status and quality of life.

Scores vary from 1 (not at all) to 4 (very much) with the exception of the last two questions (global health status and quality of life) ranging from 1 (very poor) to 7 (excellent). Scores obtained are standardized, getting a score between 0 and 100, facilitating comparisons. A higher score means a better function and quality of life, however, in symptom subscales, a higher score means more symptom presence.

Disease-specific questionnaires, BIL21 (for CCA) and PAN26 (for PA), will also be provided to assess patient's QoL (ANNEX XIII). These questionnaires will be filled in during the follow-up visits.

7.5.3 COVARIABLES

Other variables may have an effect on the results and for this reason, they will be measured and considered when the results are analyzed. These variables are:

- **Sex:** it is a qualitative nominal dichotomous variable, expressed by male or female. It will be obtained from the patient's ID card or any other official document and registered in the data collection document.
- **Age:** it is a quantitative continuous variable, expressed in years. It will be obtained from the patient's ID card or any other official document and registered in the data collection document.
- **Body mass index (BMI):** it is a quantitative continuous variable categorized in qualitative ordinal. It will be calculated at the beginning of the study. It is expressed as kg/m2 and will be registered using the BMI classification (ANNEX VIII) (34).

- **ECOG performance status scale:** it is a qualitative ordinal variable**.** This scale classifies a patient according to its functional impairment. Patients with an ECOG grade ≥3 will be excluded from the trial, so basically, we will consider grades from 0 to 2 when analyzing the results. It will be calculated at the beginning of the study.
- **Tumor (pancreas/CCA):** it is a qualitative nominal dichotomous variable expressed by PC or CCA. It will be obtained when the histological diagnosis of the tumor has been done.
- **Metastatic lymphadenopathy:** they can contribute to biliary obstruction. It is a qualitative nominal dichotomous variable expressed by yes or no. It will be obtained after having the tumor extension study done.
- **Metastases:** it is a qualitative nominal dichotomous expressed by yes or no. Obtained in the extension study.
- **Length of stricture:** it is a quantitative continuous variable expressed in millimeters. We will know the length of the stricture by imaging CT, MRPC or USE.
- **Chemotherapy:** some patients will receive chemotherapy following the multidisciplinary committee decision. It is a qualitative nominal dichotomous variable expressed by yes/no.
- **Prealbumin at diagnosis:** it is an important parameter to assess nutritional status, disease severity and prognosis. It is a quantitative continuous variable expressed in g/dL.
- **Faecal elastase:** advanced PC is frequently associated with reduced exocrine pancreatic function, worsening the nutritional status, and leading to poor survival (35). Exocrine pancreatic function can be assessed with fecal elastase measurement, measured in µg/g. It is a quantitative continuous variable.
- **Management of stent dysfunction (balloon sweeping/stent over stent/stent replacement):** during the follow-up, the stent might obstruct or migrate requiring drainage. The possible treatment options include balloon sweeping, stent over stent or stent replacement. They will be applied in accordance with the cause of dysfunction. It is a qualitative nominal polytomous variable.

Table 4. ***Covariables***

COVARIABLES	DESCRIPTION	MEASUREMENT	CATEGORIES
Sex	Qualitative nominal dichotomous	ID or any other official document	Male/female
Age	Quantitative continuous	ID or any other official document	
BMI	Quantitative continuous Categorized in qualitative ordinal	Weight and height Categorized	- underweight (<18.5 kg/m^2) - normal weight (18.5-24.9 kg/m^2) - overweight (25-29.9 kg/m^2) - obesity (>=30 kg/m^2).
ECOG	Qualitative ordinal	ECOG performance status scale	- Grade 0 - Grade 1 - Grade 2
Tumor	Qualitative nominal dichotomous	Histological diagnosis	- PC - Distal CCA
Metastatic lymphadenopathy	Qualitative nominal dichotomous	Extension study	Yes/no
MT	Qualitative nominal dichotomous	Extension study	Yes/no
Length of stricture	Quantitative continuous	Imaging (mm)	
Chemotherapy	Qualitative nominal dichotomous	Multidisciplinary committee decision	Yes /no
Prealbumin at diagnosis	Quantitative continuous	Blood test (g/dL)	
Faecal elastase	Quantitative continuous	Stool test (µg/g)	
Stent dysfunction management	Qualitative nominal polytomous	Abdominal ultrasound/USE/CPRE	- Balloon sweeping - Stent over stent - Stent replacement

7.6 INTERVENTION

Patients will be randomized into two groups, in both we will provide biliary drainage, but in the intervention group, RFA will be applied prior to the stent placement. As it is a single blind trial, patients will not be aware of the treatment they have received.

7.6.1 INTERVENTION GROUP: RADIOFREQUENCY ABLATION PLUS SELF-EXPANDABLE METAL STENT

RFA will be performed during the ERCP procedure in an interventional endoscopic room by an experienced gastroenterologist. The informed consent document (ANNEX V) will be handled and explained to the patient before the procedure, not being able to start the ERCP until it is signed.

ASA (American Society of Anesthesiologists) grade of the patient will be calculated (ANNEX IX) (36). In high-risk patients (ASA$\geq$3) the presence of an anesthesiologist in the endoscopy room is recommended to control sedation and any possible complications that may arise.

According to ASGE (American society for gastrointestinal endoscopy), prophylactic broad-spectrum antibiotic will only be administered if the presence of cholangitis or if the drainage obtained is incomplete. Rectal Indomethacin will be administered to all patients to prevent post-ERCP pancreatitis, except for those who are allergic or have non-steroidal anti-inflammatory drugs (NSAIDs) contraindications.

Continuous monitoring of vital signs during all the procedure will be done. Sedation will be achieved by administering propofol according to the needs of the patient.

The patient will be lying on the left side, leaving free the area of the liver and bile ducts, where the fluoroscopic C-arm will be placed.

With a duodenoscope we will get to the papilla and cannulate the common bile duct. Contrast will be administered to perform a cholangiography, allowing us to see the stricture and determine its dimensions.

Afterwards, the RFA catheter (Habib^{TM} endoHPB bipolar radiofrequency catheter) will be passed down the duodenoscope through the working channel and introduced over a wire to the level of the stricture, under fluoroscopic guidance. The RFA catheter will be connected to an ERBE electrosurgical generator. No grounding path is needed because this device works as a bipolar system. A power of 10 W will be used for 90 seconds to provide local tissue ablation. After that, the electrode must be kept at the ablation point for 60 seconds, so that the probe cools before being moved. Once the RFA is done, if there are necrotic debris, they can be removed with a balloon sweep. Eventually, a PCSEMS will be introduced over a wire to the level of the ablation zone. *Detailed in section 3.3.2 Endoscopic biliary radiofrequency.*

After the CPRE procedure, patients will remain under observation to discard immediate complications and to ensure that the effects of sedation disappear progressively.

A detailed report about the ERCP procedure will be made, specifying the findings, material used and any event that may have arisen.

In the event of stent obstruction during the follow-up, drainage will be provided. SEMS occlusions will be treated by balloon sweeping to remove sludge and debris or by placing a second stent within the lumen of the obstructed stent. Stent migration is rare but can occur, needing a new ERCP to replace it.

7.6.2 CONTROL GROUP: SELF-EXPANDABLE METAL STENT ALONE

Patients of the control group will undergo the same procedure with the exception of RFA, which will not be applied.

All the pre and post-ERCP measures performed will be the same as those in the intervention group. The same type of stent used in the intervention group will be placed, a PCSEMS.

7.7 SAFETY

Endoscopic biliary RFA has been previously applied in numerous studies and has demonstrated having an acceptable safety profile, *as it is explained in section 3.3.2.4 - complications.*

Potentially, thermal injury could lead to adverse effects on the surrounding tissues such as bile duct perforation or bleeding, but most of the studies have not reported any of these complications. Exceptionally haemobilia and liver infarction have been described in RFA procedure for hilar tumors. Abdominal pain after the procedure has been reported more frequently when RFA is used than when it is not.

However, the main complications are related to ERCP procedure and not to RFA. The most common ERCP complications are the following *(explained in more detail in section 3.3.2.4 - complications):*

- Acute pancreatitis
- Cholangitis
- Hemorrhage
- Perforation

7.8 DATA COLLECTION

Data information will be collected from the assessments and medical history in different times and registered into a database created for the clinical trial.

- **TRIAL ENTRY**

  Patients with suggestive symptoms of malignant biliary obstruction, mainly jaundice and constitutional syndrome, will be referred to their reference hospitals. There, patients will undergo a detailed clinical history, a physical examination, and the corresponding tests in order to make a diagnosis. Firstly, an abdominal ultrasound will be performed to identify biliary dilatation and if it is possible the cause of it. Afterwards, an MRCP will be carried out to identify the stricture and its anatomical

location, and a CT will provide stage information. USE and fine needle aspiration will allow histological diagnosis. Moreover, a blood test including hepatic and nutritional parameters (albumin and prealbumin), and tumoral markers as CA19-9 must be performed. With all this information the tumor committee will evaluate the case.

If it turns out to be an unresectable distal malignant obstruction caused by CP or CCA and meets the inclusion and none of the exclusion criteria, the patient will be informed about the possibility of entering the clinical trial. The Information Sheet will be given to them having time to read and think about it (ANNEX II) The informed consent must be signed if the patient agrees to participate in the trial (ANNEX III).

All the demographic data, clinical history and MBO characteristics will be registered in the data collection document (ANNEX VI) and registered in the database. International Classification of Diseases for Oncology Third Edition (ICD-O-3) topographic codes will be used when collecting data, C24.0 for extrahepatic CCA and C25 for PC (37). Furthermore, other covariables like BMI, that will be measured by a member of the nursing department, or fecal elastase determination, will also be collected at the beginning of the clinical trial.

All patients will be assigned a numeric code to guarantee confidentiality of the information and to implement the simple randomization.

- **INTERVENTION**
    - <u>Pre intervention assessment:</u>

      Before undergoing ERCP, the gastroenterologist will explain the procedure (without mentioning if RFA will be applied or not, as it is a single masked study) and the patient must sign the ERCP informed consent to proceed. A preanesthetic questionnaire will be completed, and a nurse will record the

overall health status of the patient (ANNEX X). Furthermore, ASA scale will be assessed.

- Intervention: the treatment (*intervention is described in section 7.6*) will not be deferred more than seven days after the trial entry of the patient. The date and time of the intervention, if RFA has been applied or not, cardiorespiratory parameters, dose of propofol used, and any other observations will be registered. If any complication arises during the procedure will be recorded.
- Postintervention assessment:

  Patients will remain under observation. Analgesic will be given if required and any possible complications will be recorded.

- **FOLLOW UP**

The patient will be followed by the research team over a 24-month period. An oncologist will also visit the patient to monitor the progress of the disease. A close follow-up will be done because of the disease's bad prognosis and short life expectancy.

Once a month, a follow-up assessment will be conducted. In this visit a gastroenterologist, who will not be the same as the one who performed the ERCP, will assess various parameters and record them in the follow-up data collection document (ANNEX XI).

- Clinical assessment: to detect possible complications from the procedure, biliary obstruction or tumoral progression. It will be important to ask for the presence of jaundice, abdominal pain, or fever.
- Blood test**:** completed blood count and blood chemistry, including liver function parameters.
- QoL questionnaire: the EORTC QLQ-C30 questionnaire, BIL21 (for CCA) and PAN26 (for PC) will be answered to assess the quality of life of the patients participating in the trial.

Face to face visits and telematic will be interspersed so as not to have the patient come to the hospital every month (Figure 6).

Every three months, an abdominal ultrasound will be conducted to assess the dilatation of the biliary tree, which means that the stent is no longer permeable. It will also be used to evaluate the presence of liver metastasis.

Every 6 months, a CT will be performed.

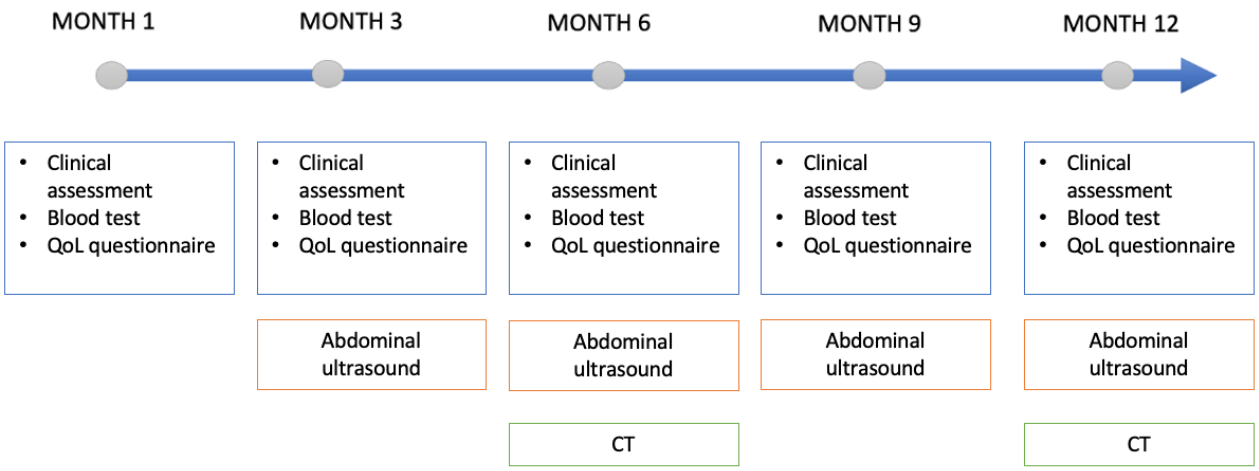

Figure 6. ***Face to face visits during the first follow-up year*** **Can also be applied to the second follow-up year.*

Any complications and hospitalizations that occur during the follow-up period will be collected.

In the event of stent blockage, we will collect the date of the occlusion and provide adequate drainage if considered, *as detailed in 7.6 - intervention*.

Regarding palliative chemotherapy, patients will be treated following the multidisciplinary committee decision. This variable will be considered when analyzing the results.

During the follow-up, death will be a common event as 1-year and 5-year overall survival in these patients is about 21% and 5% respectively (14). Dead date will be registered and used to calculate survival rates.

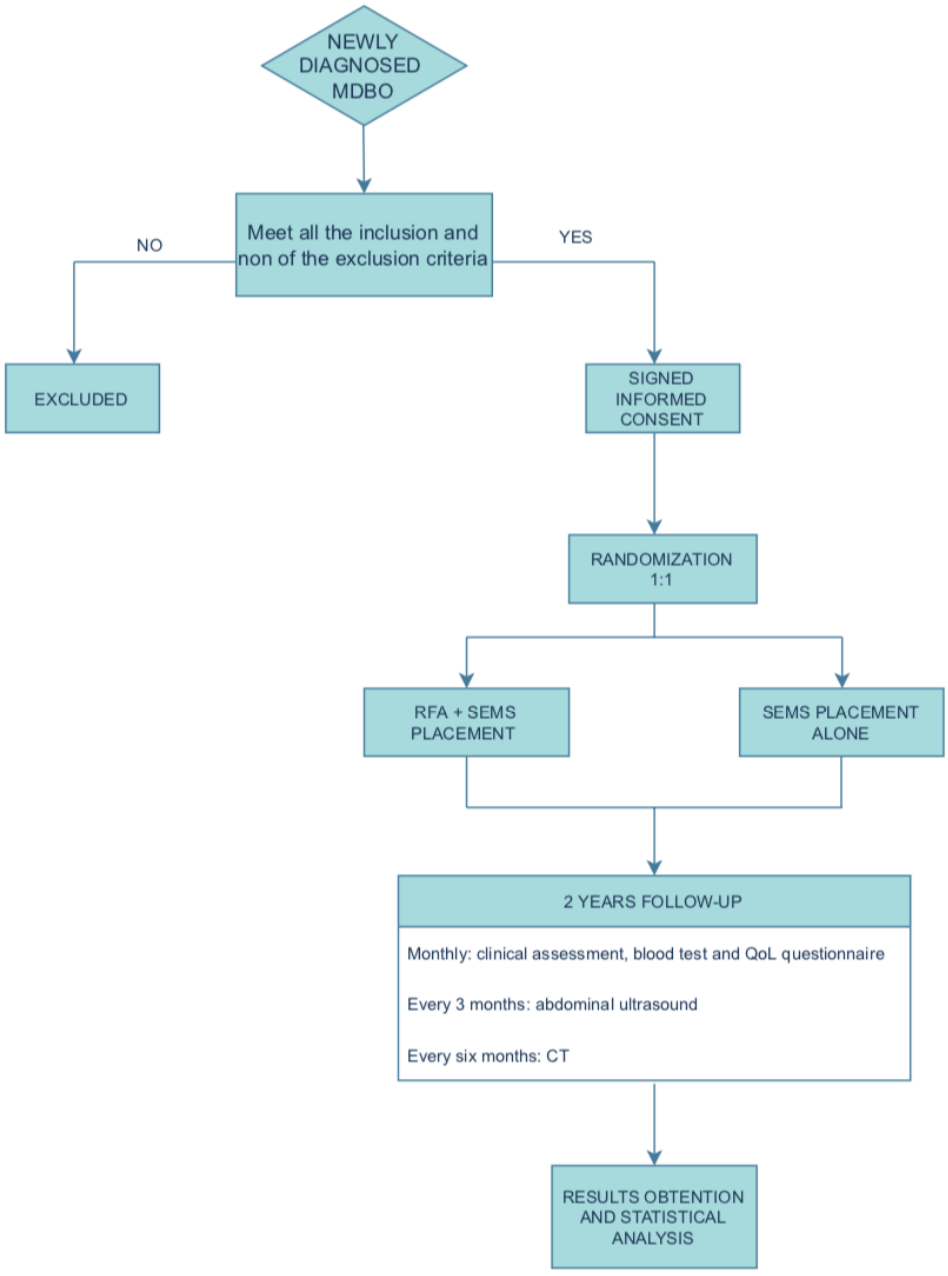

Figure 7. ***Data collection flow diagram***

8 STATISTICAL ANALYSIS

8.1 DESCRIPTIVE ANALYSIS

The main dependent variable, survival rate (qualitative nominal dichotomous), will be summarized by means of percentages. The number of hospitalizations and quality of life scores will be summarized using medians and interquartile range, because both are quantitative discrete variables. The stent patency (quantitative continuous variable) will be estimated by Kaplan-Meier curves.

All these analyses will be stratified by the intervention groups. Additional stratification will be done by the covariables. Quantitative covariables will be categorized in quartiles.

8.2 BIVARIATE INFERENCE

The survival rates between the two groups (RFA and non-RFA groups) will be tested by the chi-square. If in any of the cells of the contingency table the expected number of cases will be lower than 5, the Fisher's exact test will be used. The difference of medians of the number of hospitalizations and quality of life scores between the two groups will be tested by the Mann-Whitney's U. The difference between the Kaplan-Meier curves of both groups will be tested by the log-rank test.

These analyses will also be stratified by the covariables. Quantitative covariables will be categorized in quartiles.

8.3 MULTIVARIATE ANALYSIS

The survival (or not) of a subject according to the intervention will be assessed by logistic regression controlling for the covariables.

The number of hospitalizations and the QoL scores will be adjusted in Poisson regressions controlling for the covariables.

For the assessment of the stent patency in the two groups we will adjust a Cox regression, again, controlling for the covariables.

9 ETHICAL AND LEGAL CONSIDERATIONS

This clinical trial will be conducted according to the medical ethics requirements defined on the World Medical Association Declaration of Helsinki *"Ethical Principles for Medical Research involving Human Subjects" (June 1964, last reviewed in 2013)* and the basic ethical principles of Beauchamp and Childress from 1970 and reviewed in 2009:

- **Principle of autonomy:** as it is stated on the *"Ley 41/2002, de 14 de noviembre, Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica"*, all patients will be provided with an information form (ANNEX II) containing all the clinical trial information. Patients will have time to decide and to pose all the doubts they may have. If they agree to take part in the study, the informed consent (ANNEX III) must be signed.
- **Principle of non-maleficence**: all patients participating in the study will receive biliary decompression by placing a stent, which is nowadays the standard palliative treatment. Regarding RFA, it has been demonstrated to have an adequate safety profile and, for this reason, the principle of non-maleficence is expected to be respected.
- **Principle of beneficence:** this principle is expected to be respected, as we aim to increase survival rates by applying a local treatment to the tumor.
- **Principle of Justice:** all patients meeting the inclusion and none of the exclusion criteria will be offered to participate in the trial, avoiding any discrimination.

This clinical trial will also comply with the regulations established in the *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos* and *"Real Decreto Legislativo 1/2015, del 24 de Julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitario"*. Moreover, this trial will take into consideration Ley *14/2007 de 3 de julio, de investigación biomédica* that regulates biomedical investigation involving humans and the invasive procedures.

Before starting the study, this protocol will be presented to the Clinical Research Ethical Committee (CEIC, Comitè Ètic d'Investigació Clínica) at HUJT for its evaluation and approval. In the case of the CEIC having objections, they will be considered, and modifications will be done to achieve their conditions. Simultaneously, the protocol will be sent to the HUGTP Ethical Committee. Once the protocol has been approved in both CEICs, the study will be carried out.

Regarding the processing of personal data and confidentiality this study will comply the the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and the "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales*".

In order to maintain confidentiality, an identification number will be automatically assigned to each patient at the beginning of the trial. All data will be recorded in a database and its access will only be available to the research team.

Investigators will publish all data and results with transparency, including any unfavorable data or event.

No conflicts of interest are declared by the investigators in this clinical trial.

10 WORKING PLAN AND CHRONOGRAM

10.1 RESEARCH TEAM PERSONNEL

This study will be carried out by a research team composed of the following:

- **Principal investigator:** responsible for the elaboration of the protocol, directing the intervention, conclusions writing and publication of results.
- **Study coordinator:** responsible for the supervision of the study and coordination of the research team.
- **Co-investigator:** in HUGTP will be a co-investigator responsible for coordinating and supervising his team. The co-investigator will meet once every 6 months with the study coordinator and the principal investigator.
- **Data manager:** in charge of applying the randomization, collecting all data and creating a database.
- **Independent Statistician:** responsible for the statistical analysis of the study.
- **Collaborators**: nursing staff, gastroenterology team, oncology team, laboratory team, radiology team and pathologists.

Meetings and training workshops will be done before starting the intervention in order to guarantee the maximum homogeneity during the clinical trial.

10.2 STUDY STAGES

Recruitment of patients will last 12 months, with a follow-up period of 24 months for each patient. This clinical trial is expected to last 4 years and will include 5 main stages detailed below and diagrammed (Table 5):

STAGE 0: **STUDY DESIGN** (September 2022 - November 2022)

- **First meeting** (September 2022):

  The development of this project is accorded by Dr. Carlos Huertas (study coordinator) and Laura Abulí (principal investigator).

- **Bibliographic research** (September 2022 - November 2022):

  Bibliographic research about MDBO, current situation, incidence and management. Current situation about intraductal RFA.

- **Protocol elaboration** (September 2022 - November 2022):

  Objectives, hypotheses, variables and methodology are established.

Study coordinator and principal investigator are the main responsible.

STAGE 1: ETHICAL EVALUATION AND STUDY APPROVAL (November 2022 - January 2023)

- **Presentation to CEIC** (November 2022 - January 2023):

  This protocol will be presented to the Clinical Research Ethical Committee (CEIC, Comitè Ètic d'Investigació Clínica) at HUJT. Simultaneously, the protocol will be sent to the HUGTP Ethical Committee. Any modification will be done in order to achieve CEIC's conditions.

- **Insurance contracting** (November 2022 - January 2023):

  A liability insurance will be contracted.

Study coordinator and principal investigator are the main responsible.

STAGE 2: COORDINATION AND TRAINING (January 2023)

- **First meeting of the research team** (January 2023):

  A first meeting with principal investigator, study coordinator and HUGTP co-investigator will be held to clarify all different phases of the trial and to distribute and organize tasks.

- **Training workshops** (January 2023):

  The gastroenterologists from both centers responsible for performing the RFA will attend a practical workshop at HUJT. The main objective is to ensure homogeneity of the RFA technique in both centers in order to obtain representative results.

  All the team will be responsible.

STAGE 3: RECRUITMENT, INTERVENTION, FOLLOW-UP AND DATA COLLECTION (February 2023- February 2026)

- **Patient recruitment, randomization and intervention** (February 2023 – February 2024): A consecutive non-probabilistic sampling method will be carried out to recruit patients. Patients will only be accepted into the clinical trial if they meet all the inclusion and none of the exclusion criteria, and they must have read and signed the informed consent. Afterwards, they will be randomized into two groups. In the intervention group, RFA will be applied previous to SEMS placement. In the control group SEMS placement will be performed without the previous appliance of RFA.
- **Follow-up and data collection** (February 2023- February 2026):
  Patients will be followed for 24 months after RFA. During the follow-up visits, clinical assessments, blood tests, QoL questionnaires, abdominal ultrasounds and CTs will be performed. Face to face and telematic visits will be interspersed.
  Investigators, co-investigators and study coordinator will be the main responsible. The data manager will register all data into a database.

  During this stage, once every 6 months the study coordinator, the principal investigator and the co-investigator will meet telemetrically in order to evaluate if the protocol is being fulfilled.

STAGE 4: DATA ANALYSIS AND INTERPRETATION (March 2026 -June 2026)

- **Statistical analysis** (March 2026 - April 2026):
  The analysis will be performed once the data has been collected. All information collected about survival, stent patency, hospitalizations and QoL will be analyzed.
  The statistical analysis will be performed by an independent statistician who will be masked for the intervention groups.
- **Statistical interpretation** (May 2026 -June 2026):
  The final statistical analysis will be interpreted by the principal investigator and study coordinator. Afterwards, discussion and conclusion of the study will be elaborated.

<u>STAGE 5:</u> PUBLICATION AND DISSEMINATION OF THE RESEARCH FINDINGS (June 2026- October 2026)

- **Paper preparation:**

  A paper to show the study results and conclusions will be generated.

- **Congress presentation:**

  Attendance to a national and an international congress (*Sociedad Española de Endoscopia Digestiva* and *European Society of Gastrointestinal Endoscopy)* where results will be presented.

- **Publication:**

  Application to different scientific journals to publish the findings.

The principal investigator and study coordinator will be the main responsible.

Table 5. ***Chronogram***

	2022				2023							2024						2025						2026				
	Sep	Oct	Nov	Dec	Jan	Feb	Mar-Apr	May-Jun	Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul-Aug	Sep-Oct
STAGE 0																											
1st meeting																											
Bibliographic research																											
Protocol elaboration																											
STAGE 1																											
CEIC																											
Insurance contracting																											
STAGE 2																											
1st meeting of the research team																											
Training workshop																											
STAGE 3:																											
Patient recruitment and intervention																											
Follow up and data collection																											
STAGE 4																											
Statistical analysis																											
Statistical interpretation and discussion																											
STAGE 5																											
Paper preparation																											
Congress presentation																											
Publication																											

11 BUDGET

PERSONNEL EXPENSES

The budget does not include the cost of the principal investigator, study coordinator, co-investigator and collaborators as they are part of the national health system.

A data manager will be hired to collect data and create a database. The approximate salary will be 35€/hour with a total cost of 1.750 € for 50 hours.

An independent statistician will be hired to perform the statistical analysis of the data collected. The approximate salary will be 40€/hour with a total cost of 1.800 € for 45 hours.

INSURANCE POLICY

If the CEIC considers this study as an invasive procedure, a liability insurance will be required to cover any adverse events that can result from the intervention. The estimated cost will be 40.000 euros.

EXECUTION EXPENSES

Habib™ endoHPB bipolar radiofrequency catheter will be used to apply the radiofrequency ablation of the tumoral obstruction. This catheter is already used in HUJT in other locations, so there will be no problems when ordering them as it is a common procedure in the hospital, same in HUGTP. A RFA catheter will be required for each patient of the trial, resulting in a total of 118 catheters. Every catheter costs 1.200 €.

Patients with MBO will undergo an ERCP and SEMS placement to provide drainage whether they are included in the study or not. For this reason, the costs related to ERCP procedure and SEMS placement will not be included in this study.

As these patients need to be followed by the oncology team and by gastroenterologists periodically, whether they enter into the study or not, most of the follow-up cost regarding blood tests, echography and CT's, will not be included into trial costs. The only cost we need to include is the printing of the QoL questionnaires.

Study information sheet, informed consents, and QoL questionnaires are required to be printed for every participant. The printing cost is 0,05€ per page.

TRAVEL AND COORDINATION EXPENSES

Before the intervention, a practical workshop will be held in *Hospital Universitari Josep Trueta*. The co-investigator, another gastroenterologist and a nurse from *Hospital Universitari Germans Trias i Pujol* will have to go to Girona. We estimate a cost of 80€ for each researcher in terms of travels and diets, a total of 240€.

The meetings between the study coordinator, the principal investigator and the co-investigator held once every six months will be telematic through videoconference, so no travel expenses are expected.

PUBLICATION AND DISSEMINATION EXPENSES

The study coordinator and the principal investigator will attend a national congress (*Sociedad Española de Endoscopia Digestiva*) and an international congress *(European Society of Gastrointestinal Endoscopy - ESGE)* in order to disseminate the results to the scientific community. An admission fee will have to be paid, 500 and 800 euros respectively. Travel costs, accommodation and diets must be added. For this reason, we estimate a total cost of 1.000 € per person for the national congress and 1.800 € for the international congress.

Once the paper is ready, it will be published as a journal article. We will need an English correction (500 €) and preparation of the open access (1.800 €), resulting in a total cost of 2.300 €.

Table 6. ***Budget of the trial***

ITEM	QUANTITY	COST	SUBTOTAL
PERSONNEL COSTS			
Statistician	45 hours	40€/hour	1.800 €
Data manager	50 hours	35€/hour	1.750 €
INSURANCE POLICY			
Trial policy	1	40.000 €	40.000 €
MATERIAL AND EXECUTION			
Habib™ endoHPB catheter	118	1.200€	141.600 €
Printing costs	1.400 pages	0.05€/page	70€
TRAVEL AND COORDINATION			
RFA workshop	3 attendants	80€	240 €
PUBLICATION AND DISSEMINATION			
National congress - *Sociedad Española de Endoscopia Digestiva* **International congress** - *European Society of Gastrointestinal Endoscopy (ESGE)*	1 national congress 1 international congress	National: 1.000€/person International: 1.800€/person	5.600€
Article publication expenses: - English correction - Open access	1	2.300 €	2.300 €
			TOTAL: 193.360 €

12 LIMITATIONS

The following limitations have been detected throughout the design of this protocol and will be considered when analyzing the results:

- This clinical trial will be carried out as a **multicentric study**, including two Catalan hospitals. If the study was conducted just in one hospital, the sample size achieved during a recruitment period of 1 year would not be big enough, and therefore, the trial power would be low. Moreover, if we had enlarged the recruitment period by more than a year, the total duration of the trial would be over four years, not opting for the possibility of financing.

  Multicentric studies in which an operator dependent technique is performed, may lead to inter and intravariability (between hospitals and between gastroenterologists from the same hospital). However, we do not expect to have an important variability as the gastroenterologist will keep the probe inside the stricture during a specific time and power, which will be the same in both hospitals. In addition, a practical workshop will be done to ensure homogeneity.

- A single blind trial will be conducted, as it is impossible to blind the gastroenterologist who will perform the procedure. This can lead to a **detection bias**. To minimize it, the gastroenterologist responsible for the follow-up, will not be the same as the one who performed de ERCP, not knowing whether the patient has received RFA or not. Furthermore, the statistician analyzing the results will also be masked.

- Patients will be followed for 2 years, so there is a considerable risk of **withdrawals**. Patients in this study have low survival rates due to their malignancies, therefore death will be a common cause of trial dropout. For this reason, we estimated a high dropout rate when calculating the sample size, about 20%.

- Regarding **inclusion/ exclusion criteria**, only distal MBO caused by CCA and pancreatic cancer will be selected for the study, so the protocol will not be applicable to proximal causes of MBO, like hilar CCA. Moreover, we have excluded patients who have limited life expectancy due to significant comorbidities. As our main outcome is survival rate, these patients would influence our final survival results.

- **Confounding factors** will be considered when performing the statistical analysis and interpretation of the results.

- The sampling method will be consecutive non-probabilistic, which has an implicit risk of selecting a non-representative sample leading to a **selection bias**. However, it is one of the non-probabilistic methods that induces less biases. To minimize it, randomization will be performed to distribute patients in a 1:1 ratio.

13 IMPACT

Pancreatic cancer and cholangiocarcinoma are the main causes of MBO, with an increasing incidence over the past few decades. Pancreatic cancer is the third leading cause of cancer death in Spain (14). Diagnosis is usually delayed because many patients remain asymptomatic until the disease is significantly advanced. Generally, the possibilities for the tumor being resectable are low, being palliative treatment with stent placement the main option for these patients, no local treatment is currently available.

Intraductal RFA is a local treatment for MBO that aims to reduce the tumoral burden.

Nowadays, survival rates of these patients are significantly low, being at 5 years under 10% (13). If the hypotheses are true, survival rates will increase when RFA is applied. In addition, RFA will enlarge stent patency, reduce complications leading to a decrease in the number of hospitalizations and, therefore, patients will have a better QoL.

As less hospitalizations will be required, we believe RFA will reduce the total costs of these patients.

To date, most of the studies published had limited numbers of patients and were often uncontrolled. In this trial, we have implemented randomization, single masking, and the necessary sample size has been calculated to obtain statistically significant results.

The conclusions will be of great value at the time of introducing or not intraductal RFA as a routine procedure in common clinical practice. Furthermore, results and relevant information obtained could be used in future studies about RFA for MBO.

14 FEASIBILITY

We consider this clinical trial to be feasible taking into account the following points.

This trial will be conducted in two Catalan hospitals, HUJT and HUGTP, both having the necessary resources and suitable facilities to accomplish the study. Advanced endoscopy rooms will be required along with experienced gastroenterologists and nurses. A practical RFA workshop will be carried out to avoid any variability between centers and gastroenterologists.

RFA will be performed during the ERCP procedure just before placing the stent, so no extra interventions will be needed. ERCP with biliary stent placement is the routine procedure to achieve biliary decompression.

RFA catheter is already available in HUJT and HUGTP as it is used for other indications, such as ablation of ampullary tumors or stent ingrowth/overgrowth ablation. We do not expect to have any problems when ordering the necessary catheters to carry out the trial, since it is a common procedure in both hospitals.

A multicentric study will be carried out so as not to enlarge the estimated time of recruitment more than a year. For this reason, the total intervention and follow-up period will be approximately three years, existing the possibility of financing as the price of the study is high.

Coordination of both centers will be achieved by holding meetings once every six months.

It will be necessary to hire a data manager who will collect data and create a database, and a statistic who will analyze the results.

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16 ANNEXES

16.1 ANNEX I: NCCN GUIDELINES. Criteria defining resectability status of pancreatic cancer (17)

Resectability status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis, superior mesenteric artery or common hepatic artery)	No tumor contact with the superior mesenteric vein or portal vein or ≤ 180º contact without vein contour irregularity.
Borderline resectable	Pancreatic head/uncinate process: -Tumor contact with common hepatic artery without extension to celiac axis or hepatic bifurcation. -Tumor contact with the superior mesenteric artery of ≤180º. -Tumor contact with variant arterial anatomy Pancreatic body/tail: -Tumor contact with the celiac axis of ≤180º. -Tumor contact with the celiac axis of >180º without involvement of the aorta and gastroduodenal artery, thereby permitting a modified Appleby procedure.	-Tumor contact with the superior mesenteric vein or portal vein of >180º, contact of < 180º with contour irregularity of the vein or thrombosis of the vein but with suitable proximal and distal vessel target, allowing for safe and complete resection and vein reconstruction. -Tumor contact with the inferior vena cava.
Locally advanced	Head/uncinate process: -Tumor contact with superior mesenteric artery >180º. -Tumor contact with de celiac axis >180º. Pancreatic body/tail: -Tumor contact of >180º with superior mesenteric artery or celiac axis. -Tumor contact with the celiac axis and aortic involvement.	Unreconstuctible superior mesenteric vein/portal vein of tumor involvement or occlusion (can be due to tumor or bland thrombus)

16.2 ANNEX II: INFORMATION FORM

FULL D'INFORMACIÓ PER AL PACIENT SOBRE L'ASSAIG CLÍNIC

Nom de l'estudi: *Ablació per radiofreqüència intraductal en l'obstrucció biliar distal maligne no ressecable.*

Centre assistencial:

Investigador principal: Laura Abulí Suñé

Benvolgut/da,

Ens dirigim a vostè per proposar-li participar, de forma totalment voluntària, en un estudi d'investigació dut a terme als serveis d'Aparell Digestiu de l'Hospital Universitari Doctor Josep Trueta de Girona i l'Hospital Universitari Germans Tries i Pujol de Badalona. Aquest estudi ha sigut aprovat per el Comitè d'Ètica i Investigació clínica dels hospitals corresponents i per l'Agència Espanyola del Medicament i Producte sanitari.

La nostra intenció és que vostè entengui el motiu pel qual es realitza aquest estudi i què significa formar-ne part, per tal de poder decidir si desitja participar-hi. Li preguem que llegeixi aquest document atentament i qualsevol consulta o aclariment no dubti a consultar-nos-ho.

DESCRIPCIÓ I OBJECTIU DE L'ESTUDI

Els tumors de pàncrees i de via biliar en estadis avançats, els quals provoquen una obstrucció de la via biliar, no solen ser operables, de manera que els possibles tractaments van encaminats a millorar la qualitat de vida i allargar la supervivència dels pacients.
En aquests casos, a part de la quimioteràpia, el tractament habitual és la col·locació d'una pròtesi biliar a nivell de l'obstrucció per facilitar el drenatge de la bilis.

L'evidència científica però, defensa que la ablació per radiofreqüència dins el conducte de la bilis, és un nou tractament amb un perfil de seguretat adequat, que permetria reduir la càrrega del tumor, i possiblement augmentar la supervivència dels pacients, tot no ser un tractament amb finalitat curativa.

L'ablació per radiofreqüència es realitza mitjançant un catèter, el qual s'introdueix dins el conducte de la bilis fins al punt on hi ha la obstrucció. Un cop col·locat, es despendrà energia que cremarà part del tumor. Posteriorment, es col·locarà una pròtesis al conducte de la bilis.

En aquest assaig clínic es compararan dos tractaments, per una banda, fer radiofreqüència abans de posar la pròtesi o només posar la pròtesi, tal i com es fa actualment. El principal objectiu és estudiar si la supervivència del grup que rep la radiofreqüència és major en comparació al grup que només se li posarà la pròtesis. A més, s'avaluarà la qualitat de vida i el nombre de hospitalitzacions durant el seguiment, i el temps des de que s'aplica la radiofreqüència fins a que la pròtesis s'obstrueix en els dos grups.

METODOLOGIA I INTERVENCIÓ

En aquest estudi participaran un total de 118 pacients. Cadascun d'ells serà distribuït de manera aleatòria en un dels dos grups:

- **Grup intervenció:** s'aplicarà la radiofreqüència abans de posar la pròtesis. Seguidament a la mateixa intervenció se'ls col·locarà la pròtesis
- **Grup control**: es farà el tractament habitual, només col·locant la pròtesis

Els pacients no sabran a quin grup han sigut assignats per tal que la informació recollida durant el seguiment no es vegi influenciada pel fet d'haver o no rebut la radiofreqüència.

Després de la intervenció, els pacients seran seguits durant un període de 24 mesos. Es farà una visita cada mes, intercalant visites telemàtiques i presencials per a la major comoditat del pacient. Paral·lelament, el pacient serà seguit per oncologia. Tot i participar en l'estudi, podrà rebre quimioteràpia si el comitè multidisciplinari de tumors creu que en el seu cas està indicada.

BENEFICIS I RISCOS DE L'ESTUDI

El principal benefici que s'espera en aquest estudi és augmentar la supervivència i qualitat de vida dels pacients al aplicar la radiofreqüència abans de la col·locació de la pròtesi.

Els riscos de la prova s'esperen que siguin els propis de la CPRE (colangiopancreatografia retròg rada endoscòpica). En els estudis previs que s'han realitzat sobre la radiofreqüència no s'han vist efectes secundaris importants relacionats a aquesta, tret de dolor abdominal en alguns casos. Els principals riscos de la CPRE són la hemorràgia, pancreatitis, colangitis i perforació. Abans de realitzar la prova, els riscos se li explicaran de nou i haurà de donar el seu consentiment per escrit.

ALTERNATIVES AL PROCEDIMENT

Si el pacient no vol participar a l'estudi, se li realitzarà el procediment habitual, col·locació de una pròstesis biliar.

En referència al seguiment, els pacients que decideixin no entrar a l'estudi rebran la mateixa atenció en quant a visites de control, proves d'imatge necessàries i seguiment per oncologia amb tractament amb quimioteràpia si s'escau. Els qüestionaris realitzats durant el seguiment per valorar la qualitat de vida no es realitzaran si es decideix no participar a l'estudi.

CONFIDENCIALITAT

Des de l'inici de l'estudi, totes les dades personals recollides es gestionaran i emmagatzemaran amb total confidencialitat, tenint en compte la legislació actual *Llei Orgànica 3/2018, de 5 de desembre, de Protecció de Dades Personals i Garantia dels drets digitals*" i als reglaments 2016/679 del Parlament i Consell Europeu.

Per garantir la màxima confidencialitat, a l'inici de l'estudi se li assignarà un codi numèric mitjançant el qual s'identificaran les seves dades i informació personal. L'accés a les dades de caràcter personal quedarà restringit a l'equip investigador. No es publicarà informació personal, i les dades sempre seran utilitzades amb finalitats d'investigació.

D'acord a el que s'estableix en la legislació vigent, vostè pot exercir els drets a l'accés rectificació, oposició i cancel·lació de les dades; en cas de desitjar-ho haurà de posar-se en contacte amb l'equip investigador.

DIFUSIÓ DELS RESULTATS

Un cop finalitzat l'estudi, els resultats seran publicats en revistes científiques, sense constar cap dada personal. Els resultats i conclusions de l'estudi permetran expandir el coneixement científic sobre la radiofreqüència biliar, beneficiant a pacients en la mateixa situació. A més, els resultats d'aquest assaig clínic, podran ser utilitzats per a futures investigacions.

PARTICIPACIÓ I COMPENSACIÓ ECONÒMICA

L'equip d'investigació responsable d'aquest assaig clínic no obté cap benefici econòmic.

Com a pacient, la seva participació es totalment voluntària i no obtindrà cap compensació econòmica. En cas de no voler participar a l'estudi, podrà tractar-se amb l'equip d'especialistes sense cap canvi en la seva atenció mèdica. Per participar, haurà de firmar el consentiment informat que li facilitarem conforme ha llegit la fulla d'informació per al pacient i vol participar a l'estudi.

Vostè està en el seu dret de sortir de l'estudi durant el transcurs d'aquest si així ho desitja. Preguem que si és el cas, informi a l'equip investigador.

Abans de decidir si vol formar part de l'estudi, està en el seu dret de demanar segones opinions a altres professionals si ho desitja.

RESPONSABILITAT I ASSEGURANÇA

Aquest assaig clínic té contractada una pòlissa assegurança per tal de poder-se dur a terme, tal i com s'estableix en la legislació. En cas de patir algun prejudici o detriment en la seva salut com a conseqüència de la participació a l'estudi, vostè rebrà la indemnització corresponent.

CONTACTE

En cas de qualsevol dubte o si necessita més informació, pot posar-se en contacte amb l'equip investigador de l'hospital corresponent mitjançant: _____

Gràcies per la seva atenció.

16.3 ANNEX III: INFORMED CONSENT FORM

CONSENTIMENT INFORMAT

Jo, _____, amb document d'identificació personal (DNI/NIE) _____, declaro que:

- He rebut una copia de la fulla de informació per al pacient.
- He llegit i comprès tota la informació facilitada en la fulla de informació per al pacient.
- He pogut platejar qualsevol dubte que m'ha sorgit, i aquest ha sigut resolt adequadament.
- Estic conforme amb la quantitat d'informació facilitada.
- Comprenc que la meva participació en aquest estudi és voluntària i no remunerada.
- Comprenc els beneficis i riscos que comporta participar en aquest assaig clínic.
- Comprenc que les meves dades personals seran confidencials i que puc sol·licitar la retirada i eliminació d'aquestes en qualsevol moment de l'estudi.
- Autoritzo que les meves dades i la meva història clínica pugui ser utilitzada per l'equip investigador per a fins relacionats amb l'estudi.
- He entès que puc revocar el meu consentiment informat sobre la participació a l'estudi, sense necessitat d'especificar el motiu i sense que aquest fet afecti a la meva assistència.

En conseqüència,

- Dono lliurament la meva conformitat a participar en l'estudi *Ablació per radiofreqüència intraductal en l'obstrucció biliar distal maligne no ressecable.*

☐ Sí ☐ No

Signatura del pacient **Signatura de l'investigador**

Data:_____

16.4 ANNEX IV: WITHDRAWN CONSENT

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____ , amb document d'identificació personal (DNI/NIE)_____, revoco el consentiment informat per a la participació en l'assaig clínic: *Ablació per radiofreqüència intraductal en l'obstrucció biliar distal maligne no ressecable.*

Signatura del pacient **Signatura de l'investigador**

Data: _____

16.5 ANNEX V: ERCP INFORMED CONSENT

CONSENTIMENT INFORMAT CPRE

Primer cognom	
Segon cognom	
Nom	
Data naixement	**Sexe**
NHC	**DNI**
CIP	**Episodi origen**

Nom del procediment

Colangiopancreatografia retrògrada endoscòpica (CPRE)

Descripció del procediment

És la introducció d'una sonda òptica flexible per la boca per arribar fins a la desembocadura de la via biliar i/o de pàncrees per a examinar aquests conductes radiològicament.
L'exploració és realitza amb el pacient estirat sobre la taula de radiologia. Se li injecta un fàrmac sedant que li produirà somnolència. Posteriorment, se li introduirà un tub flexible per la boca i s'avançarà cap a l'estómac fins a arribar fins al duodè, on hi ha un petit orifici anomenat papil·la, que és on desemboca el conducte biliar i pancreàtic.
S'introdueix una petita sonda per aquest orifici i s'injecta contrast radiològic per comprovar si hi ha alteracions en els mencionats conductes. Al mateix temps, se'n fan radiografies. Durant l'exploració vostè pot notar molèsties a la gola l'abdomen, així com sensació de nàusea i eructes, que son passatgers i acaben la majoria de les vegades espontàniament. L'exploració dura entre 15 i 60 minuts, depenent del que es trobi durant l'exploració.

Objectiu i beneficis esperables

L'objectiu de l'exploració és arribar al diagnòstic de les malalties de la via biliar i del pàncrees i, si fora necessari realitzar una tractament endoscòpic. Si hi ha estretors o càlculs en els conductes explorats, serà necessari realitzar un tall per ampliar l'orifici de la papil·la amb l'ajuda d'un bisturí elèctric (esfinterotomia). Amb això s'aconsegueix un bon buidament de la bilis i l'extracció dels càlculs, o bé introduir uns petits tubs (pròtesis) en la via biliar i/o pancreàtica per a salvar les estretors. És el millor mètode per a diagnosticar i tractar els càlculs del colèdoc, sobretot si el pacient està intervingut de vesícula. A més, és molt útil en les obstruccions de la via biliar i/o pancreàtica, quan no es preveu fer una intervenció al pacient. Permet obtenir mostres de teixits (biòpsia) per a conèixer la naturalesa benigna o maligna de les lesions trobades. A causa de la dificultat de la tècnica, no sempre s'aconsegueixen els objectius diagnòstics terapèutics desitjats.

Alternatives al procediment

La Colangio per ressonància magnètica (colangio-RMN) és una tècnica radiològica no invasiva que permet veure la via biliar i la via pancreàtica per mitjà de contrast, però amb menor precisió que la CPRE, i a més, té l'inconvenient de no ser terapèutica. Hi ha tècniques radiològiques intervencionistes que poden ser una alternativa, però no permeten la presa de biòpsies i són més dificultoses. Una altra possibilitat és el tractament quirúrgic, amb un nombre més gran de complicacions i mortalitat (morbimortalitat).

Conseqüències previsibles

La realització d'una CPRE, correctament indicada, aconseguirà el diagnòstic de les malalties dels conductes explorats i el tractament endoscòpic adequat.

Conseqüències previsibles de la no realització

Com és lògic, comportarà una inexactitud diagnòstica en molts casos, amb el conseqüent retard en l'aplicació de tractament adequat que, fins i tot, pot ser quirúrgic.

Riscos

Riscos freqüents:

A pesar de l'adequada elecció de la tècnica i de la seva correcta realització, poden presentar-se efectes indesitjables amb freqüència d'un 1-3 %, com perforació, infecció, aspiració, pancreatitis, hemorràgies, etc. Totes aquestes complicacions són rares i excepcionalment requeriran tractaments quirúrgics urgents. Amb més freqüència, es presenten nàusees, dolor abdominal i augment de les amilases, que passen espontàniament o amb tractament mèdic. La sedació pot tenir efectes adversos i la injecció de contrast pot produir reaccions al·lèrgiques.

Riscos pocs freqüents:

Excepcionalment, poden observar-se arítmies o parada cardíaca, depressió o parada respiratòria, accident vascular cerebral agut i subluxació mandibular, que poden ser greus i requerir tractament mèdic o quirúrgic incloent-hi risc mínim de mortalitat del 0'5-1 %, però existeix, i vostè té el dret moral i legal de conèixer-lo. En alguns casos, als mesos o anys de realitzat una esfinterometria, poden aparèixer nous càlculs que poden requerir novament una CPRE terapèutica, o la pròtesi pot obstruir-se o sortir de la seva posició (migració), per la qual cosa s'haurà de repetir la tècnica.

Riscos personals i professionals

A més dels riscos ja descrits, per les meves circumstàncies especials, mèdiques o d'altre tipus, es poden esperar els següents riscos: _____.

Autorització

He rebut la suficient informació verbal i/o escrita sobre la intervenció quirúrgica que em realitzaran. He pogut fer preguntes sobre aquest procediment. He comprès la informació que m'ha estat donada. Per tot això conscientment autoritzo que es porti a terme el procediment. També dono el meu consentiment perquè si en el moment de l'acte quirúrgic sorgeix alguna complicació, l'equip mèdic modifiqui el procediment previst i es pugui resoldre el problema. Així mateix autoritzo una transfusió sanguínia si fos necessària durant la intervenció. Puc canviar de opinió en qualsevol moment i revocar el consentiment abans de la realització del procediment, si així ho crec convenient. Aquest consentiment es formula d'acord amb el que estableix la Llei 16/2010, de 3 de juny, de modificació de la Llei 21/2000 de 29 de desembre, sobre els drets d'informació concernent la salut i l'autonomia del pacient i la documentació clínica, publicada al DOGC núm.5647 del 10 de juny de 2010.

Servei sol·licitant **Professional que informa** **Número d'identificació**

Signatura i DNI del/la pacient o responsable **Data** **Signatura del professional**

☐ Accepta

☐ No accepta

Revocació consentiment informat

Jo, En/Na _____ revoco el consentiment prestat en data_____i declaro per tant que, després de la informació rebuda, no autoritzo a sotmetre'm al procediment de colangiopancreaticografia retrògrada endoscòpica (CPRE).

16.6 ANNEX VI: DATA COLLECTION DOCUMENT/ DOCUMENT RECOLLIDA DE DADES

<table>
<tr><td>CODI PACIENT:_____
DATA DE NAIXEMENT:___ /___ /___
SEXE: Home ☐ Dona ☐
ADREÇA:_____
TELF CONTACTE:_____</td><td>DATA ENTRADA ESTUDI: ___ /___ /___</td></tr>
<tr><td>ANTECEDENTS MÈDICS:

ANTECEDENTS QUIRÚRGICS:</td><td>AL·LÈRGIES:

MEDICACIÓ ACTUAL:</td></tr>
<tr><td>CARACTERÍSTIQUES TUMORALS
Codi topogràfic: C.24 (CCA) ☐ C.25 (CP) ☐
Longitud estenosis: _____ mm
Limfadenopaties metastàtiques: Si ☐ No ☐
MT: Si ☐ No ☐</td><td>PARÀMETRES NUTRICIONALS
Albúmina: _____
Prealbúmina: _____
Elastasa fecal: _____</td></tr>
<tr><td colspan="2">IMC: _____</td></tr>
<tr><td colspan="2">ECOG: 0 1 2 3 4 5</td></tr>
<tr><td colspan="2">ASA: 1 2 3 4 5 6</td></tr>
<tr><td>INTERVENCIÓ
Data intervenció: ___ /___ /___
RFA: si ☐ no ☐
Durada: _____
Constants:
TA: ____ FC:_____FR:____ SAT O2: ____
Propofol: _____</td><td>OBSERVACIONS PROCEDIMENT:</td></tr>
<tr><td>CANDIDAT A QT PAL·LIATIVA: si ☐ no ☐</td><td></td></tr>
</table>

16.7 ANNEX VII: ECOG PERFORMANCE STATUS SCALE (38)

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but a ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

16.8 ANNEX VIII: BODY MASS INDEX (34)

BODY MASS INDEX

Underweight	Below 18.5
Normal weight	18,5-24,9
Overweight	25,0-29,9
Obesity class I	30,0-34,9
Obesity class II	35,0-39,9
Obesity class III	40 and above

16.9 ANNEX IX: ASA PHYSICAL STATUS CLASSIFICATION SYSTEM (36)

ASA PHYSICAL STATUS CLASSIFICATION SYSTEM

ASA I	**A normal healthy patient**
ASA II	**A patient with mild systemic disease:** current smoker, social alcohol drinker, pregnancy, obesity, well-controlled DM/HTN, mild lung disease
ASA III	**A patient with severe systemic disease:** poorly controlled DM/HTN, BMI >40, active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, end stage renal disease undergoing scheduled dialysis, history (>3months) of myocardial infarction, cerebrovascular accident or coronary artery disease/stents.
ASA IV	**A patient with severe systemic disease that is a constant threat to life**: recent myocardial infarction, cerebrovascular accident, coronary artery disease/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, disseminated intravascular coagulopathy, acute respiratory disease or end stage renal disease not undergoing regularly scheduled dialysis
ASA V	**A moribund who is not expected to survive without the operation**: ruptured abdominal/thoracic aneurysm, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	**A declared brain-dead patient**

16.10 ANNEX X: PREANESTHETIC QUESTIONARY

ENQUESTA PREANESTÈSICA

Si us plau, ompli aquest qüestionari, és important per vostè.

Edat:_____ **Alçada:**_____ **Pes**:

Està en dejú de mínim 6 hores: Si ☐ No ☐

1. Si consumeix alcohol regularment indiqui la quantitat:
2. Si és fumador, indiqui el número de cigarretes diari:
3. Indiqui els fàrmacs que pren habitualment (o fotocopia de la recepta electrònica):_____

_____

_____.

4. Si pren algun d'aquests fàrmacs anticoagulants indiqui-ho: Adiro o AAS, Clopidogrel, Sintrom, etc: ____

_____.

5. És vostè al·lèrgic a algun fàrmac/aliment? Si☐ No☐
6. En cas de resposta afirmativa indiqui quin:_____.
7. L'ham operat alguna vegada? Si ☐ No ☐
8. En cas afirmatiu indiqui de què i l'any de la intervenció _____

_____.

9. Va tolerar bé l'anestèsia? Si ☐ No ☐
10. En cas negatiu, quin va ser el motiu? _____

_____.

Si pateix alguna malaltia marqui a continuació:

11. Malalties del cor (infart, debilitat cardíaca, buf al cor, o altres): Si ☐ No ☐
12. La pressió alta: Si ☐ No ☐
13. Malalties del pulmó: pneumònies, tuberculosi, bronquitis, asma: Si ☐ No ☐
14. Dorm amb CPAP Si ☐ No ☐
15. Malalties de fetge: hepatitis, cirrosis: Si ☐ No☐
16. Malalties del ronyó Si ☐ No☐
17. És vostè diabètic/a Si☐ No ☐
18. Neoplàsies o tumors: Si☐ No ☐
19. Si pateix alguna malaltia que no està inclosa al qüestionari, faci-ho a continuació:

16.11 ANNEX XI: FOLLOW-UP DATA COLLECTION DOCUMENT

<table>
<tr><td>CODI PACIENT:_____
DATA DE NAIXEMENT:___ /___ /___
SEXE: Home ☐ Dona ☐
ADREÇA:_____
TELF CONTACTE:_____</td><td>DATA ENTRADA ESTUDI: ___ /___ /___

DATA VISITA SEGUIMENT: ___ /___ /___</td></tr>
<tr><td colspan="2">VALORACIÓ CLÍNICA I EXPLORACIÓ FÍSICA:</td></tr>
<tr><td>RESULTATS ANALÍTICA SANGUÍNIA:</td><td>PUNTUACIÓ QUESTIONARI QUALITAT DE VIDA:</td></tr>
<tr><td>INFORME ECOGRAFIA ABDOMINAL:</td><td>INFORME TC ABDOMINAL:</td></tr>
</table>

16.12 ANNEX XII: EORTC QLQ-C30 QUESTIONNAIRE

AXSANA-Study SPANISH (SPAIN)

Patient-ID: ES - __ __ __ - __ __ __

EORTC QLQ-C30 (versión 3) Date:

Estamos interesados en conocer algunas cosas sobre usted y su salud. Por favor, responda a todas las preguntas personalmente, indicato el número que mejor se aplique a su caso. No hay contestaciones "acertadas" o "desacertadas". La información que nos proporcione será estrictamente confidencial.

		En absoluto	Un poco	Bastante	Mucho
1.	¿Tiene alguna dificultad para hacer actividades que requieran un esfuerzo importante, como llevar una bolsa de compra pesada o una maleta?	1	2	3	4
2.	¿Tiene alguna dificultad para dar un paseo largo?	1	2	3	4
3.	¿Tiene alguna dificultad para dar un paseo corto fuera de casa?	1	2	3	4
4.	¿Tiene que permanecer en la cama o sentado/a en una silla durante el día?	1	2	3	4
5.	¿Necesita ayuda para comer, vestirse, asearse o ir al servicio?	1	2	3	4

Durante la semana pasada:		En absoluto	Un poco	Bastante	Mucho
6.	¿Ha tenido algún impedimento para hacer su trabajo u otras actividades cotidianas?	1	2	3	4
7.	¿Ha tenido algún impedimento para realizar sus aficiones u otras actividades de ocio?	1	2	3	4
8.	¿Tuvo sensación de "falta de aire" o dificultad para respirar?	1	2	3	4
9.	¿Ha tenido dolor?	1	2	3	4
10.	¿Necesitó parar para descansar?	1	2	3	4
11.	¿Ha tenido dificultades para dormir?	1	2	3	4
12.	¿Se ha sentido débil?	1	2	3	4
13.	¿Le ha faltado el apetito?	1	2	3	4
14.	¿Ha tenido náuseas?	1	2	3	4
15.	¿Ha vomitado?	1	2	3	4
16.	¿Ha estado estreñido/a?	1	2	3	4

Por favor, continúe en la página siguiente

SPANISH (SPAIN)

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
17. ¿Ha tenido diarrea?	1	2	3	4
18. ¿Estuvo cansado/a?	1	2	3	4
19. ¿Interfirió algún dolor en sus actividades diarias?	1	2	3	4
20. ¿Ha tenido dificultad en concentrarse en cosas como leer el periódico o ver la televisión?	1	2	3	4
21. ¿Se sintió nervioso/a?	1	2	3	4
22. ¿Se sintió preocupado/a?	1	2	3	4
23. ¿Se sintió irritable?	1	2	3	4
24. ¿Se sintió deprimido/a?	1	2	3	4
25. ¿Ha tenido dificultades para recordar cosas?	1	2	3	4
26. ¿Ha interferido su estado físico o el tratamiento médico en su vida familiar?	1	2	3	4
27. ¿Ha interferido su estado físico o el tratamiento médico en sus actividades sociales?	1	2	3	4
28. ¿Le han causado problemas económicos su estado físico o el tratamiento médico?	1	2	3	4

Por favor en las siguientes preguntas, ponga un círculo en el número del 1 al 7 que mejor se aplique a usted

29. ¿Cómo valoraría su salud general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

30. ¿Cómo valoraría su calidad de vida en general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

16.13 ANNEX XIII: EORTC QLQ-BIL 21 AND QLQ-PAN 26

EORTC QLQ – BIL21

Los pacientes a veces dicen que tienen los siguientes síntomas o problemas. Por favor, indique hasta qué punto ha experimentado usted estos síntomas o problemas durante la semana pasada. Por favor, responda rodeando con un círculo el número que mejor describa su caso.

Durante la semana pasada:		**En absoluto**	**Un poco**	**Bastante**	**Mucho**
31.	¿Ha tenido dificultad al comer?	1	2	3	4
32.	¿Se ha sentido saciado/a al poco tiempo de comenzar a comer?	1	2	3	4
33.	¿Ha tenido problemas con su sentido del gusto?	1	2	3	4
34.	Debido a la enfermedad o tratamiento, ¿estuvo limitado/a en los tipos de comida que usted puede comer?	1	2	3	4
35.	¿Ha tenido la piel o los ojos amarillos (ictericia)?	1	2	3	4
36.	¿Ha tenido picores?	1	2	3	4
37.	¿Le ha preocupado tener la piel amarilla?	1	2	3	4
38.	¿Ha estado menos activo/a de lo que le gustaría?	1	2	3	4
39.	¿Se ha sentido "más lento/a"?	1	2	3	4
40.	¿Ha sentido que le faltaba energía?	1	2	3	4
41.	¿Ha tenido dolor durante la noche?	1	2	3	4
42.	¿Ha tenido dolor en la zona del estómago?	1	2	3	4
43.	¿Ha tenido dolor de espalda?	1	2	3	4
44.	¿Ha tenido sensación de hinchazón en el abdomen?	1	2	3	4
45.	¿Se ha sentido estresado/a?	1	2	3	4
46.	¿Se ha sentido menos capaz de divertirse?	1	2	3	4
47.	¿Le ha preocupado su salud en el futuro?	1	2	3	4
48.	¿Le ha preocupado su familia en el futuro?	1	2	3	4
49.	¿Hasta qué extremo le han aquejado los efectos secundarios del tratamiento?	1	2	3	4
50.	¿Ha tenido dificultades con las bolsas o los tubos de drenaje?	1	2	3	4
51.	¿Le ha preocupado perder peso?	1	2	3	4

EORTC QLQ - PAN26

Los pacientes a veces dicen que tienen los siguientes síntomas o problemas. Por favor, indique hasta qué punto ha experimentado usted estos síntomas o problemas durante la semana pasada. Por favor, responda rodeando con un círculo el número que mejor describa su caso.

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
31. ¿Ha tenido molestias abdominales?	1	2	3	4
32. ¿Ha tenido sensación de hinchazón en el abdomen?	1	2	3	4
33. ¿Ha tenido dolor de espalda?	1	2	3	4
34. ¿Ha tenido dolor durante la noche?	1	2	3	4
35. ¿Ha notado incomodidad en algunas posiciones (por ejemplo, al tumbarse)?	1	2	3	4
36. Debido a la enfermedad o tratamiento ¿Estuvo limitado/a en los tipos de comida que usted puede comer?	1	2	3	4
37. Debido a la enfermedad o tratamiento ¿Estuvo limitado/a en la cantidad de comida que usted puede comer?	1	2	3	4
38. ¿Ha notado cambios en el gusto de comidas o bebidas?	1	2	3	4
39. ¿Ha tenido problemas de indigestión?	1	2	3	4
40. ¿Ha notado molestias por gases (flatulencias)?	1	2	3	4
41. ¿Le ha preocupado perder peso?	1	2	3	4
42. ¿Ha notado debilidad en sus brazos y piernas?	1	2	3	4
43. ¿Se ha notado la boca seca?	1	2	3	4
44. ¿Ha tenido picores?	1	2	3	4
45. ¿Ha tenido la piel o los ojos amarillentos?	1	2	3	4
46. ¿Tiene ruidos abdominales frecuentes?	1	2	3	4
47. ¿Ha tenido urgencia de defecar?	1	2	3	4
48. ¿Se ha sentido menos atractivo físicamente debido a su enfermedad y tratamiento?	1	2	3	4
49. ¿Se ha sentido insatisfecho con su cuerpo?	1	2	3	4
50. ¿Hasta que extremo le han aquejado los efectos secundarios del tratamiento?	1	2	3	4

	En absoluto	Un poco	Bastante	Mucho
51. ¿Le ha preocupado su salud en el futuro?	1	2	3	4
52. ¿Ha estado limitado al planear actividades con antelación (por ejemplo, quedadas con amigos)?	1	2	3	4
53. ¿Ha recibido un soporte adecuado por parte de sus profesionales de la salud?	1	2	3	4
54. ¿La información recibida sobre su patología y tratamiento ha sido adecuada?	1	2	3	4
55. ¿Ha tenido menos interés respecto al sexo?	1	2	3	4
56. ¿Ha sentido menos placer sexual?	1	2	3	4