FINAL DEGREE PROJECT

EVALUATING THE SAFETY OF PERCUTANEOUS PRIMARY AND SECONDARY BILIARY STENTING AS PALLIATIVE TREATMENTS FOR UNRESECTABLE MALIGNANT BILIARY OBSTRUCTIONS

AN OPEN LABEL, RANDOMIZED AND CONTROLLED NON-INFERIORITY SAFETY CLINICAL TRIAL

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"Si quieres ir rápido ve solo, si quieres llegar lejos ve acompañado"

– Proverbio africano

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ABBREVIATIONS

AFP: Alpha-fetoprotein

AJCC: American Joint Committee on Cancer

ALP: Alkaline phosphatase

AMA: Antimitochondrial antibody

AN: Anesthesiologist

ANA: Antinuclear antibody

BMI: Body mass index

BrT: Total serum bilirubin

BTC: Biliary tract cancers

CA 19-9: Carbohydrate antigen 19-9

CBD: Common bile duct

CC: Clinical coordinator

CCA: Cholangiocarcinoma (dCCA - distal, pCCA – perihilar)

CCSPT: Consorci Corporació Sanitària Parc Taulí

CEA: Carcinoembryonic antigen

CEIC: Clinical Research Ethics Committee

CHD: Common hepatic duct

CIRSE: Cardiovascular and Interventional Radiological Society of Europe

CRO: Clinical Research Organization

CT: Computed tomography

EC: English corrector

ECIO: European Conference on Interventional Oncology

ECOG PS: Eastern Cooperative Oncology Group Performance Status

EORTC: European Organization for Research and Treatment of Cancer

ERCP: Endoscopic retrograde cholangiopancreatography

EUS: Endoscopic ultrasonography

GBC: Gallbladder carcinoma

GGT: Gamma-glutamyl transpeptidase

HP: Healthcare professionals

ITT: Intention-to-treat

MBO: Malignant biliary obstructions

MI: Main investigator

MRCP: Magnetic resonance cholangiopancreatography

MRI: Magnetic resonance

NCCN: National Comprehensive Cancer Network

NSAIDs: Non-steroidal anti-inflammatory drugs

PBS: Percutaneous biliary stenting

PDAC: Pancreatic ductal adenocarcinoma

PP: Per-protocol

PS: Primary biliary stenting

PTBD: Percutaneous transhepatic biliary drainage

PTC: Percutaneous transhepatic cholangiography

QoL: Quality of Life

RI: Radiologist

SA: Statistical analyst

SEMS: Self-expandable metal stents

SERAM: Sociedad Española de Radiología Médica

SERVEI: Sociedad Española de Radiología Vascular e Intervencionista

SPSS: Statistical Package for Social Sciences

SS: Secondary biliary stenting

UMBO: Unresectable malignant biliary obstruction

US: Ultrasound

WHO: World Health Association

WMA: World Medical Association

ABSTRACT

Background: Malignant biliary obstructions (MBO) involve different biliopancreatic and metastatic neoplasms that show-up with late or unspecific symptoms, leading to a differed diagnosis and dismal prognosis. These patients present debilitating symptoms and complications, related to hyperbilirubinemia, which is also a criterion to contraindicate chemotherapy. Percutaneous biliary stenting (PBS), which can be done as primary stenting (PS) or secondary stenting (SS), has demonstrated to improve clinical outcomes and patient's quality of life (QoL). Even though there is some evidence positioning PS as a safer technique than SS, with equivalent efficacy, current clinical practice is still based on SS.

Objectives: The purpose of this study is to evaluate and compare the occurrence and severity of complications, technical and clinical success, total time of hospitalization, and QoL in patients with unresectable MBO undergoing PS or SS as palliative treatments.

Design: This study is designed as a single-institution, prospective, open-label, randomized and controlled non-inferiority safety clinical trial, developed from November 2022 to August 2027 at the Interventional Radiology Department of *Consorci Corporació Sanitària Parc Taulí* (CCSPT).

Methods: This clinical trial will enroll 236 patients with unresectable MBO, when endoscopic biliary stenting is not feasible or fails, who will be randomly allocated into PS and SS (ratio 1:1). Technical success will be evaluated during the intervention; clinical success and QoL will be assessed at 3 or 6 weeks after the procedure; occurrence of complications (main outcome), severity of complications, and total time of related hospitalization, will be assessed within the different steps of the procedure and during 30 days after its finalization. Additionally, we will perform an interim analysis to determine the safety of both interventions, and promptly stop the study if futility or extreme beneficence/maleficence is found in any group.

Keywords: malignant biliary obstructions, jaundice, percutaneous biliary stenting, primary stenting, secondary stenting, complications, severity of complications, technical success, types of stents, stent patency, adequate bilirubin decline.

1. INTRODUCTION

1.1. ANATOMY OF THE BILIARY SYSTEM

CLASSIC BILIARY ANATOMY

The *Coinaud* classification (**Figure 1**) is the most common used system to describe hepatic anatomy, in which the liver is constituted by eight hepatic independent functional units named segments, which are distributed into the right hepatic lobe (segments V-VIII), left hepatic lobe (segments II-IV), and caudate lobe (segment I) (1,2). Intrahepatic ducts follow portal vein and hepatic artery, originating the Glisson or portal triad, which combined with the hepatic veins, delimit these segments in an horizontal plane (superior/inferior) and a coronal plane (anterior/posterior), respectively (2).

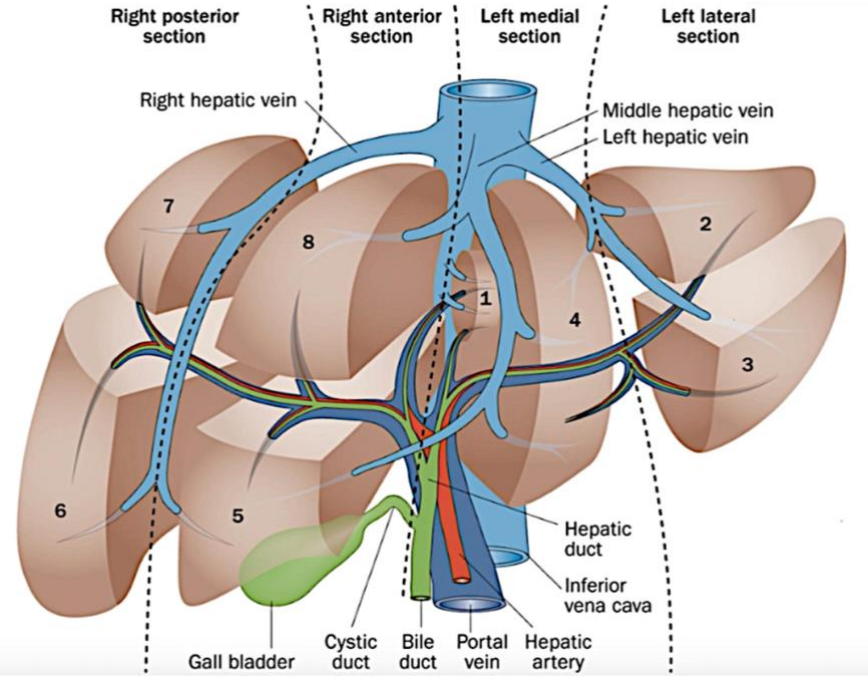


***Figure 1**: Couinaud's segmental anatomy of the liver. Extracted from (3).*

Commonly, the right and left hepatic ducts emerge from the liver and converge in a "Y" shape to form the common hepatic duct (CHD), near the liver hilum (4). The right hepatic duct is composed by the right posterior duct, which has a more horizontal course and drains VI and VII hepatic segments; and the right anterior duct, which has a more vertical course and drains V and VIII hepatic segments (2,5). The left hepatic duct is formed by segment II, III, and IV, and arises from the umbilical fissure along the inferior border of segment IV (2,6).

The CHD runs 3-4cm and meets the cystic duct from the gallbladder, composing the common bile duct (CBD), which measures between 7 and 11cm in length, and has an internal diameter of 8mm at physiologic pressures (**Figure 2**) (4,7). The CBD descends the hepatoduodenal ligament, anterior to the portal vein and lateral to hepatic artery, courses posteriorly, behind the head of the pancreas and the duodenum, and enters the second portion of the duodenum either alone (25% of cases) or after joining the Wirsung duct (main pancreatic duct), finally forming the ampulla of Vater (75% of cases) (2,7).

There are circular and spiral fibers of smooth muscle surrounding the distal ends of CBD (choledochal sphincter), main pancreatic duct (pancreatic sphincter) and hepatopancreatic ampulla (common intraduodenal sphincter), all together constituting the sphincter of Oddi complex (**Figure 2**) (2,4). This complex has two main aims, the first one is to allow the bile storage in the gallbladder, and the second one is to prevent reflux of enteric content and bacteria into the biliopancreatic tract (8).

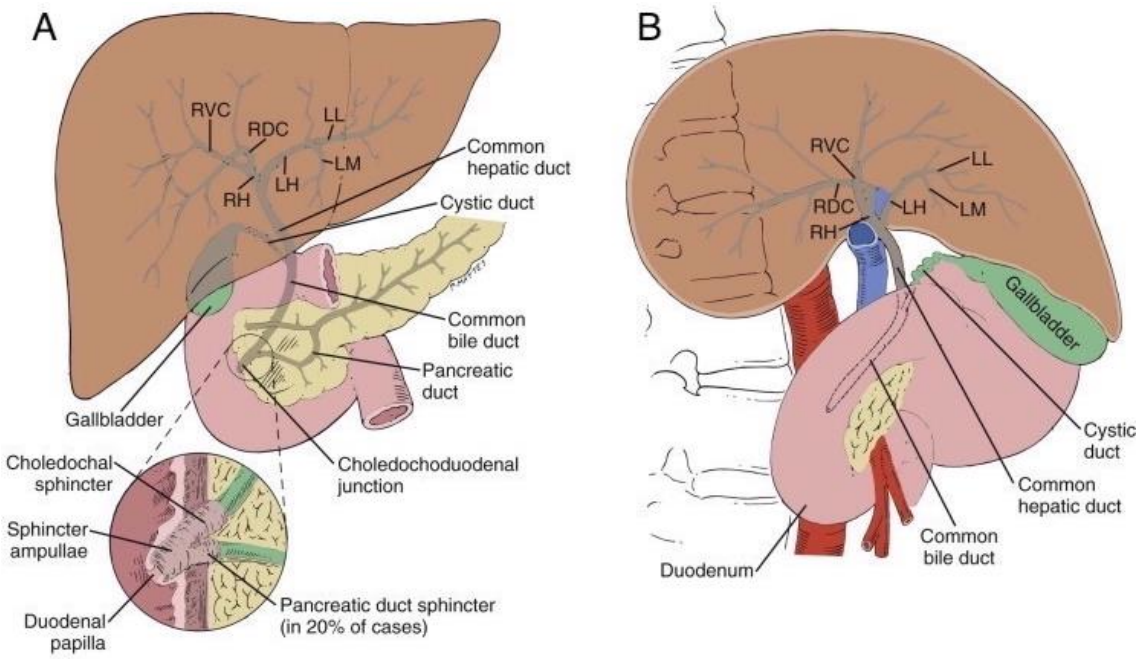


***Figure 2**: Classic biliary anatomy in anteroposterior (A) and lateral (B) view. Extracted from (9). Abbreviations: **LH** – Left hepatic duct, **LM** – Left medial duct, **LL** – Left lateral duct, **RH** – Right hepatic duct, **RDC** – Right posterior duct, **RVC** – Right anterior duct.*

ANATOMICAL VARIANTS OF EXTRAHEPATIC BILIARY TREE

It is estimated that 40% of the population presents bile duct variations, which are important to consider when intervening the biliary system in order to ensure the safety and efficacy of procedures (2). Usually, these variations are evaluated under magnetic resonance cholangiopancreatography (MRCP), since it is a non-invasive, safe and accurate technique (10).

The main variations of the biliary tree involve bifurcation level variants (see *annex 1*), that according to "Huang et al., 1996", depend either on right posterior duct insertion (right hepatic duct variants) and IV hepatic segment insertion (left hepatic duct variants) (11). Less commonly, anatomic variations can affect the cystic duct insertion (see *annex 1*), which in 90% of cases measures 2-4cm in length and presents a tortuous course before unifying laterally to the CHD to form the CBD (2).

1.2. PHYSIOLOGY OF THE BILIARY SYSTEM

BILE COMPOSITION

Bile is mainly composed by bile acids (80%), lecithin and phospholipids (16%), non-esterified cholesterol (4%), conjugated bilirubin, proteins (albumin and immunoglobulin A), hormone and drug metabolites, and mucus (8).

Primary bile acids (cholic and chenodeoxycholic), the main constituent of bile, are synthetized by cholesterol, which is combined with glycine or taurine. Their main functions are dissolving cholesterol in bile, and emulsification of fat and liposoluble vitamins (A, D, E, K) into micelles to allow their absorption in the digestive tract (12).

Indirect bilirubin is a catabolic metabolite proceeding from the heme group of the hemoglobin. It is conjugated inside the hepatocytes and excreted into the duodenum, where enteric microbiota transforms 80-90% of it into urobilinogen and stercobilinogen, products eliminated by feces. The resting 10-20% is reabsorbed at ileum by enterohepatic circulation, where it is newly excreted on bile or filtrated by the kidney (11,12).

BILIAR EXCRETION

Bile is continuously produced by the hepatocytes in the liver (500-600 ml/day) and flows through the right and left bile ducts reaching the CHD and CBD. As the bile duct sphincter is closed, bile cannot reach the duodenum and flows back into the cystic duct, and it is stored in the gallbladder (4). There, bile can be concentrated up to 15g/100ml by absorption of water and electrolytes, which pass into mucosa's intercellular space (8). When food reaches the duodenum, especially when it is lipid-rich, the epithelium secretes cholecystokinin, a peptide hormone that stimulates the contraction of the gallbladder and Oddi sphincter relaxation, allowing bile pass into the duodenum (4,8).

Approximately, 95% of bile acids (mainly unconjugated ones) are reabsorbed in small bowel by passive and active diffusion. Then, they reach portal blood and travel to the liver, where they can be re-conjugated by hepatocytes, which only need to produce the 5% loss. This process is known as enterohepatic circulation (8,12).

1.3. MALIGNANT BILIARY OBSTRUCTIONS

1.3.1. CONCEPT AND MAIN ETHIOLOGIES

Biliary obstruction is an impairment of bile flow from liver to the duodenum, caused either by malign or benign etiologies, producing significant morbidity and mortality (14).

Malignant biliary obstructions (MBO) are caused due to tumor infiltration, extrinsic compression, and desmoplastic or inflammatory responses to tumors (15). Leading etiologies behind them are cholangiocarcinoma and head pancreatic adenocarcinoma. Less frequent causes to consider are gallbladder carcinoma, ampulloma, hepatocellular carcinoma, lymphoma, and metastasis to regional solid organs or lymph nodes (16).

Biliary tract cancer

Biliary tract cancers (BTC) are a group of invasive tumors, commonly adenocarcinomas, arising from the biliary epithelium, which include gallbladder carcinomas (GBC), intrahepatic or extrahepatic cholangiocarcinomas (CCA), and ampulla of Vater carcinomas (ampulloma) (17). Even though ampullomas can be classified as BTC, they have a different clinical course and management, also being their histologically pattern as pancreato-biliary or intestinal (18).

Epidemiology and risk factors

BTC total incidence is less than 1% of all human cancers, and in Spain the incidence was estimated to be 6.1 cases / 100.000 habitants during 2022 (19). The most frequent subtype is GBC, which is twice more typical than CCA, while ampulloma is the less prevalent. It is important to consider that these incidence rates vary on sex, age, and ethnicity. For instance, both GBC and CCA are more frequent in old patients; however, while GBC is more associated to women, CCA is more related to men (17). Besides, risk factors differ within GBC and CCA (**Table 1**) (17,20).

***Table 1**: Main risk factors related to biliary tract carcinomas (self-made table). Information extracted from (17,20)*

Gallbladder carcinoma	Cholangiocarcinoma
Personal or familiar history of gallstones	Liver infections (hepatitis B or C, fluke infestation)
Multiple pregnancies	Cirrhosis
Low physical activity	Primary sclerosing cholangitis
Chronic infection for Salmonella (Salmonella typhi and parathyphi)	Hepatolithiasis
Helicobacter isolation (H. bilis and pylori)	Congenital liver polycystic disease
	Biliary malformations
	Obesity, diabetes, smoking, thorotrast contrast

Cholangiocarcinoma classification

As seen previously, CCA can be categorized as intrahepatic or extrahepatic.

Intrahepatic cholangiocarcinomas, which represent 30% of CCA, are originated peripherally to second-order bile ducts within the liver (17). They behave as primary liver cancers, accounting for 10-15% of its tumors, and being the second most common neoplasm in this group, after hepatocarcinoma (18).

Extrahepatic cholangiocarcinomas include perihilar tumors (pCCA), also known as Klatskin tumors, which account for 50% of CCA; and distal neoplasms (dCCA), which constitute the 20% of CCA (17). The cystic duct insertion anatomically delimits pCCA (involving the CHD and its bifurcation into right and left ducts, above the cystic duct) and dCCA (affecting the CBD, below the cystic duct) (20,21). Additionally, pCCA can be classified according to its longitudinal spread, using the Bismuth-Corlette classification (**Table 2**, **Figure 3**) (20).

***Table 2**: Bismuth-Corlette classification system. Adapted from (20).*

Type I	Tumor limited to CHD, below the confluence of left and right hepatic ducts
Type II	Tumor reaching the confluence but not involving right or left hepatic ducts
Type III	Tumor occluding CHD with either right (IIIA) or left (IIIB) hepatic duct
Type IV	Tumor involving CHD and both right and left hepatic ducts, multicentric tumor, or bilateral intrahepatic segmental affectation

*Abbreviations: **CHD** – common hepatic duct*

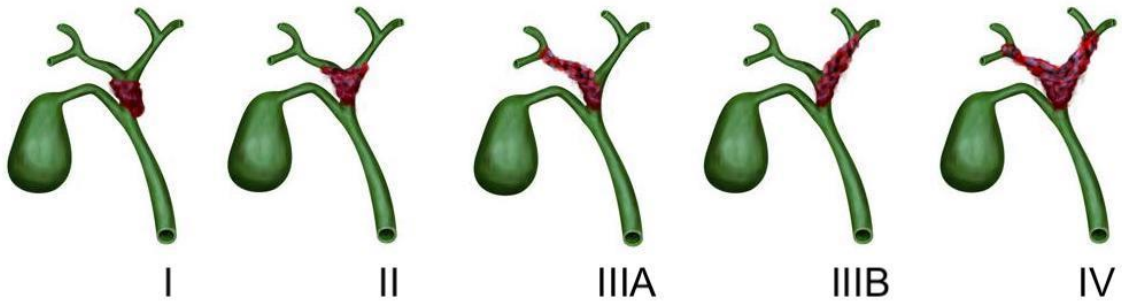


***Figure 3**: Bismuth-Corlette classification. Adapted from (22). The brown color simulates the tumor expansion.*

Pancreatic cancer

Epidemiology and risk factors

Pancreatic ductal adenocarcinoma (PDAC), which represents more than 90% of pancreatic cancers, is the third cause of death by cancer in Europe (17,23). In Spain the incidence was estimated to be 19.5 cases /100.000 habitants in 2022, which is increasing over the years (19).

The main risk factors involved in PDAC are advanced age, smoking, alcohol, overweight, late onset diabetes mellitus, and chronic pancreatitis. It is important to bear in mind that 10% of the cases are familiar cancers, considered when there are two or more first grade family members affected by PDAC, mainly involving BRCA1, BRCA2, ATM, PALB2, MLH1, MSH2, MSH6, PMS2, CDKN2A and P53 mutations (17,23).

Metastatic disease from other primaries

Epidemiology and etiopathogenesis

Metastases from distant primary non-hepato-pancreato-biliary cancers are less frequent causes of MBO (up to 14%). The most common primary tumors include renal cancer, lung cancer, gastric cancer, and colorectal cancer (**Table 3**). They can affect the biliary drainage by direct invasion, pancreatic or biliary metastases, hilar lymph node metastasis, liver metastasis, and peritoneal carcinomatosis (24).

***Table 3**: Main metastatic causes of biliary obstruction. Adapted from (24)*

Primary tumor	Main characteristics	Major causes of obstruction
Renal cell carcinoma	Most pancreatic metastases resectable with good prognosis	Pancreatic metastasis (biliary obstruction rare)
Lung cancer	Most reported in small cell neoplasms	Pancreatic metastases
Gastric cancer	Normally associates gastric outlet obstruction, requiring double stenting	Lymph nodes, liver metastases, direct invasion
Colorectal cancer	Most common in left sided tumors and young patients; jaundice in 10% of cases, intraductal growth can mimic biliary cancer	Liver metastasis (25-30% of patients), lymph nodes

1.3.2. DIAGNOSIS

Clinical manifestations

MBO usually presents with cholestatic symptoms, due to direct hyperbilirubinemia, which mainly involves painless jaundice (yellow coloration of skin and mucosa), pruritus, choluria (abnormal darkness of urine due to excess urobilinogen), and hypocholia (pale feces due to lack of stercobilin). Less commonly it shows up with cholangitis, expressed with fever and leukocytosis, anorexia and weight loss, nausea, and vomiting (12,16).

Initial assessment

It is recommended to start with a blood test to evaluate liver and renal function, coagulation status, viral hepatitis serology, and autoimmune liver markers, involving AMA (antimitochondrial antibody) and ANA (antinuclear antibody). Normally, increased liver parameters include alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) and total bilirubin (BrT); occasionally transaminases can be slightly increased.

Tumoral markers, involving carbohydrate antigen (CA19-9), carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) are more useful for surveillance (14,25).

The initial radiological test to confirm biliary obstructions should be abdominal ultrasound (US) with doppler, which is a non-invasive and available technique that can demonstrate biliary dilation, presence of gallstones, and assess vessel patency (14).

Then, a cross-sectional imaging should be performed, to stablish a benign or malign underlying cause, guide tissue sampling, and determine the local extension in malign etiologies. The most common used technique is computed tomography (CT), which can be complemented by MRCP in case of doubts (14,16).

The MRCP is the Gold Standard technique to assess biliary tract, since it is non-invasive, it has high rates of accuracy discerning on the subjacent cause, it is useful to stablish biliary tree anatomy with its variations, and it evaluates the presence of satellite and distant lesions in the liver (16,18). Usually, benign strictures show smooth margins, symmetric biliary dilation, and narrow short segments; while malignant strictures have irregular margins, asymmetric dilation of biliary radicals, and affect long segments, because of their infiltrative growth pattern (26).

Pathological diagnosis

The next step is to obtain tissue sampling under guidance in order to confirm the diagnosis of an underlying malignant cause, and course a molecular profiling, useful to select targeted therapies during patient's management (16,17).

The sampling method differs on tumor location and size. While core biopsies using US, CT, or endoscopic ultrasound (EUS) guidance are preferred in large masses; intraductal lesions are best assessed by using brush cytology, forceps biopsy, or core biopsy under endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) (14,16).

Patients with delimited tumors who are suspected to be eligible for curative resection, will undergo surgery, directly analyzing the anatomical piece, avoiding any transperitoneal biopsy to eliminate the risk of tumor seeding (18).

1.3.3. ONCOLOGIC STAGING

The staging in MBO is based on the 7th edition of American Joint Committee on Cancer (AJCC), which determines the prognosis of the patient and best treatment option, according to local and distal disease, assessed under cross-sectional imaging (16,27). Besides, the eastern cooperative oncology group performance status (ECOG PS) is also important to assess patient's condition and their ability to tolerate therapies, specifically for chemotherapy schemes and surgery (**Table 4**) (28).

***Table 4**: Eastern Cooperative Oncologic Group Performance Status. Extracted from (28).*

Grade	Performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, 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 out any selfcare; totally confined to bed or chair
5	Dead

1.3.4. DIFFERENTIAL DIAGNOSIS

The main differential diagnosis for MBO are benign bile duct strictures and obstructions, which involve several pathologies related to iatrogenic, inflammatory, ischemic, infectious and autoimmune processes (**Table 5**) (14,29).

***Table 5**: Etiologies causing benign biliary obstructions and strictures. Adapted from (30).*

Most common causes	Less common causes
Choledocholithiasis and acute cholecystitis	Bile duct ischemia and vasculitis
Pancreatitis (acute or chronic)	Radiotherapy or radiofrequency ablation
Post-hepatobiliary surgery (cholecystectomy, liver transplantation, bilioenteric anastomosis)	Chemotherapeutic agents
	Portal biliopathy or trauma
Endoscopic post-sphincterotomy	Mirizzi syndrome
Sphincter of Oddi dysfunction	Tuberculosis and parasite infestation
Primary sclerosing cholangitis	HIV cholangiopathy
IgG4 cholangiopathy	Recurrent pyogenic cholangitis
	Choledochal cysts

*Abbreviations: **IgG4** – immunoglobulin G4, **HIV** – human immunodeficiency virus.*

1.3.5. MANAGEMENT

Resectable disease

Even though curative resection is the main goal of diagnosis, it is rarely indicated because these neoplasms remain asymptomatic or show unspecific symptoms during early-stage disease. Actually, less than 40% of BTC and 20% of PADC are localized disease (AJCC stage I-II) and have the opportunity to undergo surgical resection (16,17).

It is difficult to define exact criteria for resectability in CCA, but the main factors to consider should be the patient's clinical condition, tumor biology, technical experience of the surgeon, local involvement of major vessels and bile ducts (unresectable if portal vein, hepatic artery or second order biliary ducts are involved), and future liver remnant, which should be at least of 30% in all cases (31). In contrast, PDAC has an exhaustive definition of criteria determining its resectability/unresectability according to National Comprehensive Cancer Network (NCCN) guidelines (*see annex 2*).

Additionally, in PADC the resection should be performed in specialized institutions with high-volume of cases (recommended > 20 pancreatic procedures/year) to reduce procedure associated mortality under 5%. Furthermore, as these kind of tumors have high rates of recurrence despite adequate resection, adjuvant chemotherapy is recommended in patients whose ECOG PS is 0-1 (17).

Unresectable disease

Locally advanced disease should be discussed by a multidisciplinary board before and after treatment induction to assess any possibility to undergo surgical resection. In patients without this option, the elective treatment involves chemotherapy to increase their quality of life (QoL) and overall survival, limited to patients with ECOG PS 0-2 (17).

Patients with metastatic disease should be advised to participate in clinical trials. Meanwhile, they can be treated with chemotherapy when they have ECOG PS 0-2 (17).

Moreover, whenever possible, a comprehensive tumor molecular characterization should be performed since it allows specific targeted therapies in some patients (17).

1.3.6. SUPPORTIVE CARE

Pain management

Pain is usually treated using opioid drugs, combined with adjuvant medication (gabapentin, pregabalin, nortriptyline, duloxetine) to assess neuropathic pain. Plexus neurolysis should be considered in refractory individuals, as it has better pain control and less adverse events than opioids (17).

Obstructive jaundice

The obstruction of the biliary tract can lead to debilitating symptoms and complications. Furthermore, it may produce hyperbilirubinemia, which is a contraindication for chemotherapy (32,33). The placement of biliary drainages and/or stents, either performed endoscopically or percutaneously, have shown to improve these issues (16).

The type of approach mainly depends on the level of obstruction (**Figure 4**) (34,35):

- Low bile ducts, considered below the insertion of the cystic duct, are best managed endoscopically, because a single stent can drain the whole biliary tree and it has fewer bleeding risks than percutaneous approach. However, when it is not indicated or fails, percutaneous approach is then indicated (16,17,32).
- High bile obstructions, delimited above the common hepatic duct, are better treated percutaneously, because this approach allows the targeting of specific ducts, optimizing biliary drain, and it has a lower risk of cholangitis, since it avoids ampulla of Vater disruption, preserving sphincter function and sterility of the biliary tract.

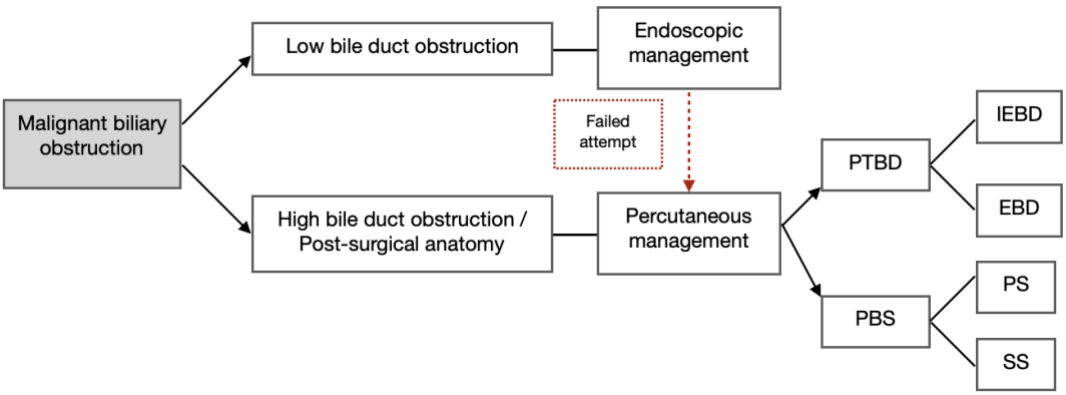


***Figure 4**: Palliative management of malignant biliary obstructions. Adapted from (34). Abbreviations: **PTBD** – percutaneous biliary drainage; **IEBD** – internal-external biliary drainage; **EBD** – external biliary drainage; **PBS** – percutaneous biliary stenting; **PS** – primary stenting; **SS** – secondary stenting.*

Pancreatic complications

There are two major pancreatic complications to consider. Firstly, gastric outlet obstruction, which can be treated with a duodenal stent. Secondly, pancreatic exocrine insufficiency, which contributes to fat malabsorption, and consequently causes maldigestion, steatorrhea, and weight loss, which can be detected with elastase-1 stool test, and requires enzyme therapy supply at starting doses of 75.000UI/day (17).

1.3.7. PROGNOSIS

MBO have dismal prognosis with low overall survival, due to their late-showing symptoms and low rates of resectability. The 5-year-survival rate in CCA is approximately 20.3% and 8.6% in pancreatic cancer in Spain (19). The instauration of an early and systematic palliative care for MBO improves patient's clinical outcomes and QoL (17).

1.4. PERCUTANEOUS BILIARY STENTING

1.4.1. RELLEVANT CONCEPTS

Biliary stenting

Biliary stenting refers to the deployment of stents, also known as prothesis, inside the biliary tract, which can be performed either endoscopically or percutaneously. A stent is a tube, used to beat the resistances causing the luminal stricture and restore the normal functioning of the biliary tract; or treat biliary leaks (36).

Measurement units in interventional radiology

Interventional radiology procedures involve different devices that are catalogued using different measurement units (37).

- Wires are measured using inches (“). The most common include the microwires which measure 0.018”, and the standard guide wires, which measure 0.035”.
- Needle diameter is measured in gauges (G), which is an inversely proportional unit. The lower the gauge number is, the larger the diameter of the needle is. The most used needles measure 22G, which fit a microwire of 0.018”, and 18G, which fit a standard guide wire of 0.035”.
- Catheters, sheaths, biliary drainages, and sometimes stents, are measured in French (Fr), which is equivalent to 1/3 of a millimeter and 0.013” (3Fr = 1mm).

1.4.2. TYPE OF STENTS

There are four types of biliary stents, including plastic stents, self-expandable metals stents (SEMS), biodegradable stents, and drug-eluting stents (**Figure 5**). The main difference between them is their expansion (greater in SEMS), patency (longer in SEMS), and costs (lower in plastic stents) (38–40).

The prothesis selection varies according to type of obstruction (benign or malignant), risk of reintervention and life expectancy (41). Normally, plastic prothesis and biodegradable stents are used for benign strictures, malignant strictures with a lifespan lower than 4 months, and bile leaks. In contrast, SEMS are indicated in malignant obstructions with a life expectancy more than 4 months, since their mean patency (8.5 months) is larger than in plastic stents (34,36,41).

Plastic stents

Plastic stents are made of polyethylene, polyurethane, Teflon, and other plastic polymers. Their diameters range from 5Fr-12Fr, and their length from 1-18cm. Characteristically, plastic stents usually have side holes to maintain biliary drainage if the prothesis tip blocks up; however, this trait could ease sludge formation, explaining their short patency (38). They are usually placed endoscopically since their short-term patency, requiring more exchanges. Their required stent length should be based on cholangiography and be the shortest as possible, while ensuring an adequate drainage, extending 1-2cm in the distal side and 1cm inside the duodenum (36,38).

Biodegradable stents

Biodegradable stents are commonly made of polydioxanone, a material often used to make absorbable surgical sutures, which degrades over 3-6 months via a hydrolytic process. Their main strength is that they do not need to be removed, but they still lack some improvements in degradation rate and mechanical support (39,42).

Self-expandable metal stents

SEMS were firstly made of stainless steel, but nowadays are mostly made of nitinol, which is a combination of nickel and titanium (36,38). There are different formats, including uncovered (bare), partially covered, or fully covered stents, whose inner and outer coverage is composed of polytetrafluoroethylene, silicon, and polyurethane. Their diameters range from 6-10mm, and their length from 4-12cm. Besides, they can be recaptured until their 80% of delivery, improving stent placement accuracy (38).

It is important to remark that these stents are made of a shape-memory alloy, what means that they partially expand immediately after delivery, and gradually expand to their real size over time (38).

Drug eluting stents

There is limited data about their clinical benefits related to human. The existent trials mainly involved paclitaxel and gemcitabine drug-eluting biliary stents, and despite their expected advantage, they have comparable efficacy with SEMS, without significantly increasing stent patency or survival rates in patients affected by MBO (40,43).

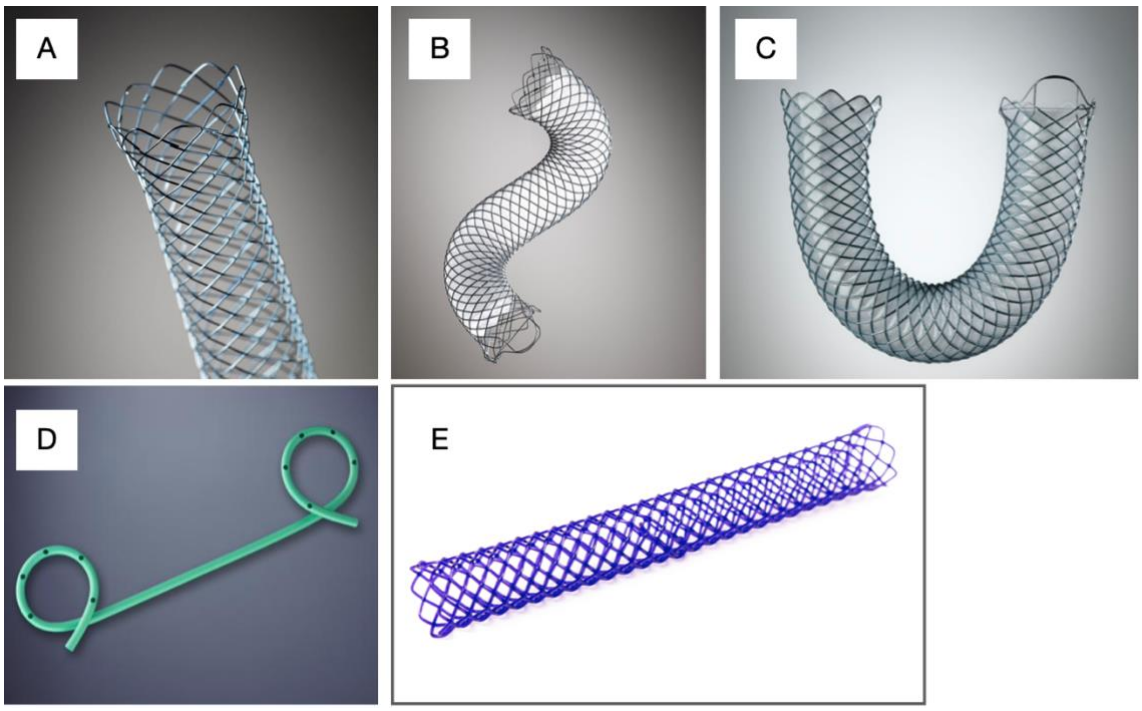


***Figure 5**: Types of stents. Adapted from (44–46). **A** – uncovered self-expandable metal stent, **B** – partially-covered self-expandable metal stent, **C** – covered self-expandable metal stent, **D** – plastic stent, **E** – biodegradable metal stent.*

1.4.3. MECHANICAL PROPERTIES OF SEMS

Major mechanical properties involved in clinical outcomes are radial and axial force (38):

- **Radial force**: It is the expanding force of the stent, and it is related to stent patency in two ways, immediate stent expansion affects short-term outcomes, while chronic resistant radial force against tumor compression affects long-term results.
- **Axial force**: It corresponds to the straightening of prothesis when they are bent, causing compression to biliary structures in both ends of stent. The increasing in axial force could be the explanation of biliary kinking and development of cholecystitis and pancreatitis.

1.4.4. INDICATIONS OF PERCUTANEOUS BILIARY STENTING

The main indication for percutaneous biliary stenting (PBS) is the definitive treatment of benign or malign strictures, in order to relieve cholestatic symptoms (jaundice, pruritus, anorexia, nausea, vomits, weakness) or manage its main complications (cholangitis or sepsis). Moreover, in MBO they are also used to decrease bilirubin levels, necessary to allow chemotherapy when indicated. Besides, they are also used to resolve bile leaks, usually appearing after abdominal surgeries, being cholecystectomy the main one. PBS is usually considered when biliary stenting is not feasible or fails endoscopically (34,36).

1.4.5. CONTRAINDICATIONS OF PERCUTANEOUS BILIARY STENTING

The main contraindications for PBS can be categorized as absolute or relative (**Table 6**).

Absolute contraindications

The principle absolute contraindication is uncorrectable coagulopathy since PBS is a high-risk bleeding technique (15,47). Additionally, the presence of interposed colon, vascularized tumors, or numerous cysts across the needle path could definitive contraindicate percutaneous biliary procedures (48,49).

Relative contraindications

The most common relative contraindications are correctable coagulopathy, which can be solved administrating platelet pools or plasma; allergy to iodinated contrast, which can be managed making corticoid prophylaxis or using gadolinium contrast; and tensive ascites, which can be relieved under paracentesis or using a left-sided access (15,34).

***Table 6**: Main contraindications for percutaneous biliary stenting (self-made table). Information extracted from (15,34,49)*

Absolute contraindications	Relative contraindications
Uncorrectable coagulopathy (quick test < 50% and/or total platelet count < 50.000/mm3) Unsafe access due to presence of vascularized tumors, extensive hepatic cyst disease, or colon transposition	Correctable coagulopathy Allergy to iodinated contrast Cholangitis or sepsis Tensive ascites Multiple segmental or subsegmental isolations Short lifespan (< 30 days)

1.4.6. PROCEDURE TECHNIQUE

PBS can be performed as primary stenting (PS), which involves a single-phase procedure where the stent is delivered directly, or secondary stenting (SS), which is a multiple-phase technique that firstly involves the introduction of an internal-external percutaneous transhepatic biliary drainage (PTBD), followed by stent deployment some days after (34).

In both procedures, if there is an inadequate flow through the prothesis or into the duodenum, placing a safety temporary catheter to preserve the access for 24-48 hours is highly recommended. The presence of abdominal pain, fever, or bile leakage around this safety catheter, suggest an inadequate bile flow. Additionally, these catheters can be used to re-evaluate partially unexpanded stents, and decide whether to apply balloon dilation or not; assess papillary disfunction; or diagnose bowel palsy (34).

Even though, both are accepted and standardized procedures, there is evidence based on retrospective studies suggesting that PS is a safer technique than SS, with a lower risk of cholangitis, sepsis and haemobilia, and with equivalent efficacy and survival rates in patients affected by MBO (50–55). However, SS is still the most common used technique and some randomized and controlled clinical trials are still necessary to support this premise, favoring the systematic application of PS (34).

Both PS and SS are extensively explained in “5.6. Study intervention”.

1.4.7. COMPLICATIONS IN PERCUTANEOUS BILIARY INTERVENTIONS

General complications

Bleeding

Percutaneous biliary interventions are considered at high-risk of bleeding because biliary ducts are in close contact with portal veins and hepatic arteries (56).

There are two types of bleeding (**Table 7**, **Figure 6**) (35):

- Venous bleeding: It develops in few days after the intervention, and it is caused by the passage of the biliary drainage catheter over a hepatic or portal vein branch. Patients with internal-external drains show intermittent dark blood in the drainage bag and/or melena. It is diagnosed by a percutaneous cholangiography (PTC), and it is managed upsizing the diameter of the catheter to tamponade the vessel, which will finally thrombose and stop bleeding.
- Arterial bleeding: It occurs some weeks after the procedure, and it is produced by the passing of the biliary drain across a hepatic artery branch. Patients present with red blood draining through and/or around the drain. Its diagnosis is made under angiography, and it can be embolized by direct visualization of the bleeding point or using anatomic references (treatment of the closest arterial branch from the drain).

There are three main risk factors related to bleeding:

Firstly, there is data suggesting that left-sided access has a higher risk of bleeding, because contrary to what happens in the right lobe, in the left lobe the hepatic artery and the portal vein are anterior to the bile ducts. To reduce this risk, it is preferable to select a right-sided access and canulate peripheral bile ducts. Otherwise, it is important to consider that right-sided access is more related to pleural complications and intercostal artery injuries (57).

Secondly, the insertion of a PTBD before the stent insertion, as it is done in SS, can produce a maintained mechanical irritation or artery wall damage since the initial access, explaining why arterial bleeding appears later (**Figure 6**) (57).

Thirdly, this can also be increased by pre-stent or post-stent balloon dilation because it produces tumor laceration and bleeding, which is usually unnecessary because SEMS partially expand after delivery, but totally expand over time (15,42).

***Table 7**: Clinical signs of portal vein vs hepatic artery injury. Extracted from (58).*

Portal Vein Injury	Hepatic Artery Injury
Intermittent bleeding	Constant and pulsatile bleeding
Dark blood	Bright red blood
Typically hemodynamically stable	Hemodynamic instability
No large drop in hematocrit	Falling hematocrit by > 13% of baseline
Melena	Melena

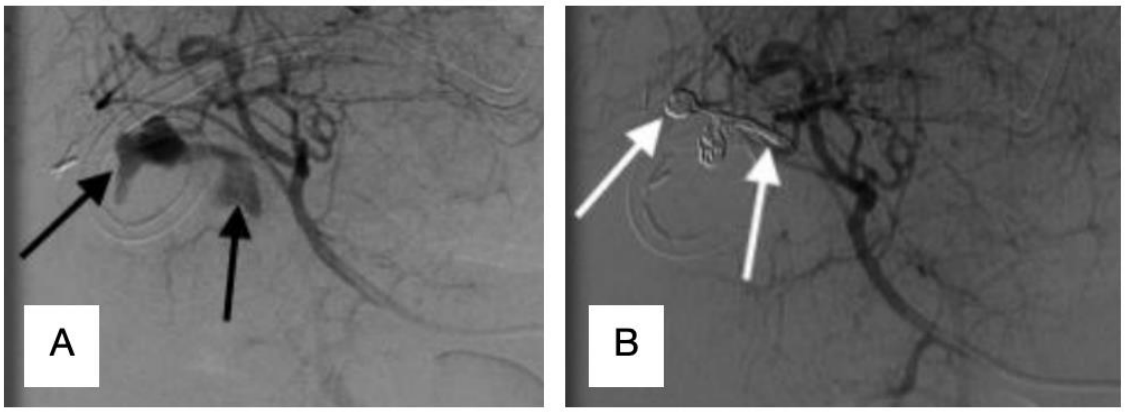


***Figure 6**: Angiography showing arterial bleeding due to biliary drain erosion (A) and its embolization (B). Adapted from (58).*

Cholecystitis / Pancreatitis

The risk increases when the catheter or stent crosses the origin of the cystic or pancreatic duct. Furthermore, this complication is more likely to happen when using covered SEMS or internal-external PTBD. This complication is managed with antibiotics with or without the placement of a percutaneous cholecystostomy (35).

Sepsis

Biliary interventions are considered clean-contaminated procedures. Consequently, it is highly recommended to administrate prophylactic antibiotics prior to procedure. If patients develop fever after intervention, it will be indicated to obtain blood cultures, maintain antibiotics, and add fluid resuscitation if necessary (35).

PTBD specific complications

The most common complications related to PTBD, which are the first stage in SS, include drainage occlusion or dislocation, cholangitis, bile leakage, haemobilia, biliovenous or biliopleural fistulas, pain, and sepsis (15).

Bile leakage

Bile may leak around the drain catheter, causing bile peritonitis, ascites and/or skin breakdown. It is resolved upsizing the diameter of the drainage catheter (35).

Drainage occlusion

If the drainage starts to leak after a long period of time, commonly it is caused by catheter occlusion. This can be prevented by flushing 10ml of saline forward the drain once or twice a day, as well as exchanging bile drainages every 3 months (35).

PBS related complications

Complications related to prothesis, also include bleeding and biliary infections (35). Furthermore, there are some specific stent-related complications to consider, which are prothesis occlusion and dislodgement, both implicated in stent disfunction (36).

Stent occlusion

While acute stent occlusion usually develops due to haemobilia with formation of an obstructive clot, long-term occlusion can be caused due to sludge, tumor ingrowth or tumor overgrowth (42). Firstly, bile sludge, which is caused by bacterial bilirubinate salt production, is more common in plastic stents. Secondly, tumor ingrowth is more typical in uncovered SEMS, since malignant cells can invade its cells (**Figure 7**) (36).

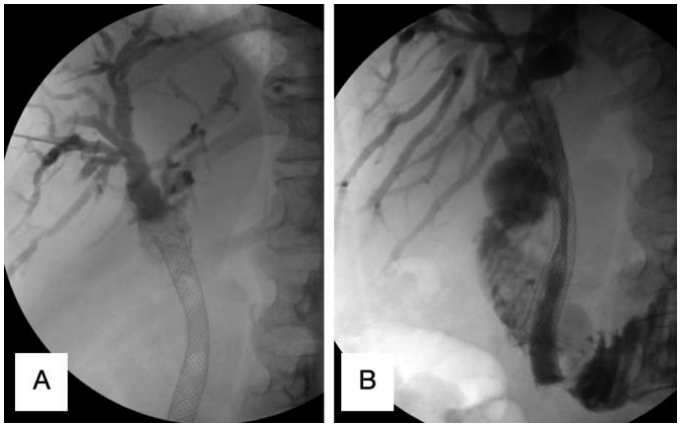


Figure 7*: Stent occlusion due to tumor overgrowth (A) and ingrowth (B). Extracted from (59)*

Stent dislodgement

Stent migration is more related to covered SEMS, which are smooth and have poor adherence to bile duct walls. This risk has been managed by the introduction of covered SEMS with flared ends, barbs and partial coverings (36).

2. JUSTIFICATION

Malignant biliary obstructions (MBO), involving different biliopancreatic and metastatic neoplasms, usually show-up with late or unspecific symptoms, leading to a differed diagnosis, without the opportunity for surgical resection, which is the only curative option, and consequently conditioning their poor prognosis (16,17).

Moreover, patients affected with MBO present with cholestatic symptoms, such as painless jaundice, pruritus, choluria, and hypocholia; and potential complications, mainly cholangitis and sepsis (12,16). Besides, the consequent hyperbilirubinemia is a criterion to contraindicate chemotherapy in those patients (32,33).

The placement of percutaneous biliary stents (PBS) as a palliative treatment for unressectable MBO (UMBO), when endoscopic approach is not feasible or fails, is an efficacious and safe technique to decompress the biliary tract, improving clinical outcomes and patient's quality of life (QoL), as well as allowing chemotherapy administration if total bilirubin levels normalize (BrT ≤ 2mg/dl) (16).

PBS can be either placed under primary stenting (PS), which involves a single-phase procedure in which the stent is directly delivered at the obstruction location; or under a secondary stenting (SS), which is a multiple-phase intervention that firstly involves the introduction of an internal-external percutaneous transhepatic biliary drainage (PTBD), followed by a differed stent deployment after some days (34).

Even though, both PS and SS are accepted and standardized procedures, there is evidence based on some retrospective studies suggesting that PS could be a safer technique than SS, with lower risks of cholangitis, sepsis and haemobilia; presenting an equivalent efficacy and survival rates in patients affected with UMBO (50–55). However, SS is still the most widely used technique in the current clinical practice in our environment, possibly due to the feeling of security when having a constant access to the biliary tract, even if this could be one of the main reasons behind its higher morbidity.

Moreover, SS is a staged procedure requiring more days of hospitalization, a minimum of three sedations (once each step), and the patient needs to carry out an external drainage for at least 2-4 days, potentially extending in time if it complicates. All these facts could contribute negatively to patient's QoL.

Furthermore, PTBD is known to be one of the risk factors related to PBS bleeding and infection. Firstly, it can cause arterial bleeding by a mechanical irritation or artery wall damage, also increasing the risk of acute stent occlusion in the second step of SS. Secondly, it seems to raise the risk of infections, since it crosses the origin of the cystic and pancreatic ducts, maintains the ampulla of Vater opened to enteric bacteria, and its daily requires of flushes that push some external bacteria into the biliary tract (35,57).

This clinical trial will contribute to these issues with more scientific evidence than the previous retrospective studies, and its main aim will be to determine whether PS is at least non-inferior in terms of safety in UMBO when compared to SS, since it is the main barrier to the systematic application of this technique. Efficacy will be also assessed, evaluating technical and clinical success, in order to accept both procedures as comparable ones. Accordingly, we will pose a non-inferiority safety clinical trial, supported by "González-Bermejo et al., 2022" (60).

3. HYPOTHESIS

3.1. MAIN HYPOTHESIS

The main hypothesis of this study is that percutaneous primary biliary stenting (PS) as a palliative treatment for patients with unresectable malignant biliary obstructions (UMBO) will be, at least, **non-inferior** to secondary biliary stenting (SS) **in terms of safety**, defined as total incidence of complications, using a non-inferior margin of 9%.

3.2. SECONDARY HYPOTHESES

- PS as a palliative treatment for patients with UMBO will show **less serious complications** when compared to SS.
- PS as a palliative treatment for patients with UMBO will present **comparable technical success** as SS.
- PS will have **similar clinical success** as SS in palliative patients with UMBO.
- The implementation of PS as a palliative treatment will **shorten time of hospitalization** in patients suffering of UMBO when compared to SS.
- Patients with UMBO undergoing PS as a palliative treatment, will experience an **increased quality of life** (QoL) when compared to those patients undergoing SS.

4. OBJECTIVES

4.1. MAIN OBJECTIVE

The main objective of this study is **to determine the safety** of PS and SS by registering and comparing the **occurrence of complications** in both procedures, using a non-inferiority margin of 9%.

4.2. SECONDARY OBJECTIVES

- To evaluate the **severity of complications** in PS and SS as palliative treatments for patients with UMBO using the CIRSE classification system for complications.
- To compare the **technical success** of PS and SS as palliative treatments for patients with UMBO, defined as correct stent placement and expansion with continuous contrast flow through the duodenum.
- To analyse the **clinical success** of PS and SS as palliative treatments for patients with UMBO, defined as a normalization in total serum bilirubin levels (BrT ≤ 2mg/dl).
- To record and compare the **total days of hospitalization** related to complications, during and after performing palliative PS and SS in patients suffering of UMBO.
- To assess whether patients with UMBO undergoing PS as a palliative treatment, experience a significant improvement in their **QoL** when compared to patients undergoing SS, by using the QLQ-30 questionnaire.

5. MATERIALS AND METHODS

5.1. STUDY DESIGN AND SETTING

This study will take place in the Interventional Radiology Department of *Consorci Corporació Sanitària Parc Taulí* (CCSPT) as a single-institution study protocol, prospective, open-label, randomized and controlled non-inferiority clinical trial to evaluate the safety of percutaneous primary biliary stenting (PS) as a as a palliative treatment for patients with unresectable malignant biliary obstructions (UMBO), compared to percutaneous secondary biliary stenting (SS).

5.2. STUDY POPULATION

This study will include all the patients at CCSPT with unresectable primary or metastatic malignant tumors causing symptomatic or complicated biliary obstructions.

5.3. STUDY SUBJECTS

This research will include all the patients at CCSPT with unresectable primary or metastatic malignant tumors causing symptomatic or complicated biliary obstructions who meet the following inclusion criteria and do not meet the exclusion criteria.

INCLUSION CRITERIA:

Patients with unresectable malignant biliary obstruction (UMBO), including primary and metastatic tumors, causing cholestatic symptoms (jaundice, pruritus, anorexia, weakness), cholangitis and/or raised total bilirubin levels (BrT) being a contraindication for chemotherapy, in which previous endoscopic retrograde cholangiopancreatography (ERCP) was not possible or a failed attempt. The previous informed consent signature is required to enter the study (*see annex 8*).

EXCLUSION CRITERIA:

- Patients under the age of eighteen.
- Pregnant women.
- Patients presenting septic shock.
- ECOG Performance status ≥ 4 (**Table 4**).
- Incompatibility to undergo deep sedation (pre-anaesthetic validation).

- Uncorrectable coagulopathy (INR > 1.5 and/or platelet count < 50.000/mm3).
- High malignant obstruction Bismuth type IV (**Table 2**).
- Patients who have undergone previous biliary stent placement at the same target location or local surgeries significantly modifying biliary system anatomy.

WITHDRAWAL CRITERIA:

Patients taking part in the study will be informed about this study objectives and main complications before signing an informed consent. It is important to consider some withdrawal and termination basis.

1. Individuals who do not want to participate in the study, even though they comply inclusion criteria and do not fulfill exclusion criteria.
2. Individuals who revoke the previously signed informed consent. All patients have the right to voluntary withdraw from this study at any moment, communicating their decision to any physician involved in the research (*see annex 9*).
3. Patients who are impossible to be contacted and continuously avoid follow-ups planned in the protocol, will be considered as study losses.
4. Impossibility to cross the obstruction or stricture during the procedure, and consequently not allowing the delivery of the biliary stent percutaneously.
5. Patients with a delayed recognition or newly developed exclusion criteria.
6. Patient's death, registering the main cause.

All patient's loss during the study must be registered with their data and withdrawal cause. Moreover, data obtained previously, will be used for study results.

5.4. STUDY SAMPLE

SAMPLE SIZE

This clinical trial is designed to evaluate the non-inferiority of PS compared to SS in terms of safety (primary endpoint). In a two-sided test, with an alfa level of 1% (since we need a greater sample size to perform a non-inferiority clinical trial), a statistical power equal to 80%, and assuming a non-inferiority margin (δ) of 9%, 107 patients will be required in each group. Assuming a drop-out rate equal to 10%, we will finally need 118 subjects per group, being the **total sample size of 236 subjects**.

The non-inferiority margin of safety, regarding total number of complications, was accepted to be 9%, based primarily on "Inal et al., 2003" (50), which is considered as the referent study. In a more recent work "Chatzis et al., 2013" (51), a non-inferior margin of 15% can be calculated. However, the main limitation on this research was their reduced sample size (N = 61). Finally, "Inal et al., 2003" was selected for the non-inferiority margin, because it does not carry this study limitation and their sample size (N = 126) is more correlatable to the needed one in the current study.

Computations were carried out with Prof. Dr. Marc Saez' software based on the package 'pwr' of the free statistical environment R (version 4.2.2).

SAMPLE SELECTION

The sample will be selected using a non-probabilistic consecutive sampling method in which all the patients at our medical institution accomplishing the inclusion criteria and not fulfilling the exclusion criteria will be offered to participate in the study.

ESTIMATED TIME OF RECRUITMENT

Considering the needed sample size of 236 patients, and an approximately available sample of 89 patients per year, based on the activity data from 2021 at our institution (*see annex 3*), the estimated time of recruitment of this study will last approximately **2 years and 8 months**.

Additionally, after completing the first year of recruitment and/or achieving a recruitment number of 76 patients (38 patients per group), we will perform an interim statistical analysis to ensure the safety of this clinical trial (see *5.8. Study safety*).

SAMPLE RANDOMIZATION:

All patients meeting the inclusion criteria and not the exclusion criteria who consent to participate in this clinical trial, will be assigned an identification numerical code to ensure their privacy. Then, all individuals will be randomly allocated into one of two intervention groups (PS or SS) in a 1:1 ratio, computed automatically by the Statistical Specialist' Software to reduce selection bias.

MASKING TECHNIQUES

This clinical trial will be open label, being the masking impossible because both the interventional radiologist and the patient will be conscious on the type of intervention being performed. Nevertheless, in order to decrease the detection bias, there will be an independent observer responsible for data collection from patient's clinical chart and updating it to the database; and then, a blinded statistician, unaware of the biliary stenting method used for each patient, will assess the outcome variables (occurrence and severity of complications, technical and clinical success, total time of hospitalization and quality of life) and evaluate the results, providing more objective information.

5.5. STUDY VARIABLES

INDEPENDENT VARIABLE:

The independent variable in this study concerns to the type of intervention that will be performed to percutaneously insert a biliary stent as a palliative treatment for patients with UMBO.

- **Group A / Experimental group**: Primary biliary stenting (PS).
- **Group B / Active control group**: Secondary biliary stenting (SS).

DEPENDENT VARIABLES:

- Main dependent variable: The main outcome variable in this study refers to the safety of both interventions quantified by **occurrence of complications** during the procedures and the 30-day period after its conclusion.
  - Secondary dependent variables:
    - **Severity of complications**: It will be expressed using the *CIRSE classification system for complications*, which includes five grades of complications according to their increasingly gravity (see *annex 4*). This variable will be evaluated as a dichotomic qualitative (yes/no) accounting for each degree of severity.
    - **Technical success**: It will be defined as the correct stent placement, overlaying the whole obstruction; with appropriate expansion in diameter, supported by stent dimensions in the device description; and constant contrast drainage to the duodenum when performing the control cholangiography after stent delivery.
    - **Clinical success**: Total serum bilirubin (BrT) levels are correlated to cholestatic symptoms (jaundice, pruritus, anorexia) and overall survival in patients with UMBO. Additionally, normalized BrT levels are indispensable to allow chemotherapy when indicated. Accordingly, clinical success will be defined as normalized BrT (≤ 2mg/dl) on follow-up at 3 or 6 weeks, since time until BrT normalization depends on its levels prior to biliary decompression (61).
      - In patients whose prior BrT levels were < 10mg/dl, this variable will be quantified before and 3 weeks after the procedure.
      - In patients whose previous BrT levels were ≥ 10mg/dl, this parameter will be determined before and 6 weeks after the procedure.

- **Total time of hospitalization**: It will be quantified within the different steps of the procedure and during the first 30 days after its finalization, only accounting for the hospitalizations related to intervention complications.
- **Quality of life**: It will be quantified using the *European Organisation for Research and Treatment of Cancer* (EORTC) QLQ-C30 standardized questionnaire (*see annex 5*) for oncologic patients, which will be answered before the intervention and 3 or 6 weeks later, depending on pre-treatment BrT, as explained in "clinical success" variable.

COVARIABLES:

- **Age**: Expressed in years at the moment of intervention using an official ID card.
- **Sex**: Catalogued as a dichotomic male/female covariate based on an official ID card.
- **Body mass index (BMI)**: Measured with the quotient between weight in kilograms and the square of height in meters, classified in four groups involving (I) Underweight (BMI < 18.5kg/m2), (II) Healthy weight (18.5-24.9kg/m2), (III) Overweight (25-29.9kg/m2), (IV) Obesity (BMI ≥ 30kg/m2).
- **Type of tumor**: Categorized in six groups including (I) Cholangiocarcinoma, (II) Gallbladder carcinoma, (III) Ampulloma, (IV) Hepatocarcinoma, (V) Pancreatic cancer, (VI) Metastatic disease or nodal compression.
- **Location of biliary obstruction**: Classified as a dichotomic low/high covariate based on previous radiological imaging techniques.
  - Low bile duct obstructions: Located under the insertion of the cystic duct.
  - High bile duct obstructions: Delimited above the common hepatic duct.
- **Previous attempt of ERCP**: Catalogued as a dichotomic yes/no covariate based on patient's medical chart.
- **Presence of cholangitis**: Catalogued as a dichotomic yes/no covariate based on patient's medical chart.

A summary of all study variables and covariables can be seen in **Table 8**.

***Table 8**: Summary of study variables and covariables.*

	Variable	Type of data	Category or value
Independent variable	Type of intervention	Dichotomic qualitative	Primary biliary stenting / Secondary biliary stenting
Main dependent variable	Occurrence of complications	Dichotomic qualitative	Presence/Absence
Secondary dependent variables	Severity of complications	Dichotomic qualitative (accounting for every grade of severity)	Yes/No
	Technical success	Dichotomic qualitative	Yes/No
	Clinical success	Dichotomic qualitative	Yes / No
	Total time of hospitalization	Discrete quantitative	Numerical (days)
	Quality of life	Discrete quantitative	Score (EORTC QLQ-30)
Covariables	Age	Continuous quantitative (measured as discrete)	Numerical (years)
	Sex	Dichotomic qualitative	Male / Female
	Body mass index	Ordinal qualitative	(I) Underweight (II) Healthy weight (III) Overweight (IV) Obesity
	Type of tumor	Nominal qualitative	(I) Cholangiocarcinoma (II) Gallbladder carcinoma (III) Ampulloma (IV) Hepatocarcinoma (V) Pancreatic cancer (VI) Metastatic disease or nodal compression
	Location of biliary obstruction	Dichotomic qualitative	Low / High
	Previous attempt of ERCP	Dichotomic qualitative	Yes / No
	Presence of Cholangitis	Dichotomic qualitative	Yes/No

Abbreviations: ERCP – Endoscopic retrograde cholangiopancreatography

5.6. STUDY EQUIPMENT AND INTERVENTION

In this clinical trial, all the patients with UMBO with impossibility to decompress the biliary tract under ERCP, who meet the study criteria and consent to participate, will be randomly allocated into two different treatment arms (PS and SS).

REQUIRED EQUIPMENT

General material

- Ultrasound scan with its sterile sheath and guidance pieces.
- Needles: subcutaneous needle (x1), 18G Chiba needle (x1), scalpel blade nº 11 (x1).
- Syringes of 10ml color differentiated (x3), syringe of 20ml (x1), extension cord (x1).
- Beakers (x2), surgical field drapes, sterile gauzes, sterile gloves.

Specific material (**Figure 8**)

- Introducer sheath (8Fr), guide wires (0.035") and diagnosis catheters (5Fr).
- Internal-external biliary drainage (8Fr), hydrocolloid dressing, drain bag (just for SS).
- Biliary bare SEMS (normally ø 10mm).

Pharmaceutical material

- Saline serum.
- Iodinated contrast.
- 10ml of lidocaine 2%.

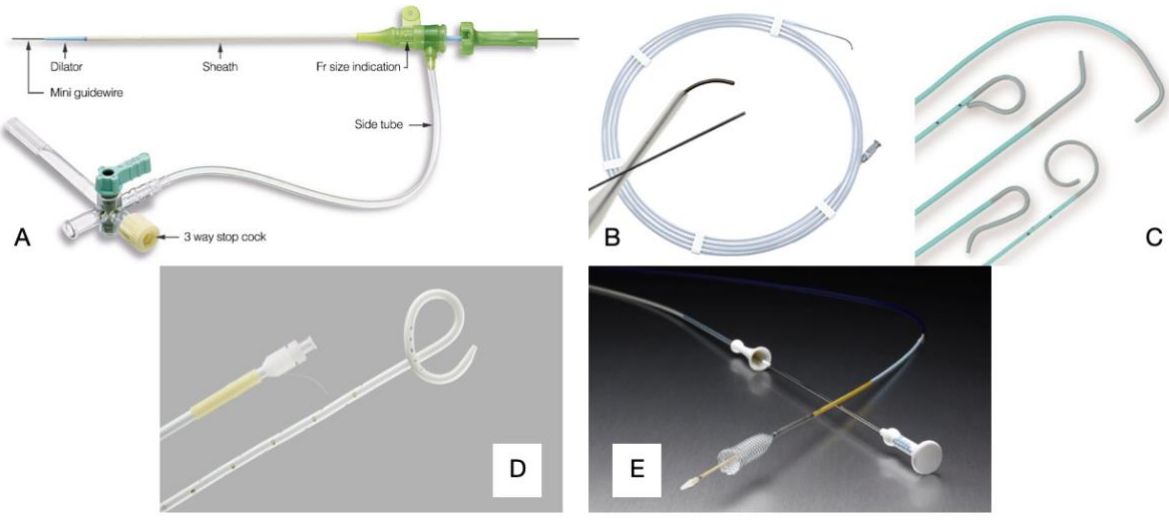


***Figure 8**: Specific material for percutaneous biliary stenting. Adapted from (44,62–65). **A** – introducer sheath, **B** – guide wire, **C** – diagnosis catheters, **D** – internal-external biliary drainage, **E** – self-expandable metal stent.*

PRE-TREATMENT PREPARATION

In order to assess the underlying disease and plan the intervention (optimal access and angle of fluoroscopy), all patients will undergo some imaging evaluation, which include sonography (US), followed by computed tomography (CT) scan or magnetic resonance (MRI) in portal venous phase, depending on availability.

Prior to the intervention, patients must do a fasting of 6 hours to prevent aspiration. Moreover, since percutaneous biliary stenting (PBS) is a high-risk bleeding procedure, patients must withhold antiplatelet drugs and anticoagulation drugs at different times varying on the drug used (**Table 9**). Patients taking long-term anticoagulation may require bridging anticoagulation with low molecular weight heparin.

Physicians will evaluate patient's coagulation, requiring an INR < 1'5 and platelet count > 50.000/mm3 to allow the procedure; and will administer prophylactic antibiotics (single shot of 2g amoxicillin) to prevent cholangitis or sepsis, secondary to biliary manipulation. Moreover, to reduce the risk of bleeding in individuals with ascites, a pre-interventional paracentesis or a left access approach will be performed.

***Table 9**: Management of anticoagulation and platelet-aggregation blocker therapy before high-risk bleeding interventional radiology procedures. Extracted from (47)*

Drug	**When to withhold**
Aspirin low dose	Do not withhold
Aspirin high dose / Clopidogrel	5 days
Prasugrel	7 days
Unfractionated heparin	4 hours (intravenous) / 6 hours (subcutaneous)
Low molecular weight heparin	24 hours
Vitamin K antagonist (warfarin, acenocoumarin)	5 days (INR ≤ 1.5)
Dabigatran / Apixaban	72 hours
Rivaroxaban / Fondaparinux	48 hours
Acova/Desirudin/Bivalirudin	4 hours

PATIENT POSITIONING AND ACCESS

Before intervention onset, CIRSE IR patient safety checklist (see *annex 6*) will be assessed. In both procedures, the patient will be in supine position, constantly monitoring for arterial pressure, cardiac rate, and oxygen saturation. After shaving and

applying local antiseptic, the patient will be covered in sterile sheets with an opening in skin access. The whole procedure will be performed under deep sedation, managed and controlled by the anaesthesiologist, and supplemented with local anaesthetic using lidocaine at 2% at the puncture site to minimize the pain and movement of the patient.

The biliary access will be achieved under US guidance, which is also useful to exclude the presence of ascites and avoid colon puncture. After localizing the most dilated biliary branch, we will infiltrate lidocaine at 2%, make a small incision with a scalpel, and canulate the biliary radical using a micro-puncture set in low or moderate dilations, or 18G Chiba needle in severe dilated ducts. When we expect to be inside the biliary tract, we will connect the needle to a syringe with contrast using an extension cord, and by aspirating and injecting some diluted contrast medium (50% contrast / 50% saline serum), we will confirm it under fluoroscopy. It is important to use small amount of diluted contrast medium to allow the correct visualization of catheters and wires, reduce the risk of cholangitis, and avoid the entrance of small bubbles interfering in US images.

The angiography C-arm will be positioned in anteroposterior or right anterior oblique view to guide the correct insertion of different devices inside the biliary tract.

Following the *Seldinger* technique (**Figure 9**), we will pass a 0.018" guide wire through the needle, remove the needle, maintaining the wire in place, make a scalpel stroke, and introduce an introducer sheath to secure our access. Finally, we can pull off the wire, which was used to support the pass of the sheath.

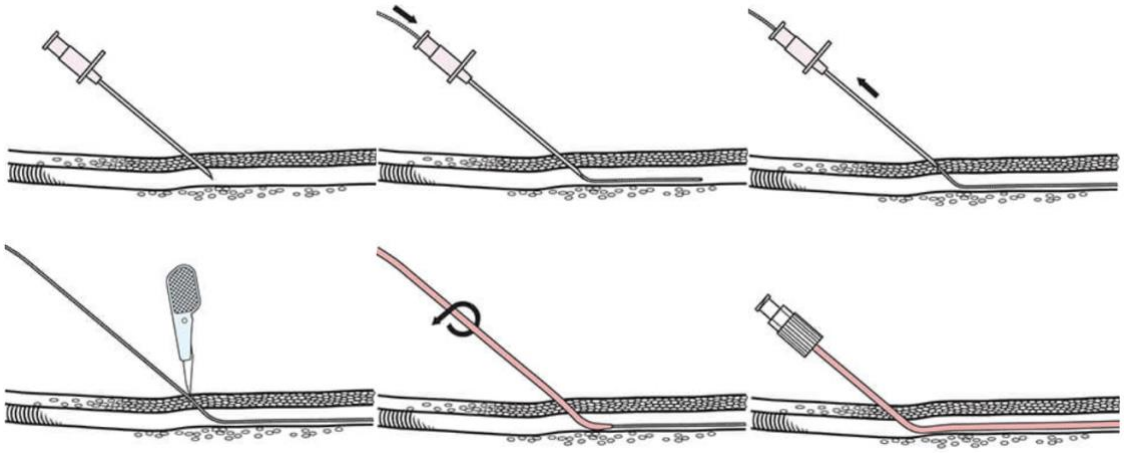


***Figure 9**: Seldinger technique. Extracted from (66)*

PERCUTANEOUS PRIMARY BILIARY STENTING

It is a single-phase procedure that consists in the straight placement of a biliary prothesis in the obstruction site to restore normal biliary flow. In this technique, after achieving the biliary access, we introduce a 0.035" guide wire to bypass the obstruction, and then we deploy the stent (**Figure 10**). Afterwards, we ensure the correct prothesis position and growth, thereby, if there is an obstruction still covering more than 30% of the inner lumen, we can increase the stent diameter with the help of specific balloons.

If the patient presents with haemobilia at the end of PS, or the interventional radiologist considers the stent placement at risk of occlusion, a temporary safety external catheter is placed for 48 hours, to maintain the access and avoid the early failure of the procedure and its related adverse events.

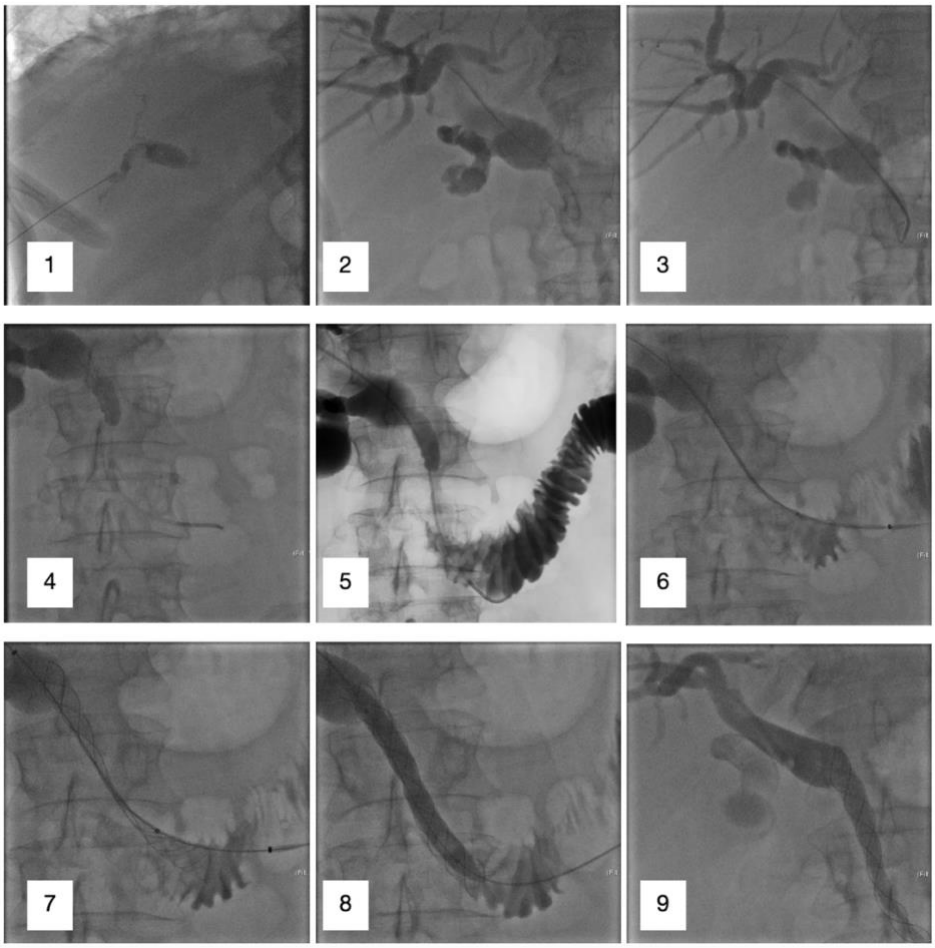


***Figure 10**: Percutaneous primary biliary stenting. Extracted from (67). 1 – cannulation of a biliary radical, 2 – guidewire placed in the furthest part of the biliary tree, 3 – angled catheter in the beginning of stricture, 4 – catheter with hydrophilic guidewire passed through the stricture, 5 – proximal and distal contrast filling to evaluate the stricture, 6 – radiopaque marks show the stent location, 7 – stent placing, 8 – stent completely delivered, 9 – final cholangiography.*

PERCUTANEOUS SECONDARY BILIARY STENTING

It is a multiple phase procedure to resettle normal biliary excretion. Between each step there is an average time of 2 to 4 days, differing on haemobilia, grade of dilation, drainage functioning and interventional room availability. Before every step, we follow pre-treatment preparation and anaesthetics (deep sedation and local analgesia).

In the first session, after creating the biliary access, we pass a 0.035" guide wire to bypass the obstruction and leave an internal-external drainage to reduce pre-obstructive dilation of the biliary tree. The drainage has a pigtail end which screws inside the duodenum and avoids its migration (***Figure 11***). At the end of this step, we verify the correct drainage position, place a hydrocolloid dressing to fix the external part of the drain, and connect it to a drainage bag. The drainage will remain externally opened during first 24-48 hours, and then if there is neither presence of haemobilia nor catheter disfunction (fever, pain, bile leakage), the external drain will be closed to maintain internal drainage, thereby reducing the risk of electrolyte loss and patient's dehydration.

In the second session, we firstly inject some diluted contrast to ensure the correct drainage location, and if accurate, we cut the threads to unscrew the pigtail. Afterwards we introduce a 0.035" guide wire overpassing the obstruction, we take out the drainage, maintaining the wire in place, and then we insert an 8Fr sheath. Later on, we unfold the biliary stent throughout the obstruction, confirming its correct position and expansion. Finally, we leave a temporary safety external catheter to control the access for 48 hours, which is again fixed using a hydrocolloid dressing and draining inside a specific bag.

In the third session, after ensuring the normal functioning of the biliary tract, we finally retire the safety catheter and embolize the access.

STERILE CONDITIONS AND RADIOPROTECTION

All interventional procedure will be done under sterile conditions, including grown, gloves and mouse-nose mask. Physicians must follow radioprotection measures, which involve wearing personal protective devices (aprons, thyroid shields, and eyewear), using protective drapes, exiting the room during image acquisition when possible, and performing the procedure at the minimum achievable dose.

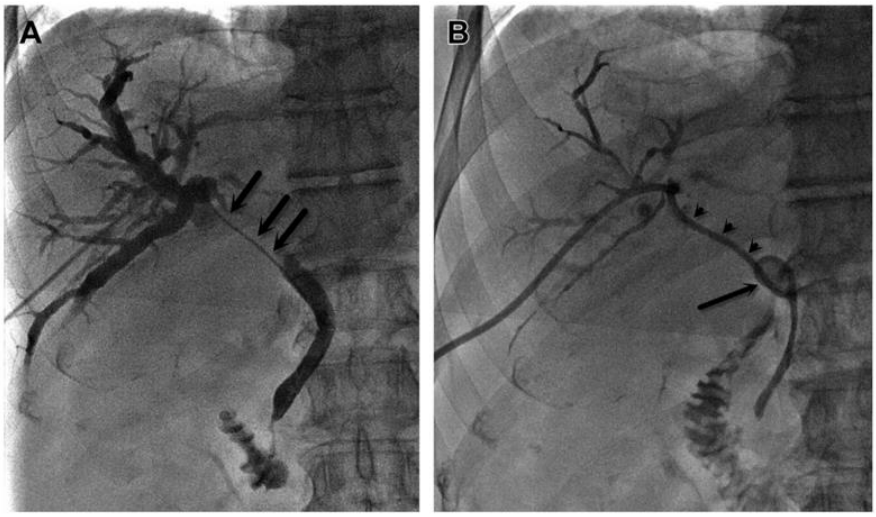


***Figure 11**: Percutaneous internal-external biliary drainage. Extracted from (34). A – cholangiography showing an occlusion of the common bile duct, B – positioning of the drainage.*

POST-NTERVENTION CARE

Patients will rest in bed for 12 hours, checking the dressing covering the puncture site to control and prevent its bleeding. Then, 2 hours later the intervention, patients will be able to progressively start their normal diet as tolerated. Besides, constants will be verified each hour during first 4 hours, and every four hours during the following 8 hours.

In case that catheter accidentally dislodges or stops working, it must be communicated to the Interventional Radiology Department. Moreover, if any acute complication develops, especially hypotension, pain or bleeding signs, it must be reported to the on-call doctor in order to manage it.

5.7. STUDY CIRCUIT AND DATA COLLECTION

Patients with cholestatic signs and symptoms will undergo an exhaustive anamnesis and clinical exploration, followed by a blood test, which will evaluate liver and renal function, bilirubin levels, tumoral markers (CA19-9, CEA, AFP) and possible underlying causes. The first image technique to confirm the obstruction of the biliary tract will be a sonography.

Afterwards, if there is a high suspicion of a malignant underlying cause, individuals will undergo a cross-sectional imaging to evaluate local and distal disease, mostly based on thoracic and abdominal CT scan, and in some cases, complemented by a MRCP.

Then, the pathological diagnosis will be made under a tissue sample, which normally will be obtained by a core biopsy US/CT/EUS-guided; and in specific cases, it will be done under ERCP or PTC.

After confirming a malignant etiology, determining it is not eligible for resectability, and when ERCP is not feasible or failed the attempt, patients will be derived at our department to place a PBS as a palliative treatment to relieve the symptoms and/or allow chemotherapy administration.

There, a physician from the research team will explain our study to all the patients that meet the inclusion criteria and do not comply the exclusion criteria. Then they will be given the "patient's information sheet" (*see annex 7*) to quietly read all the details about our study, answer their questions, and decide whether to participate or not.

If the patient agrees to get involved in our study, he/she will have to sign the "informed consent" (*see annex 8*). In addition, all candidates will be explained that they are free to withdraw from this study, without any prejudice or detriment in their clinical management, by signing the "request to withdraw study consent" (*see annex 9*).

All the patients enrolled in our study will be given a numeric code to preserve their confidence and privacy, and will be randomly allocated to one group of intervention. Then, the physician will fill the "case report form" (*see annex 10*) to collect all data related to the co-variables involved in this study.

Prior to the procedure, patients will undergo a pre-anesthetic evaluation, since the placement of a PBS requires deep sedation; and the intervention will be planned by using the information extracted from cross-sectional imaging. Whenever is required, some extra image techniques will be done to optimize the procedure.

Then, patients will be hospitalized the previous day to the intervention, and the placement of a biliary stent will be done percutaneously following PS or SS (*see 6.5. Study equipment and intervention*), varying on the prior randomization. Technical success will be evaluated at the end of the procedure (*see 5.5. Study variables*). After the intervention, patients will be under medical observation for 24 hours, and if there are no signs of acute complication and pain is well-managed, they will be discharged and will be given a surveillance schedule.

Patients will be followed-up at 48 hours since discharge, and then every week during the following 6 weeks. During these sessions, patients will undergo an extensive anamnesis and physical exploration, looking for clinical improvement and potential signs of complications, and a blood test to mainly evaluate liver function and adequate decline in bilirubin levels, to allow chemotherapy as soon as possible in indicated patients. The clinical success and the EORTC QLQ-30 questionnaire will be assessed at 3 weeks in patients whose pre-stent BrT levels were < 10mg/dl, or at 6 weeks in patients whose pre-stent BrT levels were ≥ 10mg/dl. Moreover, during the different steps of the procedures and during 30 after its finalization, physicians will report the occurrence and severity of complications, and the total time of hospitalization related to them (*see 5.5. Study variables*).

The participant flow chart is shown in **Figure 12**.

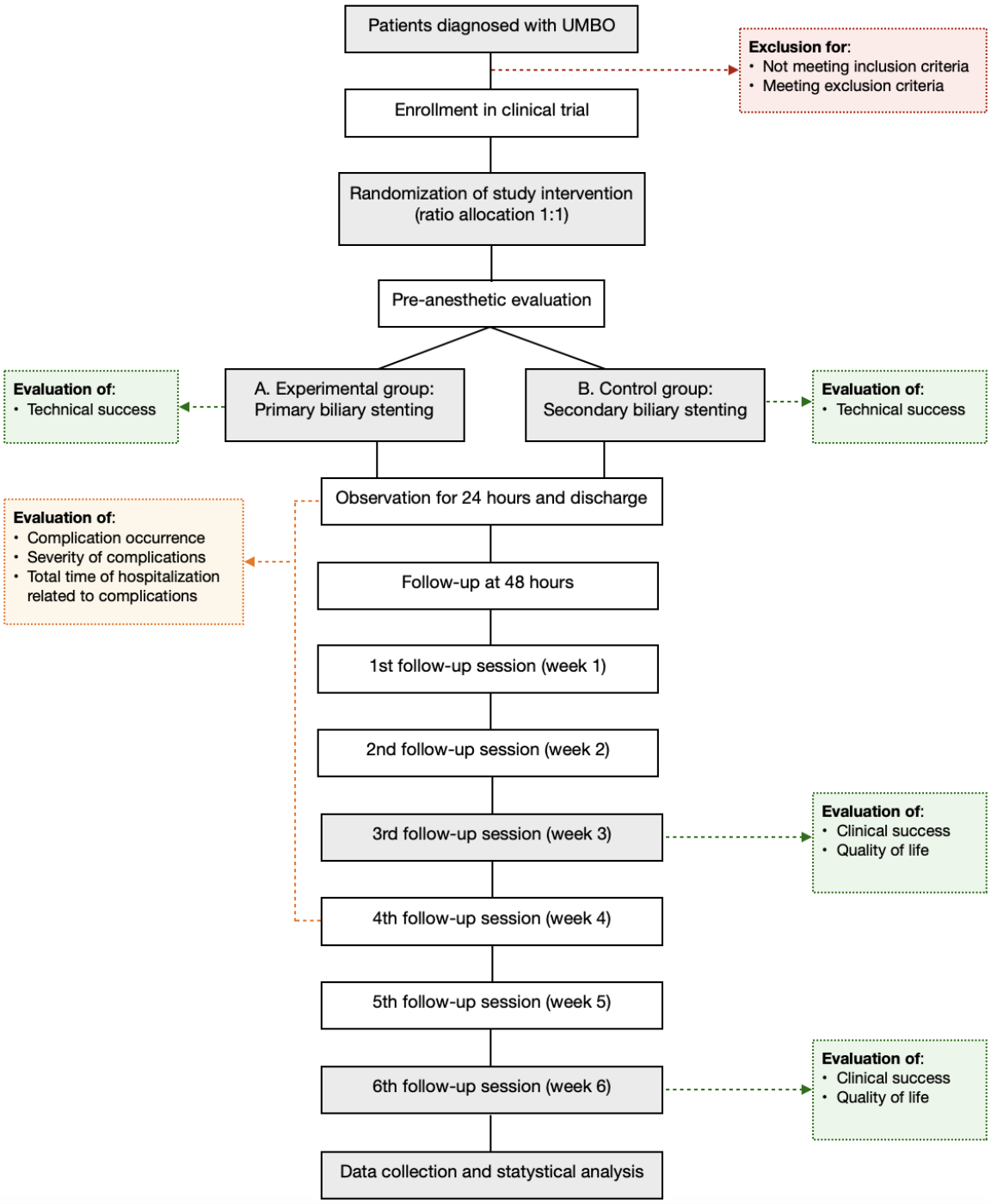


***Figure 12**: Patient's flow chart.*

5.8. STUDY SAFETY

Even though interventional radiology procedures are minimally invasive, they have inherent potential complications as other invasive specialties. Consequently, intensive safety care will be carried out in this study to ensure patient security and wellness, according to the following aspects.

- **CIRSE IR safety checklist** (*see annex 6*): Safety checklists in medicine significantly reduce morbimortality rates in patients by controlling the human error on forgetting key steps in patient preparation, intraprocedural care and post-operative care. CIRSE IR safety checklist is a modified and validated checklist from World Health Organization (WHO) surgical safety checklist and the RAD PASS from Holland, and it is divided into three sections to involve the whole procedure.
  1. Procedure planning: It contains important information as whether the patient is using anti-coagulation drugs, allergy to contrast and abnormal renal function requiring prophylaxis for contrast-induced nephropathy.
  2. Sign-in section: It includes relevant items to check if it is the correct patient, side and site to perform the planned procedure.
  3. Sign-out section: It incorporates patient orders, follow-up tests and appointments made.
- **Pain release**: Biliary system manipulation is known to be painful, thereby it will be fundamental to correctly manage patient's discomfort before and after the intervention according to their needs.
  - Pre-procedural analgesia: Biliary procedures require anaesthesiologist management, in which pain is controlled with superficial sedation, or inclusive general anaesthesia in some cases.
  - Post-procedural analgesia: Patient's pain after the procedure will be managed using the WHO analgesic ladder. First step corresponds to paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs), followed by weak opioids (codeine, hydrocodone, dihydrocodeine or tramadol) in the second step and finally moving to strong opioids (morphine, hydromorphone, oxycodone, fentanyl, methadone) as the last stage if pain is not controllable under previous

attempts. Moreover, every stair can be complemented with adjuvant treatments including antidepressants, anticonvulsants and corticosteroids within others.

- **Complication control**: All the patients will be informed about the main complications associated to the study interventions before making the decision to participate or not in this study and signing the corresponding informed consent. Since potential complications are unavoidable features of invasive treatments, physicians will recognize and manage all complications throughout the study (**Table 10**). Complications must be reported in a maximum time of 24 hours since their onset.
- **Early stop of the study**: This study will be promptly discontinued if one of the following ethical considerations is met during the interim analysis, which will be performed after the first year of recruitment and/or achieving a sample of 76 patients (38 per group).
  - Safety: The risks to the patients involved in the study unexpectedly outweigh the benefits due to severe complications.
  - Beneficence: The main study hypothesis is early proven, being unethical to maintain the exposure for a group of patients to a lower treatment arm with higher risks.
  - Futility: The interim analysis in the study demonstrates study hypothesis unprovable within the study constraints.

***Table 10**: Diagnosis and management of main complications related to percutaneous biliary stenting (self-made table). Information extracted from (15,35)*

Complication	Diagnosis	Treatment
Venous bleeding	PTC	Drainage upsizing
Arterial bleeding	Arteriography	Embolization
Cholecystitis, Pancreatitis, Sepsis	Clinical manifestations + Blood tests and cultures	Antibiotics ± Fluid resuscitation ± Cholecystostomy
Drainage bile leakage	Clinical manifestations	Drainage upsizing
Drainage occlusion	Clinical manifestations + PTC	Drainage exchange
Stent occlusion	Clinical manifestations + PTC	Balloon dilation / Re-stent
Stent dislodgement	Clinical manifestations + PTC	Re-stent

*Abbreviations: **PTC** – Percutaneous transhepatic cholangiography.*

6. STATISTICAL ANALYSIS

The statistical analysis in this study will be carried out by a blinded statistical analyst, using the IBM *Statistical Package for Social Sciences* (SPSS) software.

As being a non-inferiority clinical trial, all tests will be one-sided and will be analyzed using an alpha risk of 1%, since we need to be more rigorous than in studies that undergo a two-sided test. Accordingly, we will set a p-value < 0.01 as statistically significant and standing a 99% confidence interval for all the analysis.

In all parameters, we will calculate a p-value of one-sided or non-inferiority p-value, and a p-value of two-sided test to compare this clinical trial outcomes with other studies.

Analysis will be made by intention to treat (ITT) and per protocol (PP).

6.1. DESCRIPTIVE ANALYSIS

We will summarize occurrence of complications, severity of complications (its presence evaluated individually), technical success and clinical success, which are qualitative dependent variables, by means of proportions.

Total time of hospitalization (continuous variable, but asymmetrically distributed) and quality of life (a score discrete variable) will be summarized using medians and interquartile range. We will estimate and draw the Kaplan-Meier curves of total time of hospitalizations related to complications, according to PS and SS.

All these statistics will be also computed by both PS and SS procedures, which are the independent variables. Furthermore, we will stratify all these analyses by the covariates, in which, age will be categorized in quartiles.

6.2. BIVARIATE INFERENCE

The difference of proportions of the qualitative dependent variables between the subjects undergoing PS and SS procedures will be tested by means of Chi square, or Fisher's exact test in case that a cell has 5 or less expected cases.

The difference of medians of the discrete dependent variables will be tested through the Mann-Whitney's U test. The difference between the Kaplan Meier curves will be tested with the log-rank test.

In all these analyses we will stratify by the covariates, in which age will be categorized in quartiles.

6.3. MULTIVARIATE ANALYSIS

To assess the safety improvement related to type of intervention (global complication occurrence and individual presence according to their severity) we will use a logistic regression including the independent variables (PS or SS) and controlling for the covariates.

We will also use a logistic regression to evaluate the efficacy of the interventions (technical success and clinical success), again controlling for the covariates.

To determine non-inferiority of PS against to SS, we will compare the upper limit of the confidence interval of the difference of the safety and efficacy with the non-inferiority margin. If this upper limit is lower than the non-inferiority margin, PS will not be inferior to SS.

The QLQ-30 score according to PS and SS will be reviewed using a Poisson regression, adjusting for the covariates.

The effect of PS and SS on the total time of hospitalization will be appraised using a Cox regression controlling for the covariates.

7. ETHICAL AND LEGAL CONSIDERATIONS

This protocol will be evaluated by the **Clinical Research Ethics Committee (CEIC)** from CCSPT, being their approval mandatory before the beginning of this clinical trial. On these terms, if the CEIC presents some objections and/or recommendations, this protocol will be modified in order to accomplish all ethical basis and be accepted.

ETHICAL ASPECTS:

This clinical trial will be carried out according to human rights and ethics, established and defined in "Declaration of Helsinki" and "Principles of Biomedical Ethics from Beauchamp and Childress".

- **The Declaration of Helsinki**, as a statement of ethical principles for medical research involving human subjects, developed by the World Medical Association (WMA) in June 1964 and lastly reviewed in October 2013.
- **The Principles of Biomedical Ethics from Beauchamp and Childress**, which includes autonomy, non-maleficence, beneficence and justice, that were created in 1970 and lastly revised in 2009.
  - Autonomy: All the individuals who are offered to participate in this study will receive the "patient's information sheet" (*see annex 7*) about this study protocol using an understandable language to decide whether to participate or not. Afterwards, a written "informed consent" (*see annex 8*) from every patient that accepts to take part in this study will be required before their inclusion. Additionally, all of them will be informed that they are free to refuse to get involved or withdraw from this clinical trial at any time without any prejudice or detriment, recording their decision in "request to withdraw study consent" (see *annex 9*).
  - Non-maleficence: This clinical trial involves invasive procedures with potential complications in both treatment arms. Therefore, some security measures will be vigorously taken, in order to avoid maleficence in any of the intervened groups (see *5.8. Study safety*).
  - Beneficence: This study aims to demonstrate which interventional procedure is safest for biliary stenting as a palliative treatment in individuals with UMBO, as well as ensuring a better quality of life with fewer hospitalizations and normalized bilirubin levels to allow chemotherapy in candidate patients.

- Justice: Study population will be selected under inclusion and exclusion criteria followed by an equitable distribution to both intervention groups, avoiding any positive or negative discrimination. Furthermore, all patients in this study will be protected with a clinical trial insurance to cover any unexpected or unaccepted impair throughout the study.

This study will be developed according to the current Spanish legislation, ensuring:

- "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".
- "Ley 14/2007, de 3 de julio, de Investigación Biomédica".
- "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".

PRIVACY AND CONFIDENCIALITY

Personal and medical data from every patient involved in this study will be confidential and private, requiring their informed consent previously signed. In order to ensure patient's anonymity, numeric codes will be used for their identification. In addition, the access to this kind of data will only be available for the research team and CEIC. These are measures in accordance with the Spanish legislation:

- "Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo Europeo, de 27 de abril de 2016, relativo a la protección de personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos".
- "Ley orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".

TRANSPARENCY AND CLARITY

This clinical trial will be registered at *Registro Español de Estudios Clínicos* before its onset and its results will be published with total transparency, regardless they present with favorable data or not. Finally, the investigators in this study will declare they have no personal conflicts of interest in any aspect of this research.

8. STUDY STRENGTHS AND LIMITATIONS

This study is a single institution, open label, randomized and controlled non-inferiority clinical trial, which has some strengths and weaknesses to take into consideration.

Firstly, as a single center research, it is logistically simpler without the need for negotiations between different hospitals, it has fewer cofounding factors, and it is more economical than multicenter studies. Nevertheless, it requires a longer time for recruitment, it presents limited internal and external validity, and this specific treatment is only possible in some centers with high resources and experience. Therefore, this type of study should be the first step to achieve some evidence on percutaneous biliary stenting techniques, and it may be followed by a multiple center controlled and randomized clinical trial.

Secondly, our study cannot be blinded for the physicians nor the patient, which could lead to a detection bias. To reduce the impact of this issue, our clinical coordinator will recollect all data from this clinical trial and will upload it in the study data base; then a blinded statistician, will analyze the results without being aware of the type of intervention patients have undergone, being more objective.

Thirdly, the type of sampling we used was the non-probabilistic consecutive method, which could cause selection bias. This limitation will be decreased by employing a large simple size (N = 236 subjects), and correctly distributing the individuals into both interventional groups by an automatic randomization using a specific software.

Moreover, we expect our study to be expensive. On the one hand, being a clinical trial is the costliest type of study, but it contributes with high level of scientific evidence. On the other hand, interventional radiology procedures are expensive *per se* due to the use of last-generation devices. Even though, our study will use the same tools needed in current clinical practice for the control group, and we expect to use less gadgets for the experimental group, since we will not place an internal-external drainage and we expect to require less temporary safety catheters with its correspondent drain bags. In addition, we will request for a low-intervention clinical trial qualification, since both interventions

are accepted techniques, even if SS is the most widely used, and also for the non-commercial clinical research condition, avoiding the realization taxes costs.

Furthermore, as an operator-dependent procedure, the results of this study may vary on the interventional radiologist ability, increasing intravariability and intervariability. Thereby, it will be relevant to unify the technique of the whole research team physicians and make some workshops and trainings before the general study begins.

Besides, the main limitation as a non-inferiority clinical trial is “biocreep”, also known as the drag effect, whereby the effect of the investigated product may decline as it is compared with increasingly less effective or safe active controls. To reduce this possibility, it is important to choose a correct non-inferiority margin, which could not exceed the effect of the active comparator, because if it did so, an ineffective treatment would be wrongly considered as non-inferior.

Finally, following the latest non-inferiority clinical trials, we will work with both by ITT and PP analysis. ITT analysis considers the results during the whole follow-up period with independence of treatment complying, whereas PP analysis just takes into consideration the results of patients who strictly follow this study protocol.

9. WORKPLAN AND CHRONOGRAM

9.1. THE RESEARCH TEAM

This clinical trial research team will be configured by the following essential members:

- **Main investigator (MI)**: Individual whose main commitments will be to make an exhaustive bibliographic research on the main topic; elaborate the study protocol; join the research team to explain the protocol, answering questions and taking advice into consideration; present the final study protocol to the CEIC for its ethical evaluation and approval; and be aware of any issue developing throughout this clinical trial.
- **Clinical coordinator (CC)**: Independent observer liable for data collection from the clinical chart, database updating, and its communication to the statistician. The CC will be in close contact with the MI to notify any unexpected results from the interim analysis or any other affair during the whole clinical trial.
- **Healthcare professionals (HP)**: It includes interventional radiologists and nurses from the Interventional Radiology Department of CCSPT, which are responsible for entering data into the clinical records and performing both interventions.
- **Other personnel**: Anesthesiologist (AN), Statistical analyst (SA), Radiologists (RI), English correctors (EC).

9.2. STUDY STAGES

We expect our study to last about 4 years and 6 months. This timing may vary shorting or enlarging the research for different reasons, but mainly due to CEIC approval, and the availability of interventional radiology rooms. The chronogram can be seen in **Table 11**.

SATGE 0: PROTOCOL ELABORATION AND ETHICAL EVALUATION

- **Activity 1 – Bibliographic research and protocol elaboration** (November 2022 – January 2023): The MI will review high quality scientific papers on the main topics of the study, involving malignant biliary obstructions, percutaneous biliary stenting, primary stenting and secondary stenting. Afterwards, they will create the study protocol, mostly including hypothesis, objectives, methodological aspects, ethical and legal considerations, feasibility, clinical impact, and expected budget.

- **Activity 2 – Meeting 1** (February 2023): Presentation of this protocol to the Research Team, discussion of its main points, resolution of questions, consideration of advice, acceptance of conditions, and CC designation.
- **Activity 3 – CEIC approval** (February 2023 – May 2023): The study protocol will be evaluated and approved by the CEIC of CCSHT. The MI will make the appropriate changes to receive CEIC's acceptance. The solicitation of low-intervention clinical trial qualification and non-commercial clinical research will be also requested.
- **Activity 4 – Protocol registration** (June 2023): This clinical trial protocol will be registered at *Registro Español de Ensayos Clínicos* before its onset.

STAGE 1: STUDY COORDINATION AND TRAINING SESSIONS

- **Activity 5 – Meeting 2** (June 2023): The research team will meet to know the answers of the regulatory entities, and they will review the main points of the study protocol. Afterwards, a work chronogram will be explained, which will include periodic meetings to ensure the correct study progression.
- **Activity 6 – Training sessions** (June 2023 – July 2023): Theorical and practical formation sessions will be done to standardize both interventional procedures within the HP.

STAGE 2: GENERAL STUDY AND DATA COLLECTION

- **Activity 7 – Recruitment and randomization** (July 2023 – March 2026): This protocol will use a non-probabilistic consecutive recruitment, involving patients who consent to participate in this study, fitting the inclusion criteria and do not meeting the exclusion criteria. Afterwards, they will we randomly assigned into one of two interventional groups (ratio allocation 1:1).
- **Activity 8 – Intervention and discharge** (August 2023 – April 2026): In every session, patients will be hospitalized the previous day to intervention, undergo the biliary procedure, assessing technical success, be under observation for 24 hours and discharged. For PS this will be done in one or two sessions, varying on the need of safety catheter, whereas the SS will take a minimum of three sessions.
- **Activity 9 – Follow-ups** (September 2023 – May 2026): The follow-up sessions will be done at 48 hours since discharge and then weekly for 6 weeks. During all these sessions we will assess an exhaustive anamnesis, physical exploration, and perform

a blood test to evaluate liver function and BrT levels. At 3 or 6 weeks, varying on if pre-stent BrT levels, we will evaluate clinical success and the EORTC QLQ-30 questionnaire. Besides, within the initiation of the procedures and after 30 days of its finalization, we will collect the data from occurrence and severity of complications and the total time of hospitalization related to them.

- **Activity 10 – Data collection** (October 2023 – June 2026): Physicians will register all the information obtained in the follow-ups in patients' clinical chart. Afterwards, the CC will recollect all data, upload it into the study database, and transfer it to the SA.
- **Activity 11 – Interim analysis** (June 2024 – August 2024): When we achieve a recruitment of 76 patients (involving 38 individuals from each intervention groups), or after 1 year of general study onset, we will perform an interim analysis to ensure the safety of both procedures, avoiding the exposure of a much lower treatment arm or a harmful group to any of the participants.

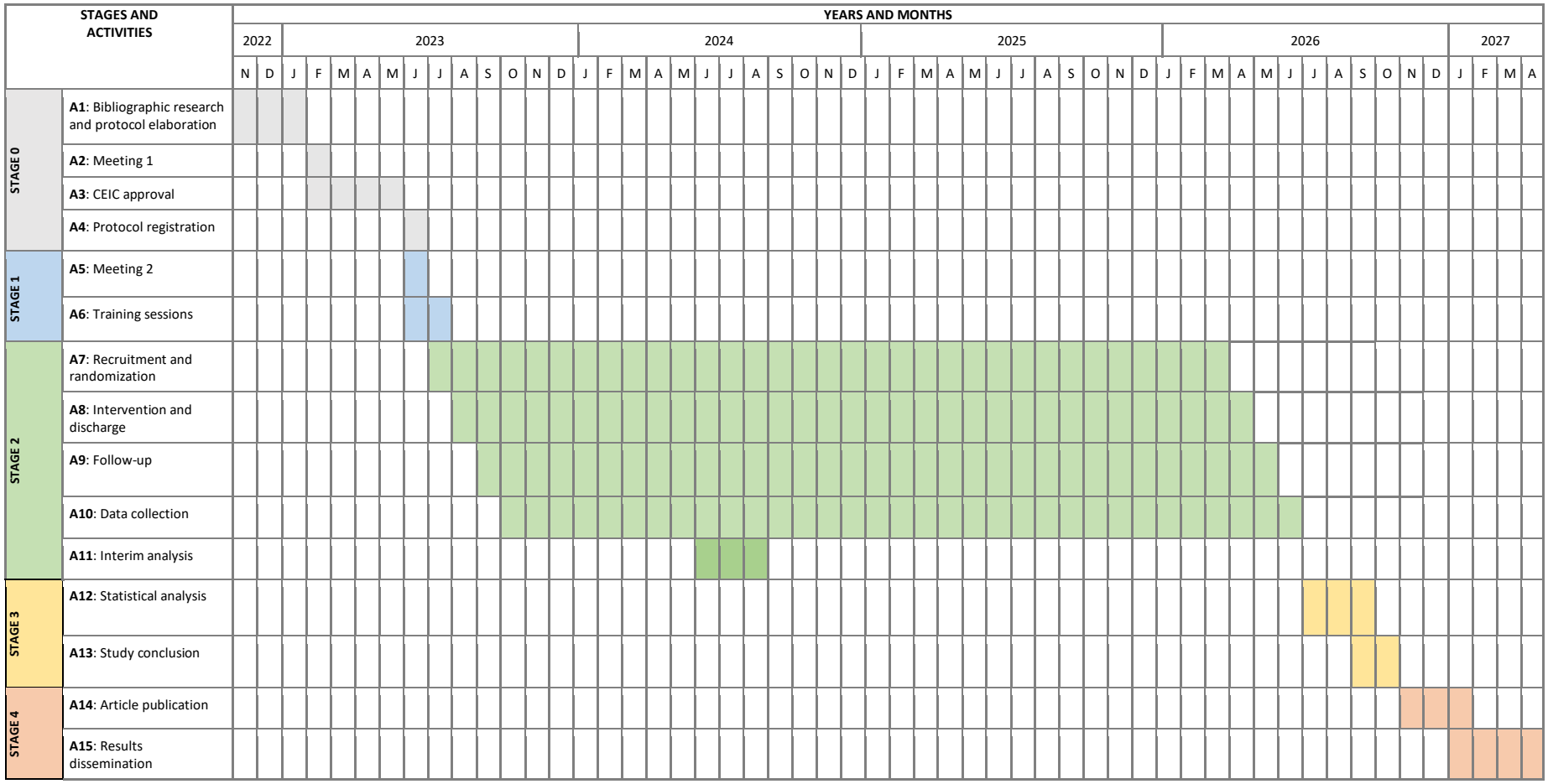
STAGE 3: FINAL DATA ANALYSIS AND RESULTS

- **Activity 12 – Statistical analysis** (July 2026 – September 2026): The SA, who will be masked for the type of intervention every patient has undergone, will make the statistical analysis and results of this study, after we have all data collected and uploaded into the database.
- **Activity 13 – Study conclusions** (September 2026 – October 2026): The statistical analysis made by SA will be used for the MI and CC to draft the discussion and conclusions of this study.

STAGE 4: PUBLICATION AND DISSEMINATION OF RESULTS

- **Activity 14 – Article publication** (November 2026 – January 2027): The MI will elaborate the final article, mainly including background, materials and methods, results, discussion, and conclusion. Then, it will be reviewed by EC, and finally sent to the most impact journals of radiology and interventional radiology, to publish it.
- **Activity 15 – Results dissemination** (January 2027 – April 2027): The results in this study, favorable or not, will be exposed in national and international conferences and congresses of interventional radiology to contribute to medicine progress.

***Table 11**: Chronogram of this study.*



Months are chronologically ordered: J – January, F – February, M – March, A – April, M – May, J – June, J – July, A – August, S – September, O – October, N – November, D – December

10. BUDGET

10.1. PERSONNEL COSTS

The main research team members (MI, CC, HP, AN and RI) involved In this clinical trial are current employees of CCSPT, what means that their activities will be enrolled as part of their normal clinical practice, and they will not cause additional costs.

10.2. SERVICES EXPENSES

Firstly, we will need the services of a SA to create the randomization software to allocate all participants into one of both intervention groups, and to make the statistical analysis. We expect to need his/her work for 10 hours annually, and 40 additional hours for final data analysis. Thereby, requiring a total of 80 hours of work, paid at 30€/hour, the final cost will be approximately 2.400€.

Secondly, we will also outsource a Clinical Research Organization (CRO) as an external control of our clinical trial, which has an approximate cost of 12.000€.

Thirdly, we will require a high-level English editor to correct the article before its publication, a service normally costing 100€ in high level of editing.

10.3. INSURANCE EXPENSES AND TAXES COSTS

As explained in the Stage 0 of our workplan, we will request for low intervention clinical trial qualification, since both techniques involved in this clinical trial are valid and can be used in current clinical practice. Moreover, the techniques used for diagnosis and follow-ups do not suppose any risk increase or work overload, compared to ordinary clinical practice. If the CEIC endorses this clinical trial condition, all our participants will be covered by the current hospital insurance. Although, it is important to take into account that clinical trial insurances normally cost 100€/participant.

Likewise, we will solicitate the condition of non-commercial clinical research, assuming no costs for the realization taxes.

10.4. MATERIAL EXPENSES

The performance of both procedures, post-intervention control and follow-up sessions will be enrolled at the CCSPT, as in normal clinical practice, because it will not require additional materials, and it will not differ from habitual workload in interventional rooms. The material costs of a biliary procedure are around 1.600€, without considering the personnel and angiograph costs, being the itemized costs as follows:

- Biliary access set = 90€
- Introducer sheath (8Fr) = 33€
- Hydrophilic stiff wire = 74€
- Super stiff Amplatz wire = 102€
- *Berenstein* catheter (5Fr) = 19€
- *Wallflex* Boston prothesis = 1.293€

Additionally, we will also require printing some documents, involving the EORTC QLQ-30 questionnaire, CIRSE IR safety checklist, patient's information sheet, informed consent, request to withdraw study consent, and case report form. In total, there will be necessary 10 pages for each patient, being a total cost of 118€ if we pay 0.05€/page.

10.5. PUBLICATION AND DIVULGATION COSTS

All the publications derived from this clinical trial will be open access. The costs of Elsevier Gold Open Access publication fee, which allows immediate and permanent access by everyone, is approximately 2.950€.

The regular cost for European Conference on Interventional Oncology (ECIO) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE), are780€ and 950€ per participant, respectively. Additionally, we expect the travel costs to be 1.500€.

In order to compensate publication and divulgation expenses, we will apply for *Sociedad Española de Radiología Vascular e Intervencionista* (SERVEI) and *Sociedad Española de Radiología Médica* (SERAM) grants.

The summary of the estimated costs to perform this clinical trial are in **Table 12**.

***Table 12**: Total estimated budget of this clinical trial (self-made table).*

Item	Quantity (nº)	Price per unit (€)	Total price (€)
Service expenses			
Statistician work	80 hours	30€/hour	2.400€
CRO	1 contraction	12.000€	12.000€
Article editing	1 contraction	100€	100€
Insurance expenses	1 contraction	23.600€	0€ (low intervention)
Material expenses			
Biliary materials	236 units	1.600€	0€ (already owned)
Printing costs	2.360 pages	0.05€/page	118€
Publication and divulgation costs			
Publication expenses	1 publication	2.950€	2.950€
ECIO congress	2 inscriptions	780€	1.560€
CIRSE congress	2 inscriptions	950€	1900€
Travel expenses	2 individuals	1.500€	3.000€
			24.028€

11. FEASIBILITY

We strongly believe this clinical trial will be feasible for different reasons.

To start with, our medical institution is provided with two interventional rooms and their respective angiographs, as well as all the material and professionals required to perform biliary interventions. Moreover, this study will not increase material costs nor workload in interventional rooms since it will be similar to the current clinical practice. Even more, we expect to reduce the costs related to PBS and require fewer days of hospitalization to perform the procedure, consequently leading to a more cost-effective intervention and relieving the burden caused by multiple-phase biliary stenting.

Likewise, it is important to remark the fact that our hospital has a large volume of interventional biliary interventions (see *annex 3*), and our research team has already been enrolled in different clinical trials. This explains why our department will be prepared to assume this clinical trial, not only for their expertise in biliary management and research, but also for the expected light recruitment, even if this study is a non-inferiority clinical trial with a large sample size, accomplished by a single institution.

Furthermore, we will request for low intervention clinical trial qualification, supported by the fact that both interventions in the experimental and control group are valid and can be used in clinical practice. In addition, we will solicitate the condition of non-commercial clinical research. Accordingly, if both requests are solved favorable, the patients taking part in this research will be covered by the hospital clinical insurance, and we will not need to pay realization taxes.

In addition, we will apply for SERAM and SERVEI grants to compensate the costs derived from printing, article edition, publication and divulgation, SA work and CRO outsourcing.

Besides, it is relevant to mention that our protocol will be evaluated and approved by the CEIC and registered at *Registro Español de Ensayos Clínicos* before its onset, to comply with the ethical aspects and to ensure total transparency. Finally, the results, favorable or not, will be published and divulgated to contribute to medicine progress.

12. CLINICAL AND HEALTHCARE IMPACT

Malignant biliary obstructions (MBO) are usually diagnosed in advanced stages with no options for surgical treatments, which is the only curative option; thereby, these patients require some palliative measures to manage their debilitating symptoms and associated complications.

The management of the obstructive jaundice can be done under percutaneous biliary stenting, either using primary stenting (PS) or secondary stenting (SS). The most common used technique is SS, probably because it allows an extended access to the biliary tract giving more security to the interventional radiologists.

However, there is some evidence determining that PS could be a safer technique, with less complications rates. That is supported by the fact that percutaneous transhepatic biliary stents (PTBS), being the first step in SS, can increase the risk of bleeding by mechanical irritation or arterial wall damage, facilitating the formation of blood clots that could acutely occlude the stent in the following step of SS. Moreover, PTBS seem to be more likely to produce cholangitis or pancreatitis, since firstly they occlude the cystic duct and pancreatic duct through their way; secondly, they maintain the ampulla of Vater permanently opened to enteric microbiota; and thirdly they require daily flushes that could push some external bacteria inside the biliary tract.

Additionally, it is likely to expect that the use of PS could improve patient's quality of life (QoL) by avoiding the complications related to PTBD, reducing the days of hospitalization and sedation required in SS, and preventing the psychological impact of carrying an exteriorized catheter with a drainage bag outside their body for some days.

Furthermore, the possible shorten in hospital stays, and anesthesia and medication requirements by implementing PS could probably reduce total healthcare costs and interventional radiology workload in our sanitary system.

This clinical trial is expected to clarify which technique is safer to perform a PBS in patients with unresectable MBO, in terms of occurrence of complications (main variable), their severity, and days of hospitalization related to them. It will also assess the technical and clinical efficacy of both procedures, and the impact in patient's QoL.

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14. ANNEXES

ANNEX 1: ANATOMIC VARIATIONS OF THE BILIARY TREE

***Table 13**: Right hepatic duct anatomic variants. Extracted from (11).*

Variant	Frequency	Description
A1	62.2%	It is the classic pattern, in which the right posterior duct unifies to the left side of the right anterior duct, originating the right hepatic duct.
A2	19%	It is the triple confluence of the right anterior duct, right posterior duct, and left duct, creating the CHD.
A3	11%	The right posterior duct merges to the left hepatic duct before its confluence with the right anterior duct.
A4	5.8%	It involves a right posterior duct that drains directly to the CHD
A5	1.6%	The right posterior duct drains into the cystic duct

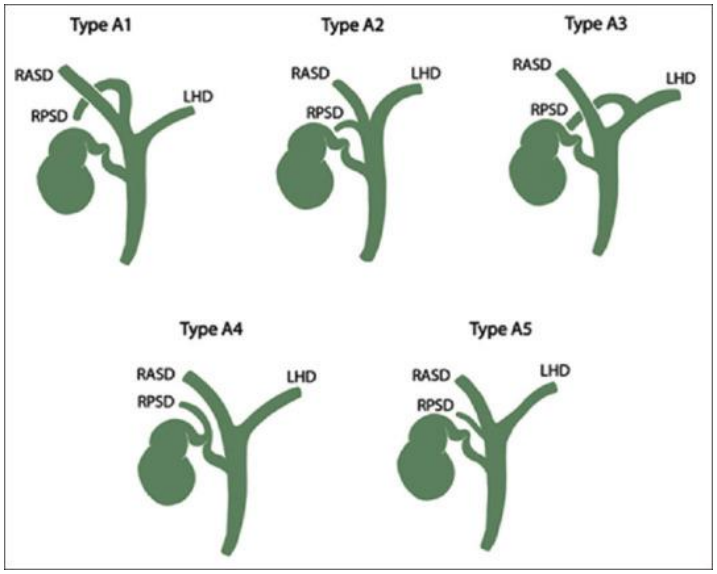

***Figure 13**: Right hepatic duct anatomic variants. Extracted from (10).*

***Table 14**: Left hepatic duct anatomic variants. Extracted from (11).*

Variant	Frequency	Description
B1	63%	Segment IV drains into the left hepatic duct.
B2	16%	Segment IV duct opens to the CHD separately from segments II and III.
B3	4%	Segment IV duct meets the right anterior bile duct.
B4	1%	Segment IV drains directly into the CHD.
B5	3%	Segment IV duct drains in segment II duct.
B6	13%	Segments II and III join firstly, and then meet the segment IV to create the left hepatic duct.

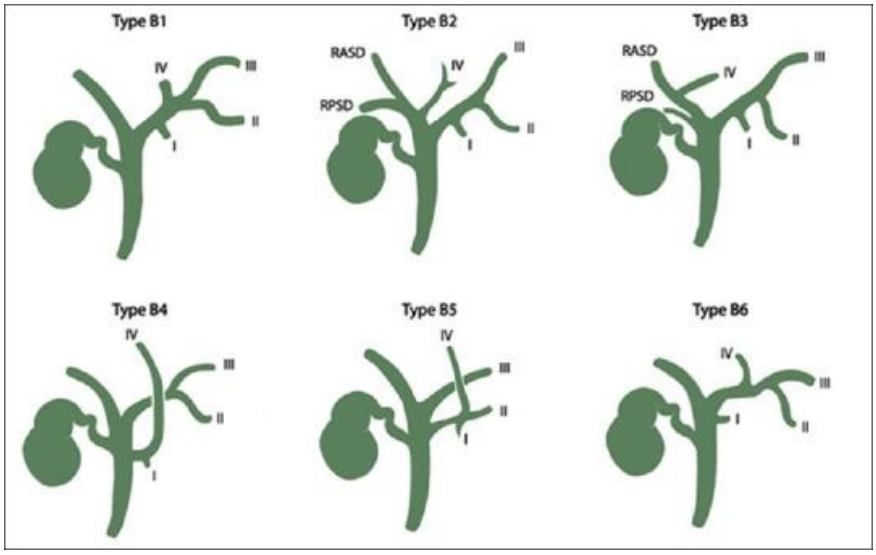

***Figure 14**: Left hepatic duct anatomic variants. Extracted from (10)*

***Table 15**: Cystic duct anatomic variants. Extracted from (5).*

Variant	Frequency	Description
Medial insertion	10-17%	It drains into the left side of the CHD
Low insertion	9%	It drains into the distal third of the CHD
Parallel course	1.5-25%	The cystic duct and CHD travel parallelly at least during a segment of 2cm

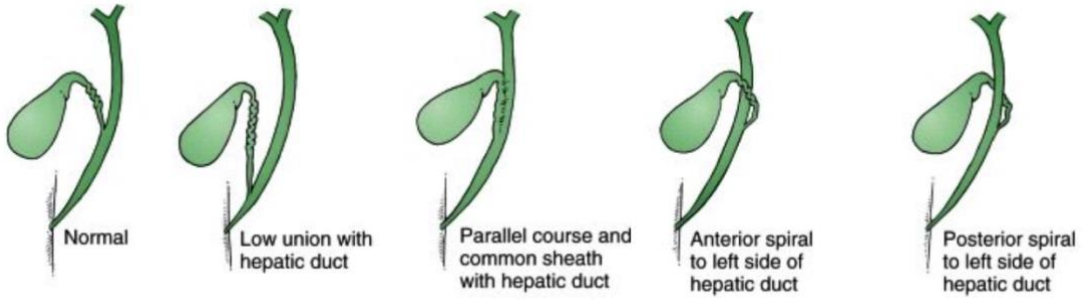

***Figure 15**: Cystic duct anatomic variants. Extracted from (9)*

ANNEX 2: CRITERIA FOR RESECTABILITY IN PANCREATIC CANCERS

***Table 16**: Criteria defining resectability in pancreatic adenocarcinomas according to NCCN guidelines. Extracted from (68).*

	Venous invasion	Arterial invasion
RESSECTABLE	▪ SMV/PV: No tumor contact, or contact < 180º without vein contour irregularity	▪ SMA, CA, CHA: No arterial tumor contact
BORDERLINE RESSECTABLE	▪ SMV/PV: Solid tumor contact ≥ 180º, contact < 180º with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. ▪ IVC: Solid tumor contact	**Pancreatic head/uncinate process** ▪ SMA: Solid tumor contact < 180º ▪ CHA: Solid tumor contact without extension to CA/hepatic artery bifurcation allowing for safe and complete resection and reconstruction. ▪ Presence of variant arterial anatomy (RHA, CHA) and the presence of tumor contact as it may affect surgical planning. **Pancreatic body/tail** ▪ CA: Solid tumor contact < 180º ▪ CA: Solid tumor contact ≥ 180º without involvement of the aorta and with intact and uninvolved GDA
UNRESSECTABLE LOCALLY ADVANCED	**Head/uncinate process** ▪ SMV/PV: Unreconstructible due to tumor involvement/occlusion ▪ Contact with most proximal draining jejunal branch into SMV **Body and tail** ▪ SMV/PV: Unreconstructible due to tumor involvement/occlusion	**Head/uncinate process** ▪ SMA, CA: Solid tumor contact ≥ 180º ▪ Solid tumor contact with the 1st jejunal SMA branch **Body and tail** ▪ SMA, CA: Solid tumor contact ≥ 180º ▪ Solid tumor contact with the CA and aortic involvement
UNRESECTABLE METASTATIC	Distant metastasis (including non-regional lymph node metastasis)	

*Abbreviations: **SMV** – superior mesenteric vein, **PV** – portal vein, **SMA** – superior mesenteric artery, **CA** – celiac artery, **CHA** – common hepatic artery, **PHA** – proper hepatic artery.*

ANNEX 3: ACTIVITY DATA FROM CCSPT 2021

Datos de actividad

Fechas del 31/12/2020 a 31/12/2021

servei
SOCIEDAD ESPAÑOLA DE RADIOLOGÍA VASCULAR E INTERVENCIONISTA

DATOS DE LOS HOSPITALES

- Consorci Corporació Sanitaria Parc Taulí de Sabadell (Barcelona)

DATOS DE LAS PROVINCIAS

- Barcelona

DATOS DE LAS COMUNIDADES AUTÓNOMAS

- Cataluña

INTERVENCIONISMO NO VASCULAR GENERAL	81	101
- ABLACIONES POR MW	2	
# ABLACIÓN HEPÁTICA	2	
- ABLACIONES POR RF	6	
# ABLACIÓN HEPÁTICA	6	
- BIOPSIAS	44	
# BAG HEPÁTICA	2	
# BAG RENAL	42	
- DRENAJES	11	34
# DRENAJE COLECCIONES	13	
# TORACOCENTESIS	10	
# CATÉTER TUNELIZADO PARACENTESIS/TORACOCENTESIS	11	11
- INFILTRACIONES / INYECCIÓN DE SUSTANCIAS	45	

Datos de actividad

Fechas del 31/12/2020 a 31/12/2021

servei
SOCIEDAD ESPAÑOLA DE RADIOLOGÍA VASCULAR E INTERVENCIONISTA

NEUROLISIS 45

- OTROS 23 15

SELLADO/TRATAMIENTO PERCUTÁNEO DE FÍSTULAS 4

TRATAMIENTO PERCUTÁNEO DE PSEUDOANEURISMAS 15 15

EXTRACCIÓN DE CUERPO EXTRAÑO NO VASCULAR 4

- PAAF 2

PAAF 2

INTERVENCIONISMO NO VASCULAR ÓRGANO ESPECÍFICO 2923 778

- BILIAR 777 317

COLANGIOGRAFÍA PERCUTÁNEA 341 14

COLANGIOGRAFÍA TRANSKEHR 32

DRENAJE BILIAR 224 111

DRENAJE BILIAR + PRÓTESIS 42

DRENAJE BILIAR + DILATACIÓN VÍA BILIAR 44

COLECISTOSTOMÍA PERCUTÁNEA 2 28

PRÓTESIS BILIAR 47 39

DILATACIÓN VÍA BILIAR 44 59

BIOPSIA BILIAR ENDOLUMINAL 20 21

TRATAMIENTO PERCUTÁNEO DE CÁLCULOS BILIARES 13 13

- CONTROLES, CAMBIOS Y RETIRADA DE CATÉTERES 1416

CAMBIO DE CATÉTER INTERVENCIONISTA 704

ANNEX 4: CIRSE IR CLASSIFICATION SYSTEM FOR COMPLICATIONS

***Table 17**: CIRSE classification system for complications. Extracted from (56).*

Grade 1	Complication during the procedure which could be solved within the same session; no additional therapy, no post-procedure sequelae, no deviation from the normal post-therapeutic course.
Grade 2	Prolonged observation including overnight stay (as a deviation from the normal post-therapeutic course < 48h); no additional post-procedure therapy, no post-procedure sequelae.
Grade 3	Additional post-procedure therapy or prolonged hospital stay (> 48h) required; no post-procedure sequelae.
Grade 4	Complication causing a permanent mild sequela (resuming work and independent living)
Grade 5	Complication causing a permanent severe sequela (requiring ongoing assistance in daily life)
Grade 6	Death

ANNEX 5: EORTC QLQ-30 QUESTIONNAIRE

The following questionnaire was obtained for academic use with the permission of the European Organization for Research and Treatment of Cancer (EORTC) (69).

SPANISH (SPAIN)

EORTC QLQ-C30 (versión 3)

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

Por favor ponga sus iniciales: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Su fecha de nacimiento (día, mes, año): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Fecha de hoy (día, mes, año): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

		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

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

ANNEX 6: CIRSE IR SAFETY CHECKLIST

Nombre del Paciente:
Número de Historia:
Fecha de nacimiento:
Sexo: Hombre ○ Mujer ○
Servicio:
Médico Remitente:

Lista de Verificación para la Seguridad del Paciente en Radiología Intervencionista*

Procedimiento:
Fecha:

CIRSE
Cardiovascular and Interventional Radiological Society of Europe

PLANIFICACIÓN DEL PROCEDIMIENTO	SI	NO	N/A
Consultado con el medico remitente	☐	☐	☐
Pruebas de imagen revisadas	☐	☐	☐
Historial médico relevante revisado	☐	☐	☐
Consentimiento informado firmado	☐	☐	
Profilaxis de la Nefropatía Inducida por Contraste	☐	☐	☐
Equipo y material específico disponible/solicitado	☐	☐	☐
Ayuno del paciente solicitado	☐	☐	☐
Exámenes de laboratorio solicitados	☐	☐	☐
Necesidad de anestesista	☐	☐	☐
Suspensión de la terapia anticoagulante	☐	☐	☐
Necesidad de cama en UCI	☐	☐	☐
Necesidad de profilaxis por reacción	☐	☐	☐

ADMISIÓN	SI	NO	N/A
Presentación de los miembros del equipo	☐	☐	
Documentación completa del paciente	☐	☐	☐
Verificar paciente/lado/sitio de intervención	☐	☐	
Ayuno del paciente	☐	☐	☐
Acceso intravenoso	☐	☐	☐
Equipo de monitorización conectado	☐	☐	☐
Pruebas de coagulación / resultados del	☐	☐	☐
Alergias y/o profilaxis revisadas	☐	☐	
Antibióticos y/u otras drogas administradas	☐	☐	☐
Informar sobre complicaciones/consentimiento	☐	☐	

ALTA HOSPITALARIA	SI	NO	N/A
Informe de la intervención	☐	☐	
Signos vitales normales durante el procedimiento	☐	☐	☐
Registro de medicación y medio de contraste utilizados	☐	☐	☐
Exámenes de laboratorio solicitados	☐	☐	☐
Todas las muestras etiquetadas y enviadas al laboratorio	☐	☐	☐
Paciente informado sobre resultados del procedimiento	☐	☐	☐
Instrucciones explicadas para después del	☐	☐	☐
Pruebas de seguimiento y de imagen solicitadas	☐	☐	☐
Consulta de seguimiento concertada	☐	☐	☐
Resultados del procedimiento comunicados al médico remitente	☐	☐	

Nombre: Nombre: Nombre:

Firma: _____ Firma: _____ Firma: _____

* * Modificado de las listas de verificación quirúrgica RADPASS y OMS

***Figure 16**: CIRSE IR safety checklist. Extracted from (70)*

ANNEX 7: PATIENT'S INFORMATION SHEET

HOJA DE INFORMACIÓN AL PACIENTE SOBRE EL ESTUDIO

Nombre del estudio: *Evaluating the safety of percutaneous primary and secondary biliary stenting in unresectable malignant biliary obstructions*

Hospital: Consorci Corporació Sanitària Parc Taulí (CCSPT)

Investigador principal: Dra. Arantxa Gelabert Barragán

Bienvenido/a,

Le invitamos a participar en nuestro ensayo clínico, realizado por el Departamento de Radiología Vascular e Intervencionista del Consorci Corporació Sanitària Hospital Taulí. Este estudio ha sido evaluado y aprobado por el Comité de Ética en Investigación Clínica (CEIC) de nuestra institución. Nuestra intención es informarle sobre los motivos que impulsan este estudio y qué beneficios puede ofrecerle, para que usted pueda escoger libremente si participar o no. Lea detenidamente el siguiente documento, pregunte al equipo cualquier duda que le surja, y tómese el tiempo que necesite para tomar su decisión de participar. Le recordamos, que siempre podrá revocar su consentimiento y retirarse del estudio sin sufrir ningún prejuicio sobre su asistencia sanitaria.

DESCRIPCIÓN Y OBJETIVOS DEL ESTUDIO

Las obstrucciones malignas de la vía biliar impiden el correcto drenaje de la bilis hacia el intestino delgado. La bilis es una sustancia producida por nuestro hígado que se encarga principalmente de facilitar la absorción de las grasas de nuestra dieta, y excretar desechos de nuestro cuerpo en las heces (principalmente bilirrubina). Por todo ello, cualquier problema que impida su correcto drenaje, produce síntomas como náuseas, vómitos, debilidad, piel amarillenta y picor generalizado, necesitando la colocación de drenajes y/o prótesis (mallas elásticas) para resolverlo.

Cuando la vía biliar no se puede desobstruir bajo endoscopia (pasando un tubo desde la boca hacia el intestino y entrar a la vía biliar), las prótesis biliares se colocan de forma percutánea (pasando tubos a través de la piel hasta el hígado y entrar en la vía biliar).

Actualmente, la técnica más utilizada de colocación de prótesis de forma percutánea es multifásica, comprendiendo tres pasos: (paso 1) colocación de un drenaje interno-externo, (paso 2) liberación de la prótesis dejando un catéter de seguridad, (paso 3) retirada del catéter de seguridad. Entre cada fase hay un promedio de 2-4 días, lo que lo hace un método largo, requiriendo varios días de ingreso, un mínimo de tres sedaciones (una por procedimiento), y asociando posibles complicaciones en cada paso.

Existe la posibilidad de realizar la misma intervención de forma percutánea en una sola fase, desplegando directamente la prótesis biliar, sin la necesidad de colocar previamente un drenaje interno-externo (paso 1). En este procedimiento, si se cree conveniente, se puede dejar un catéter de seguridad durante 24-48 horas, para asegurar que la prótesis no se cierra durante las primeras horas tras su liberación (paso 3).

Nuestro objetivo principal es comparar ambas técnicas percutáneas en el mismo subgrupo de pacientes: individuos con obstrucciones malignas e irresecables de la vía biliar en los que no se puede realizar la colocación protésica de forma endoscópica, o bien, no se ha conseguido; para demostrar que la colocación percutánea de prótesis biliares monofásica es no inferior a la técnica multifásica en términos de seguridad (ocurrencia de complicaciones) y eficacia (correcta expansión de la prótesis), en los pacientes que cumplan las características requeridas en este estudio. También valoraremos y compararemos la normalización de la bilirrubina a las 3 o 6 semanas (relevante para permitir la administración de quimioterapia), el total de días hospitalizados en relación con las complicaciones, y el impacto que tienen ambos procedimientos en la calidad de vida de estos pacientes.

METODOLOGÍA E INTERVENCIÓN

En este estudio participarán un total de 236 pacientes, los cuales serán distribuidos de forma aleatoria a uno de los dos grupos de intervención. En el grupo A o experimental, la colocación percutánea de la prótesis biliar se hará en un solo tiempo (monofásico), mientras que en el grupo B o control, la liberación de la prótesis constará de los 3 pasos (multifásica), ya previamente comentados.

Antes del procedimiento, usted recibirá una consulta preanestésica con el equipo de anestesia de nuestro centro para valorar si es seguro administrarle sedación profunda, necesaria para la colocación de la prótesis biliar.

Si usted cumple los requisitos anestésicos, se le realizará una prueba de imagen (TAC o resonancia magnética) para planificar el procedimiento según necesidad y en función de las pruebas que le hayan realizado anteriormente. Seguidamente, se le asignará un día para realizar la intervención, y se le informará de los signos de alarma que requieren de re-consulta.

Después de la colocación de la prótesis, se le realizarán dos visitas de seguimiento, una a las 3 semanas y otra a las 6 semanas, para valorar la correcta resolución de los síntomas y detectar posibles complicaciones derivadas de la intervención. Además, también se le realizarán analíticas de sangre para objetivar la mejora de la función del hígado.

BENEFICIOS Y RIESGOS DEL ESTUDIO

Las dos técnicas implicadas en este estudio están aceptadas en la práctica clínica, dado que ambas han demostrado ser eficaces para la resolución de los síntomas y normalización de la función hepática en pacientes con obstrucciones malignas biliares.

Los riesgos a los que se somete están relacionados con las posibles complicaciones derivadas de ambos procedimientos: riesgo de sangrado; riesgo de infección (colecistitis, pancreatitis, sepsis); pérdida de bilis por el drenaje; desplazamiento de la prótesis; y obstrucción del drenaje o la prótesis biliar, ambos condicionando la reaparición de los síntomas iniciales.

ALTERNATIVAS AL PROCEDIMIENTO

Si usted decide no participar en el presente estudio, la colocación percutánea de la prótesis biliar será de forma multifásica, dado que se trata del tratamiento estándar en las salas de radiología vascular e intervencionista. El seguimiento del paciente y el control de las complicaciones relacionadas con la intervención y la enfermedad será el que se estipula en el protocolo de nuestra institución.

CONFIDENCIALIDAD

Todos los datos personales y sanitarios de los participantes del estudio serán gestionados y almacenados de forma confidencial en nuestra base de datos desde el primer momento, tal y como se estipula en el "Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo Europeo, de 27 de abril de 2016, relativo a la protección de personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos", y en la "Ley orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales". Cada integrante será asignado a un código numérico, y solo tendrán acceso a dicha información los investigadores del estudio y el CEIC. Los pacientes tendrán derecho a revisar la información recopilada sobre ellos y podrán corregirla en caso de error.

DIFUSIÓN DE RESULTADOS

El protocolo será registrado en el "Registro Español de Ensayos Clínicos", previamente a su iniciación, y al finalizar el estudio, la intención es publicar los resultados en diferentes plataformas y revistas científicas, así como presentarlos a diferentes congresos de Radiología Vascular e Intervencionista, para contribuir al avance de la medicina. Remarcamos que sus datos no se publicaran bajo ningún concepto, asegurando su privacidad en todo momento.

PARTICIPACIÓN Y COMPENSACIÓN ECONÓMICA

La participación a este ensayo clínico es totalmente voluntaria y usted no recibirá ningún tipo de compensación económica por ello. Asimismo, los investigadores tampoco recibirán ninguna remuneración económica derivada de la investigación.

Si usted decide participar, deberá rellenar y firmar el consentimiento informado que le facilitaremos después de comprender la información proporcionada en esta hoja y resolver cualquier duda que le haya surgido. Nuevamente, le recordamos que puede revocar su autorización en cualquier momento del estudio sin sufrir ningún detrimento sobre su salud ni en la calidad de su asistencia sanitaria.

RESPONSABILIDAD Y ASEGURADORA

Al considerarse un "estudio de bajo nivel de intervención", respaldado por la normativa oficial europea y la legislación española actual, cualquier perjuicio sobre su salud derivado de este estudio seria cubierto por el seguro de responsabilidad civil del cual dispone nuestro centro.

CONTACTO

Ante cualquier duda antes, durante o después de la realización del siguiente estudio, podrá ponerse en contacto con: _____

ANNEX 8: INFORMED CONSENT

DOCUMENTO DE CONSENTIMIENTO INFORMADO DEL PACIENTE

Yo, _____, con documento de identificación personal (DNI/NIE) _____, declaro que:

- He leído y entendido toda la información que aparece en la "hoja de información al paciente sobre el estudio".
- Estoy satisfecho/a con la cantidad de información proporcionada.
- He podido exponer cualquier duda y se me ha resuelto adecuadamente,
- Entiendo los potenciales riesgos y beneficios derivados de participar en este estudio.
- No he ocultado ninguna información esencial sobre mis antecedentes ni mi enfermedad que puedan ser relevantes para los médicos que me atienden.
- Comprendo que mi participación es voluntaria y no remunerada.
- Comprendo que mis datos personales y médicos serán confidenciales y exclusivamente usados para fines de investigación.
- Entiendo que puedo revocar este consentimiento informado en cualquier momento sin perjudicar mi asistencia sanitaria.

En consecuencia:

- Doy libremente mi consentimiento para participar en el presente ensayo clínico, y estoy conforme con que la información obtenida pueda utilizarse en futuras investigaciones.
- Acepto que los investigadores puedan contactarme en un futuro si es preciso.

Signatura del paciente: Signatura del investigador:

☐ Acepto

☐ No acepto

Lugar y fecha: _____, _____ de ____ del año _____

ANNEX 9: REQUEST TO WITHDRAW STUDY CONSENT

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo, _____, con documento de identificación personal (DNI/NIE) _____, revoco el consentimiento informado previamente firmado para la participación en el estudio *Evaluating the safety of percutaneous primary and secondary biliary stenting in malignant biliary obstructions*.

Signatura del paciente: Signatura del investigador:

Lugar y fecha: _____, _____ de ____ del año _____

ANNEX 10: CASE REPORT FORM

HOJA DE RECOGIDA DE DATOS SOBRE COVARIABLES DE LOS PACIENTES PARTICIPANTES EN EL ESTUDIO

Nombre del estudio: *Evaluating the safety of percutaneous primary and secondary biliary stenting in unresectable malignant biliary obstructions*

Hospital: Consorci Corporació Sanitària Parc Taulí (CCSPT)

Investigador al cargo de la recogida: _____

Código numérico asignado: _____

Lugar y fecha: _____, _____ de _____ del año _____

- **Fecha de nacimiento** (día/mes/año): ____ / ____ / ________
- **Sexo**:
  - ☐ Masculino
  - ☐ Femenino
- **Índice de masa corporal** (IMC = kg/m2): **Peso** ____ kg / **Talla** ____ m
  - ☐ Bajo peso: IMC < 18.5
  - ☐ Peso normal: IMC 18.5 – 24.9
  - ☐ Sobrepeso: IMC 25-29.9
  - ☐ Obesidad: IMC ≥ 30
- **Tipo de tumor**:
  - ☐ Colangiocarcinoma
  - ☐ Carcinoma de vesícula biliar
  - ☐ Ampuloma
  - ☐ Hepatocarcinoma
  - ☐ Cáncer de páncreas
  - ☐ Metástasis/Compresión nodal
- **Localización de la obstrucción biliar**:
  - ☐ Baja (inferior a la inserción del conducto cístico)
  - ☐ Alta (superior a la inserción del conducto cístico)
- **Intento previo de ERCP**:
  - ☐ Si
  - ☐ No
- **Presencia de colangitis**:
  - ☐ Si
  - ☐ No