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Final degree project

USE OF INDOCYANINE GREEN TO REDUCE POSTOPERATIVE PANCREATIC FISTULA, THE MOST COMMON COMPLICATION OF CEPHALIC DUODENOPANCREATECTOMY

A unicentric quasi-experimental study

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ABREVIATIONS

ADPI: Inferior pancreaticoduodenal arteries

AEC: Asociación Española de Cirujanos

BL: Biochemical Leak

CDP: Cephalic Duodenopancreatectomy

CEA: Carcinoembryonic antigen

CEIC: Committee of Clinical Investigation

CT: Contrast-enhanced computed tomography

DGE: Delayed gastric emptying

DM: Data Manager

DM: Diabetes mellitus

E-AHPBA: European-African Hepato-Pancreato-Biliary Association

ERCP: Endoscopic retrograde cholangiopancreatography

EUS: Endoscopic ultrasonography

FAP: Familial adenomatous polyposis

FI: Fluorescence Imaging

FNA: Fine-needle aspiration

GI: Gastrointestinal

HC: Hospital coordinator

ICG: Indocyanine green

IHPBA: International Hepato-Pancreato-Biliary Association

ISGPF: International Study Group of Pancreatic Fistula

ISGPS: International Study Group in Pancreatic Surgery

MI: Main investigator

NCCN: National Comprehensive Cancer Network

NPO: Nothing by mouth

PDAC: Pancreatic ductal adenocarcinoma

POAP: Postoperative acute pancreatitis

POD: Postoperative day

POH: Postoperative hyperamylasemia

POPF: Postoperative pancreatic fistula

RT: Research team

SMA: Superior mesenteric artery

SMV: Superior mesenteric vein

ABSTRACT

Background: The pancreatic fistula is the most common complication after the cephalic pancreaticoduodenectomy. Despite numerous trials aimed at reducing its incidence, it still ranges between 3-45% of pancreatic operations, being the main determinant of serious postoperative morbidity and mortality and playing a major role in terms of hospital stay and economic impact. The exact pathophysiology of fistulas and why they appear is not yet known, but several studies have begun to suggest that fistulas may be related to hypoperfusion of the pancreatic remnant after surgery with following failure of the pancreatico-enteric anastomosis. On the other hand, we know that indocyanine green is a well established tool to assess intraoperative tissue perfusion.

Objectives: The aim of this study is to assess whether the use of indocyanine green significantly reduces the occurrence of pancreatic fistulas in patients who undergo duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta*. Secondary objectives are to assess whether the use of indocyanine green modifies the extent of surgical resection of the pancreas during the duodenopancreatectomy, and if it reduces the hospital stay and the 30-day mortality.

Design: It is a unicentric quasi-experimental study, aiming to compare the occurrence of pancreatic fistulas in patients who underwent the cephalic duodenopancreatectomy without indocyanine green and the patients who will undergo the surgery with indocyanine green.

Participants and methods: 132 participants will be enrolled using a consecutive sample, and a time of recruitment will be of 26 months. The data of the patients operated without indocyanine green will be extracted from an existing database of the hospital and the data of the patients who will undergo the surgery with indocyanine green will be collected during the perioperatory period and follow up. The results will be analyzed and compared by a statistician.

Keywords: Cephalic duodenopancreatectomy, Postoperative Pancreatic Fistula, Indocyanine Green, Hipoperfusion, Pancreatic Stump.

INTRODUCTION

1. PANCREAS

1.1. ANATOMY

The pancreas is a retroperitoneal organ that crosses transversely in front of the first and second lumbar vertebrae. It is divided into head (framed by the duodenal frame), neck (joins the head with the body), body and tail. The head presents an extension, or uncinate process, which is crossed anteriorly by the superior mesenteric artery and vein (mesenteric clamp) (1,2).

It contains two pancreatic ducts (1,2):

- **Main or Wirsung's duct:** runs through the entire gland in an S shape. In the most people it joins with the common bile duct and enters the duodenum as a common duct called the hepatopancreatic ampulla or Vater ampulla. The ampulla opens into a mucosal elevation of the second duodenal portion, known as the major duodenal papilla, where its contents will empty into.
- **Accessory or Santorini's duct:** it separates from the main duct at the level of the head and runs along the anterosuperior portion, flowing about 2-3 cm above the Wirsung's duct, in the minor duodenal papilla.

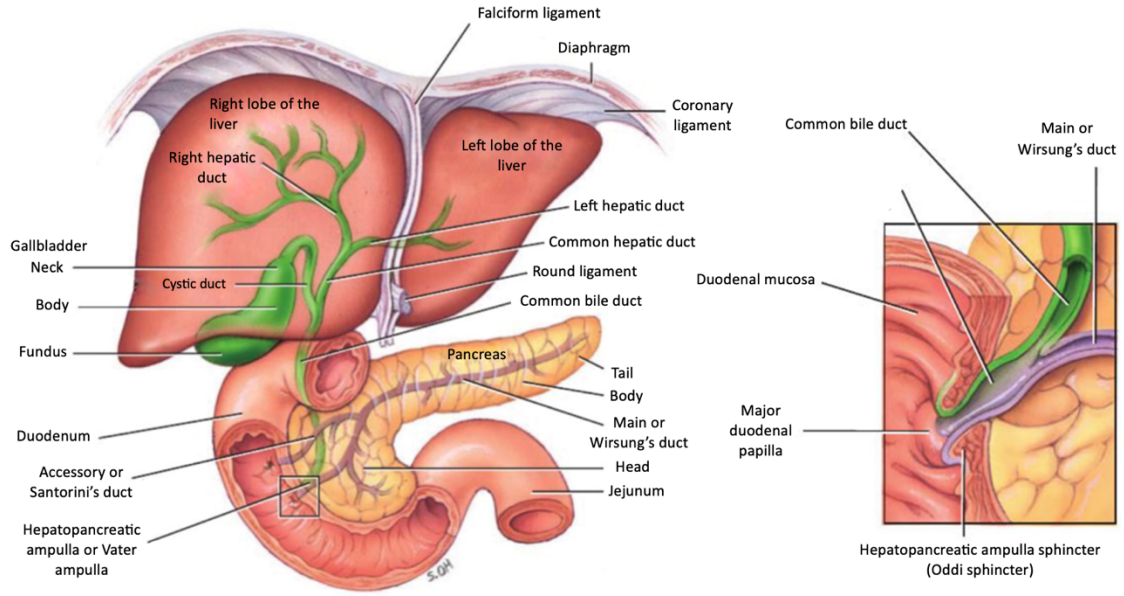


Figure 1: Relationship of the pancreas with the liver, gallbladder and duodenum. The inset shows in detail the common bile duct and Wirsung's duct, which together, form the hepatopancreatic ampulla (Vater ampulla) and empty into the duodenum. *Adapted from* (2).

1.2. VASCULARIZATION

1.2.1. Head

The **head** of the pancreas is supplied by gastroduodenal (n) and superior mesenteric (k) arteries, whose branches, the superior and inferior pancreaticoduodenal arteries, anastomose and form the pancreaticoduodenal arcade (d and f) (3–6).

1.2.2. Body and tail

The **body and tail** of the pancreas are supplied by branches of the splenic artery (3–6). There are 3 branches of the splenic artery that enter the superior surface of the body of the pancreas. These are named from right to left (3,6):

- The **dorsal pancreatic artery** (a): it pierces the superior-dorsal surface of the gland and ramifies into 2 dextral and 1 sinistral branch.
    - The **superior dextral branch** (c): it anastomoses with the superior part of the pancreaticoduodenal arcade (d).
    - The **inferior dextral branch** (e): it anastomoses with the inferior part of the pancreaticoduodenal arcade (f).
    - The **sinistral branch** (g): it anastomoses with the pancreatica magna (r) and the caudal artery (i), through its major sinistral branch – the transverse pancreatic artery (h).

  The origin of this artery is the most varied of the celiacomesenteric arteries. Most commonly (in the 40% of cases), the dorsal pancreatic artery is the first branch of the splenic artery (b), measuring 1-4 mm in diameter and runs inferiorly and to the right, for about 5 mm before entering the pancreas. It enters the pancreas 2-3 cm to the left of the portal vein. However, it can also arise from the celiac artery (j), the common hepatic artery (l), the right hepatic artery (m), the gastroduodenal artery (n), the right gastoepiplotic artery (o), the superior mesenteric artery (k), an aberrant right hepatic artery (p), or the middle colic artery (q) (3).

  A dorsal pancreatic artery in its usual position may be directly injured during pancreaticoduodenectomy by overly mobilizing the pancreas. When the artery has an anomalous origin, it is probably even more prone to injury. Specifically,

when it arises from the gastroduodenal artery or the right gastoepiplotic artery (2% of cases), blood flow into the dorsal pancreatic artery from these vessels will cease, because in the Whipple procedure these vessels are transected. It is also likely that it is more prone to be tacken when it arises from the superior mesenteric artery or an aberrant hepatic artery (3,7).

- The **pancreatica magna** (r).
- The **caudal pancreatic artery** (i).

1.2.3. Neck

There are no arteries entering the pancreas at the **neck** where the gland passes over the superior mesenteric and portal veins. This part of the gland is supplied by vessels which enter from the body or head, creating a vascular watershed between celiac and superior mesenteric arterial systems (3,7–9).

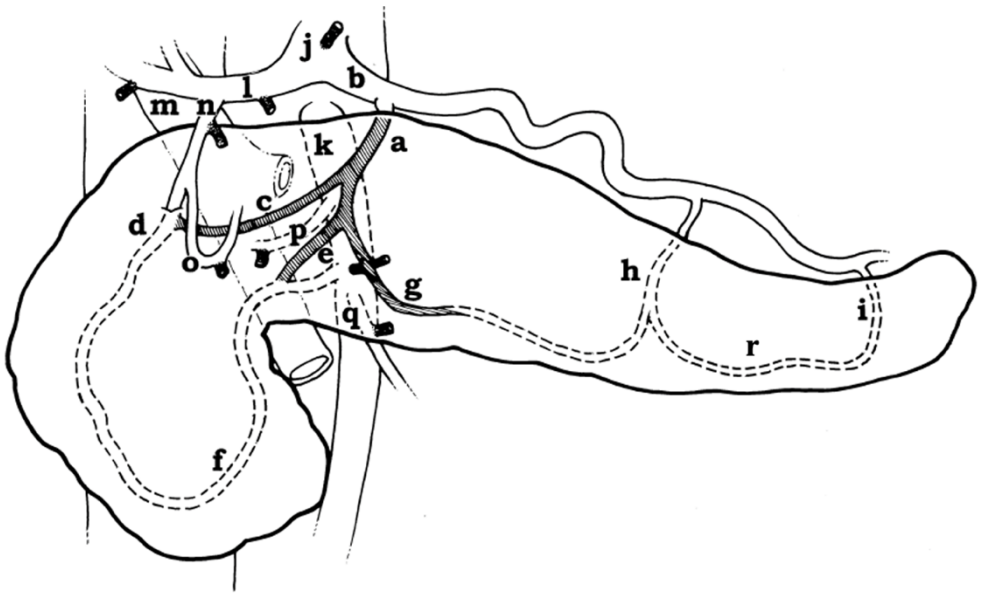


Figure 2: Pancreas vascularization. a, dorsal pancreatic artery; b, splenic artery; c, superior dextral branch; d, superior part of the pancreaticoduodenal arcade; e, inferior dextral branch; f, inferior part of the pancreaticoduodenal arcade; g, sinistral branch of the dorsal pancreatic artery; h, transverse pancreatic artery; i, caudal pancreatic artery; j, celiac artery; k, superior mesenteric artery; l, common hepatic artery; m, right hepatic artery; n, gastroduodenal artery; o, right gastroepiploic artery; p, aberrant right hepatic artery; q, middle colic artery. *Adapted from (3).*

1.3. HISTOLOGY AND FUNCTIONS

Histologically we distinguish the exocrine pancreas and the endocrine pancreas (1,2):

- **Exocrine pancreas:** formed by the pancreatic acini, forming about the 99% of the gland. The acini produce the pancreatic juice, composed by water, some salts, sodium bicarbonate and several enzymes. Sodium bicarbonate gives the pancreatic juice the alkaline pH (7.1-8.2) that neutralizes the acidic gastric juice, slows down the action of stomach pepsin, and allows the action of pancreatic enzymes in the small intestine.

  The enzymes of the pancreatic juice are pancreatic amylase, which digests starch; trypsin, chymotrypsin, carboxypeptidase and elastase, among others, which digest proteins; pancreatic lipase which digests triglycerides; and ribonuclease and deoxyribonuclease which digest nucleic acids.
- **Endocrine pancreas:** this part is formed by islets of Langerhans, situated between acini. These cells secrete the glucagon, insulin, somatostatin and pancreatic polypeptide hormones.

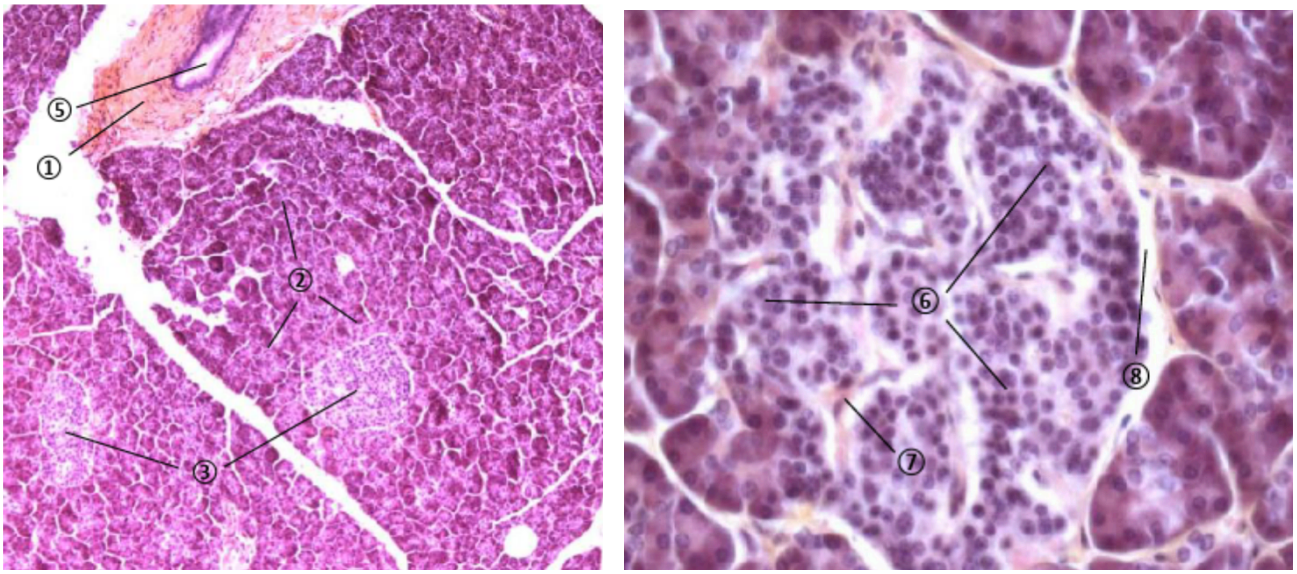


Figure 3 and 4: a) Pancreas histology; b) Islets of Langerhans. 1) Capsule, septa; 2) Exocrine compartment – serous acini; 3) Endocrine compartment – islets of Langerhans; 5) Interlobular ducts; 6) Trabecules; 7) Fenestrated capillaries; 8) Capsule. *Extracted from (10).*

2. PERIAMPULLARY TUMORS

2.1. EPIDEMIOLOGY

Most periampullary cancers originate in the pancreatic head (75%), with the remainder arising from the distal bile duct (10%), ampulla (10%), and duodenum (5%). Because of the proximity of these tumors to one another, the exact origin of the cancer is sometimes unclear.

The major histologic type of all these cancers is adenocarcinoma, although endocrine malignancies (i.e. gastrinoma), lymphoma, sarcoma, and metastases from other sources may also be found but make up a much smaller percentage.

There is a slightly higher incidence of pancreatic cancer in men than in women, and most occur after age 65 years. The highest incidence rates in the world appear to be among African-American men (11).

2.2. ETIOLOGY

There are some risk factors that increase the probability of developing periampullary tumors (11):

- **Cigarette smoking:** it is the risk factor most strongly associated with adenocarcinoma of the pancreas. The mechanism is presumed secondary to N-nitroso compounds from cigarette smoke causing activation of oncogenes such as K-ras. However, cigarette smoke has not been clearly linked as a risk factor to any of the other periampullary malignancies.
- **Diets high in the consumption of red meat, fat, and smoked or cured foods**: they have been implicated in causing cancer of the pancreas, bile duct, ampulla, and small intestine. The main causative agent here again appears to be nitrosamines. The mechanism may be different from that associated with cigarette smoking, as it is known that K-ras mutation levels in patients with cholangiocarcinoma and ampullary cancer are much lower than those observed in patients with pancreatic cancer.

- **Diabetes mellitus (DM)**: there appears to be an association between DM and pancreatic cancer.
- **Chronic pancreatitis**: there also appears to be an association between chronic pancreatitis and pancreatic cancer.
- **Sclerosing cholangitis**: associated with the cholangiocarcinoma. It is thought that a chronic inflammatory condition causes changes in cell repair and structure that may eventually lead to malignancy.
- **Familial adenomatous polyposis (FAP)**: these patients are prone to develop ampullary adenomas. These adenomas may undergo malignant transformation in a manner similar to the adenoma–carcinoma sequence known to exist for colon cancer.
- **Other hereditary syndromes:** hereditary nonpolyposis colorectal cancer, hereditary pancreatitis, ataxia telangiectasia may predispose patients to pancreatic cancer.

2.3. DIAGNOSIS

2.3.1. Clinic

Jaundice is one of the most common presenting signs in patients with periampullary malignancy. Obstruction of the bile duct occurs early in ampullary and distal bile duct cancers owing to their location.

Another common symptom in patients with periampullary cancer is **pain** described as a dull, difficult to characterize vague epigastric discomfort. When the disease is advanced, the pain progresses to a constant, severe low thoracic or upper lumbar pain (mid-back). This pain pattern usually implies a locally advanced tumor or lymphatic metastases invading the celiac nerve plexus.

Other symptoms include **anorexia** and **fatigue**. Severe **nausea/emesis** are more commonly seen in patients with duodenal/gastric outlet obstruction from a locally advanced mass. **Weight loss** can be seen early, related to the anorexia, but is more pronounced later in the course in patients with advanced disease.

Other clinical signs can be a palpable gallbladder and hepatomegaly. Painless jaundice and a palpable mass (gallbladder) in the right upper quadrant is known as Courvoisier's sign and implies a periampullary malignancy.

A palpable nodule at the umbilicus (Sister Mary Joseph's sign) or a mass felt in the pelvic cul-de-sac (Blumer's shelf nodule) on rectal or bimanual pelvic examination implies peritoneal metastases from a gastrointestinal (GI) malignancy.

A positive left supraclavicular node (Virchow's node) implies distant spread of disease.

Guaiac-positive stool may be found, especially in patients with duodenal tumors, large ampullary cancers, or pancreatic cancers that have invaded the duodenum.

Migratory superficial thrombophlebitis, or Trousseau's sign, is also a feature of advanced disease, as is evidence of ascites (11).

2.3.2. Laboratory

Leaving the clinic aside, laboratory studies can also help in the diagnosis.

Patients may exhibit anemia and low albumin levels, reflecting both the chronic nature of the disease and the nutritional sequelae.

Frequently, patients have increased alkaline phosphatase, alfa-glutamyl transferase, and bilirubin levels secondary to biliary obstruction. Marked elevation of the hepatic transaminases implies severe liver injury secondary to long-standing biliary obstruction or metastatic disease.

The prothrombin time is frequently elevated in patients with long-standing biliary obstruction.

Tumor markers such as carcinoembryonic antigen (CEA) and CA 19-9 are helpful in some patients. CEA is a marker frequently used for GI malignancies and is commonly elevated

in patients with periampullary malignancies. However, it has low specificity, being increased also in conditions such as biliary obstruction and pancreatitis. CA 19-9, another GI tumor marker, is much more specific and sensitive for pancreatic cancer than CEA but less so for ampullary and duodenal cancers (11).

2.3.3. Imaging

The radiologic test of choice for a patient with a periampullary cancer is the **contrast-enhanced computed tomography** (CT) scan with fine cuts through the periampullary region (11):

- **CT:** This scan allows accurate measurement of the size and location of the primary tumor. It is also extremely valuable in the evaluation of:
  - The surrounding lymph nodes.
  - The extra- and intrahepatic biliary system for ductal dilatation.
  - The liver for metastases.
  - The portal vein and superior mesenteric artery for evidence of invasion.
- **Endoscopic retrograde cholangiopancreatography (ERCP):** ERCP may facilitate biliary stenting for the patient with unresectable disease and is also useful for obtaining brushings of the duct from a patient with a stricture but no clear mass. ERCP can diagnose and even treat an impacted stone in the distal common bile duct, a situation that mimics a periampullary malignancy.
- **Endoscopic ultrasonography (EUS)**: EUS has gained popularity for preoperative evaluation of these patients. EUS provides more accurate information regarding tumor size, lymph node involvement, and vascular invasion than CT. Fine-needle aspiration (FNA) or biopsy can also be performed for a lesion deemed unresectable, or in patients who require tissue diagnosis prior to enrollment in preoperative protocols.

2.4. TREATMENT

Complete surgical extirpation (pancreaticoduodenectomy or the Whipple procedure) of these tumors provides the only chance for cure and the best option for long-term survival (11).

3. CEPHALIC DUODENOPANCREATECTOMY

3.1. INDICATIONS AND RESECTABILITY CRITERIA

Cephalic duodenopancreatectomy (CDP) is a key component in the treatment of various benign and malignant diseases (12).

The most frequent indication for CDP is pancreatic head adenocarcinoma. The resectability criteria have been focused on this specific type of malignant tumor, although it can be extrapolated to others (13).

The International Study Group in Pancreatic Surgery (ISGPS) suggests that criteria for borderline resectability should be applied using a specialized pancreatic protocol CT performed in the previous 4 weeks that includes all the abdomen and pelvis. Multidetector CT with high resolution and multiplanar reconstructions facilitates accurate stratification (14).

The 2017 edition of the National Comprehensive Cancer Network (NCCN) classifies the resectability of pancreatic adenocarcinomas according to the contact with arterial and venous structures (13,14):

Table 1. NCCN guidelines, version 1.2013, defining resectability status. *Adapted from (14).*

	Localized and resectable	*Borderline resectable*	*Unresectable*
Mx	No distant metastasis	No distant metastasis	Distant metastasis
Arterial criteria	Tumors with no contact with the CA, the SMA and the HA	GA encasement up to the HA with either short segment encasement or tumor with contact with the reconstructable proper HA without involvement of the common hepatic artery or the CA	Greater than 180º SMA encasement, any celiac abutment, IVC
		Contact with the SMA less than 180° or anatomical variant that can modify the surgical approach	Aortic invasion or encasement
Venous criteria	If there is contact with the PV or SMV, it must be less than 180°, without irregularity of its contour	Tumors that have contact with the SMV - PV greater than 180°; or inferior, if there is irregularity of the contour or obstruction (i.e., thrombosis) that can be reconstructed	Unreconstructible SMV/portal occlusion

**Criteria are given only for carcinomas of the head. CA, Celiac axis; GA, gastroduodenal artery; HA, hepatic artery; IVC, inferior vena cava; Mx, metastasis; NCCN, National Comprehensive Cancer Network; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.*

According to the NCCN guidelines, treatment with neoadjuvant chemotherapy is recommended in resectable borderline tumors.

Leaving aside the most frequent indication of CDP, there are also other causes for which it is performed, such as intraductal papillary mucinous tumor, neuroendocrine neoplasms, adenocarcinoma of the choledochus, serous cystadenoma, papillary adenoma, periampullary carcinoma, paraduodenal pancreatitis, chronic pancreatitis, duodenal adenocarcinoma, cystic-papillary neoplasm, among others (8,12).

3.2. CONTRAINDICATIONS OF CDP

The contraindications to perform CDP would be (13–15):

- **Anatomical contraindication:** when the neoplasm cannot be resected according to resectability criteria.
- **Oncological contraindication:** distant disease (metastasis, carcinomatosis).
- **Medical contraindication:** the patient cannot stand the surgery due to comorbidity, age, etc.

3.3. PROCEDURE

3.3.1. Classical approach

The CDP consists of complete resection of the duodenum and pancreatic head, distal bile duct and surrounding/adjacent lymph nodes and connective tissue with a reconstruction of the pancreaticoenteric continuity with a pancreaticojejunal anastomosis, hepaticojejunostomy and gastrojejunostomy. The steps to be followed in this surgery are the ones explained below (11,13,16,17):

1. **Incision and exploration of the abdomen:** duodenopancreatectomy can be performed through a medial incision from the xiphoid process to the umbilicus, or through a bilateral costal incision. With this incision the abdomen will be checked for signs of tumor dissemination (present in 10-15% of the patients, especially in those undergoing neoadjuvant chemotherapy, elevated CA 19.9 levels without jaundice, and in cases with non specific liver lesions or small ascites).

2. **Kocher's maneuver and opening of the omentum transcavity:** in the Kocher's maneuver, a surgical resection of the duodenal framework in its first 3 portions is performed, which allows the mobilization of the duodenum, the head of the pancreas and the retroduodenal and intrapancreatic sections of the common bile duct (18). This allows to explore the intercavo-aortic sulcus to rule out lymph node metastasis at this level. The first jejunal loop can also be uncrossed to the right sectioning the Treitz ligament. Then, the pancreatic area can be explored, the adhesions of the stomach to the pancreas can be sectioned and infiltration of the common hepatic artery or celiac trunk can be ruled out.

   If there is lymph node metastasis to the interaorto-caval area surgery is not continued because it is considered distant disease (metastatic). On the other hand, if there is involvement of other lymph nodes the surgery is followed because they are regional lymph nodes.
3. **Cholecystectomy and dissection of the hepatic hilum:** a standard cholecystectomy is performed by dissecting the cystic duct down to the common hepatic duct and the lymph nodes of the hepatic artery proper are dissected down to the exit of the splenic artery. The pyloric artery is ligated and sectioned, thus exposing the gastroduodenal artery. The gastroduodenal artery is then ligated leaving a 5 mm stump if the tumor extension allows it. This maneuver makes it possible to expose the portal vein on its left side and to continue the lymphadenectomy of the retroportal lymph nodes. The common hepatic duct continues to be sectioned above the mouth of the cystic duct. It is recommended to take a bile sample or remove the biliary prosthesis for culture and occlude the bile duct with a bulldog to control contamination until biliary reconstruction. In this situation we can assess the infiltration of the neck of the pancreas in its upper part.
4. **Dissection of the superior mesenteric vein (SMV) up to the neck of the pancreas and ligation of the Henle gastrocolic trunk**: the SMV is identified and dissected towards the inferior border of the neck of the pancreas. Gastroepiplotic vein and artery are ligated to prevent any traction injury. It is usually necessary to ligate and section veins from the head of the pancreas. The colic veins can be ligated and sectioned if there is involvement of the SMV or if a venous resection is to be

performed. The first jejunal vein drains into the right posterolateral part of the SMV and crosses below or above it (in 20% of the cases), of the superior mesenteric artery (SMA), at the mesentery root. It is necessary to ligate and section this vein to enter the right lateral plane of the SMA and free the uncinate process. In this step, it is also evaluated the possible infiltration of the portal vein in the neck of the pancreas.

5. **Section of the pancreatic neck and gastric antrum:** The maneuver is continued by passing the retropancreatic sulcus with a dissector over the anterior aspect of the SMV – portal vein. The inferior and superior edges of the pancreas are freed to allow two traction points to be made on both edges to allow us to section the neck without injuring the portal vein. Careful hemostasis is performed with 4/0 monofilament stitches of the pancreatic arteries of the section border. It is advisable to place a silicone tube in the Wirsung duct, which will allow us to perform the pancreatic reconstruction with the security of not injuring it. Dissection of the right lateral aspect of the SMV – portal vein is continued, ligating tributary veins of the uncinate process. The gastric antrum is sectioned, or the first portion of the duodenum if pyloric preservation is to be performed, and the stomach is retracted to the left. This maneuver can be performed before sectioning the pancreatic neck if necessary to expose it. Systematic delivery of the pancreatic resection edge for intraoperative biopsy is recommended.
6. **Section of the jejunum:** once the first jejunal loop has been uncrossed, the mesenteric vessels are sectioned and ligated in the direction of the SMV at the level of the first jejunal vein. With this maneuver, a complete skeletonization of the right hemicircumference of the SMV and portal vein in the direction of the neck of the pancreas is achieved, which allows the surgical specimen to remain only at the expense of dissecting the SMA and the retropancreatic lymphatic and neural tissue which anatomopathologically marks the retroperitoneal margin.
7. **Dissection of the superior mesenteric artery and retroperitoneal margin:** In this moment, the surgical specimen has the arterial supply intact, but its venous drainage is ligated and sectioned. Thus, there remains the dissection of the SMA. This final part of the CDP has many variations and can be performed with hemostatics, sealants or bipolar forceps. The classic approach to the SMA is from

distal to proximal (caudal-cranial). It is very important to have a high quality previous CT scan that rules out anatomical variants that can be injured in the course of the CDP. The number of branches of the SMA is variable, but the inferior pancreaticoduodenal arteries (ADPI) are very constant and easily recognizable. It is common for there to be 1 or 2 additional arteries that, in any case, arise from 3 cm from the exit of the SMA from the aorta. It is recommended to remove the lymphatic, fatty and neural tissue of the right hemicircumference of the SMA, exposing the adventitia up to its exit from the aorta, an anatomical space that has been denominated mesopancreas. In this classic approach, infiltration of the SMA can be discovered at the end of the procedure when the procedure is irreversible. Once the pancreaticoduodenal arteries have been ligated and the SMA has been skeletonized on its right lateral aspect, an anatomical space remains whose upper border is the celiac trunk, the lower border is the SMA and the upper inner border is the mesenteric-portal venous axis that must be included in the resection specimen. The removal of the surgical specimen is completed.

8. **Reconstruction:** Once the tumor and pancreas have been successfully removed, the gastrointestinal tract will be put back together. This will include:
    a. The remaining pancreas and pancreatic duct will be connected to the jejunum (In this protocol it will be performed with a Blumgart anastomosis). The Blumgart anastomosis is a new transpancreatic U-suture technique with modification of duct-to-mucosa anastomosis. This technique includes placement of four to six transpancreatic sutures and jejunal seromuscular sutures to approximate the pancreas and the jejunum using non-absorbable sutures (Prolene 3/0, Ethicon). A suture is placed through the whole pancreatic parenchyma from front to back. A seromuscular bite with vertical mattress over the jejunum is taken as the posterior outer layer, and the same suture reverted back to front through the whole pancreas again to complete the U-suture (Fig. 8a,b). 2 or 3 of the U-Sutures are placed cranial and 2 or 3 caudal to the pancreatic duct. After incision of the jejunum at the antimesenteric side, a duct-to-mucosa anastomosis is constructed using Monocryl 4/0 interrupted sutures (Fig.

8c). Finally the transpancreatic U-sutures are completed by placing the needle on the anterior seromuscular wall of the jejunum to create an anterior outer layer, thus adapting the jejunum to the pancreas (Fig. 8d,e). Then, the pancreatic remnant is totally covered with jejunal serosa (Fig 8e,f) (19) (20).

A plastic tube may be used to keep this connection open when the wirsung measures <3mm. This tube will be left in place after the surgery, and does not cause any harm.

b. The bile duct is joined to the jejunum further down. These 2 connections will allow digestive juices and bile to flow into the gastrointestinal tract again.
c. The stomach is connected to the jejunum still further down, which will allow food to pass through. In some cases a drain will be placed close to the new pancreatic and bile duct connections.
d. Abdomen will then be closed and the skin edges will be brought together with either stitches stainless steel staples.

To facilitate the understanding of the surgical procedure (CDP), we have attached intraoperative images of the different steps involved in this procedure (see **Annex 1**).

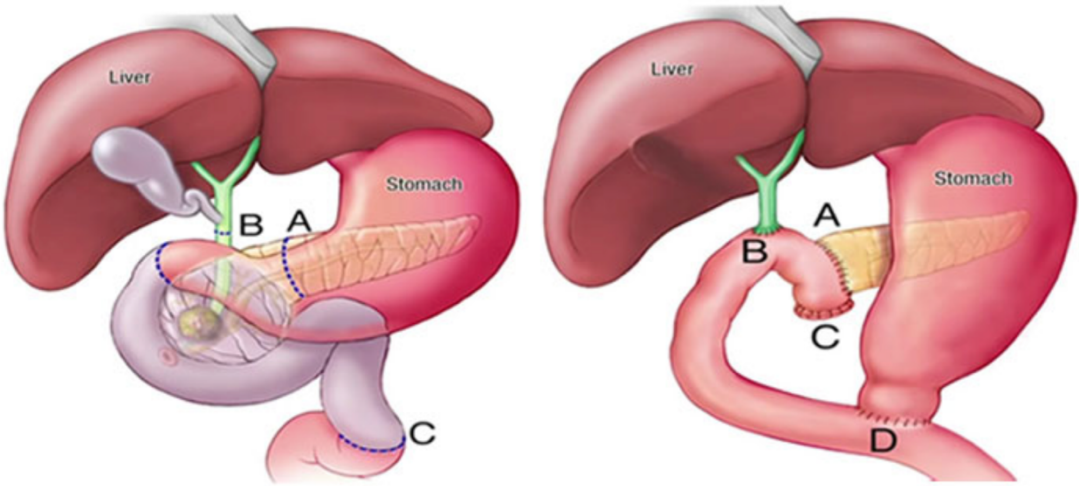


Figure 5: Summary image of duodenopancreatectomy. *Extracted from (21).*

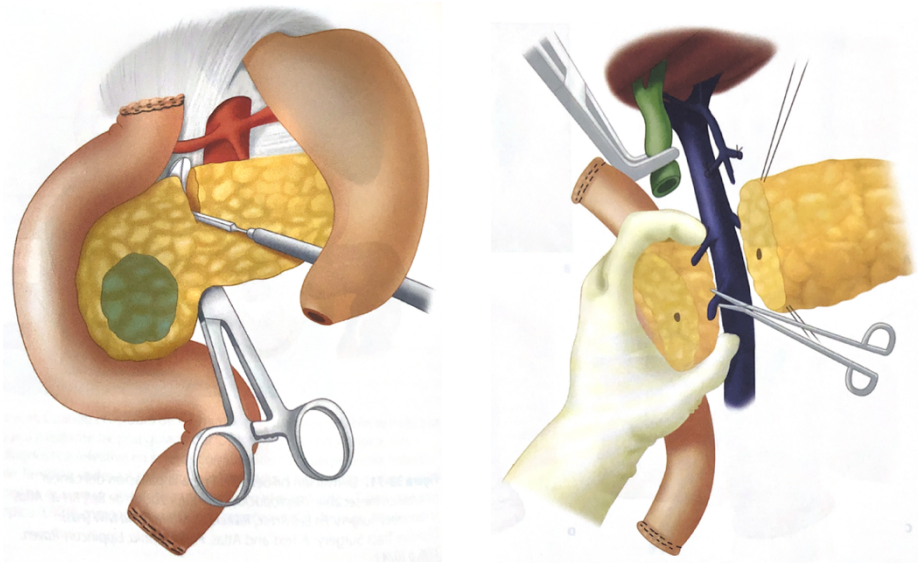


Figure 6 and 7: 6) Section of the neck of the pancreas. The pancreatic neck is separated from the anterior surface of the portal vein and then easily detached from the vein. A large blunt-tipped forceps is safe for dissection. 7) Dissection of the pancreatic head and uncinate process. These 2 structures are dissected from the right lateral surface of the SMV and portal vein after ligating the fragile venous branches. *Extracted from (16).*

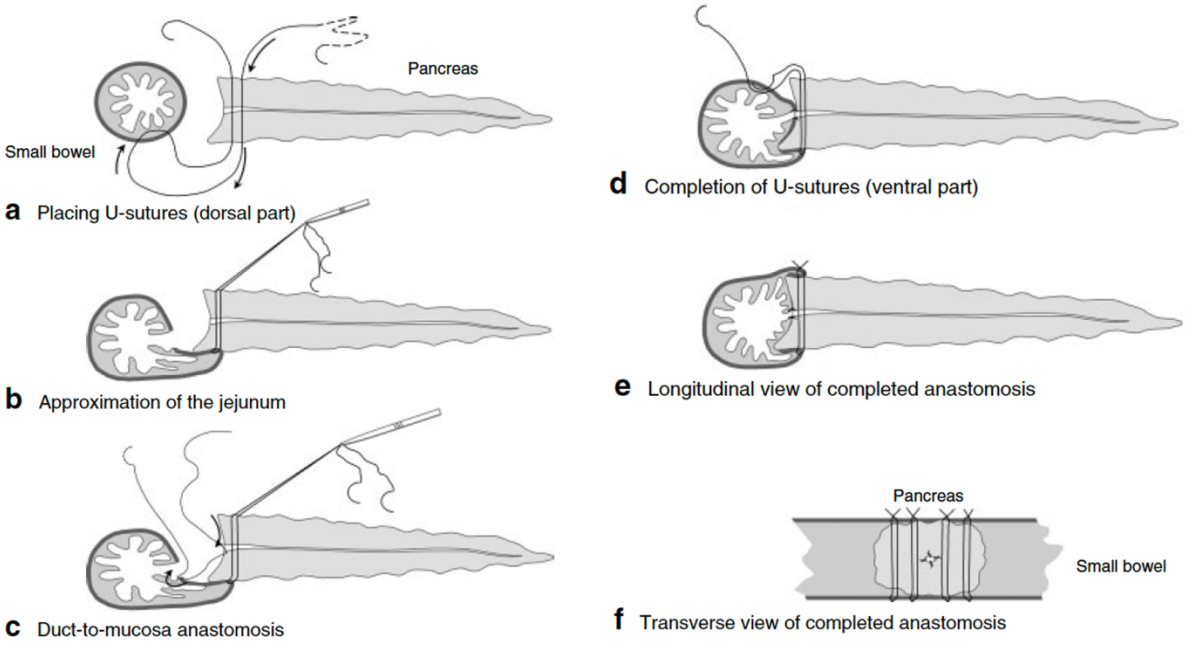


Figure 8: Blumgart anastomosis: a–e longitudinal and f transverse views. The transpancreatic U-suture technique reduces the total number of stitches and minimizes tangential shear forces of sutures at the cut end of the pancreatic remnant. The ventral and dorsal walls of the jejunum should prevent sutures from cutting through the pancreatic parenchyma when the knots are tightened. *Extracted from (20).*

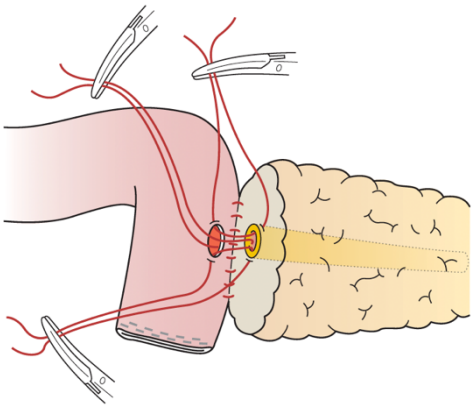


Figure 9: Technique of duct-to-mucosa pancreaticojejunostomy. *Extracted from (22).*

3.4. COMPLICATIONS

Although mortality rate after pancreatic resection has decreased to less than 5%, the morbidity remains high (from 30 to 50%) even in high-volume centers (5,9,11–13,15,23).

The most common complication of the pancreaticoduodenectomy is the postoperative pancreatic fistula (POPF), being the main determinant of serious postoperative morbidity and mortality related to pancreatic resection and playing a major role in terms of hospital stay and economic impact (4–9,11,12,23–27).

One of the most important determinants of safe CDP and to reduce the risk of POPF is the successful pancreatico-enteric anastomosis (3–5,8,9).

Other complications of CDP include delayed gastroemptying, hemorrhage, and infections, which are among the most frequent. Additionally, complications such as sepsis, reoperation, insertion of a drain, malabsorption, steatorrhea, cardiovascular phenomena and death may also occur, among others (11,16,17,28).

4. POSTOPERATIVE PANCREATIC FISTULA

4.1. DEFINITION

During the years, various definitions have been given to the concept of postoperative pancreatic fistula (POPF) (5,8,12,16,24).

In 2005, the ISGPS developed a definition of POPF universally accepted as an abnormal communication between the pancreatic ductal epithelium and another epithelial surface, which leads to a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase normal activity (12,23,24).

In addition, in 2016 the ISGPS included as a part of the definition that the POPF is also associated with a clinical relevant development/condition related directly to the postoperative pancreatic fistula, meaning that whenever an increased amylase activity is found in the fluid from an operatively placed drain, which does not impact on the clinical outcome of the patient, no fistula should be reported (24).

POPF is considered to be the most frequent major complication of the pancreaticoduodenectomy, being life-threatening and increasing the duration of hospital stay and costs, including the increase of serious postoperative morbidity, such us bleeding, intraabdominal abscesses and collections, wound infection, sepsis, delayed gastric emptying (DGE), etc. (4–9,11,12,23–27).

Table 2. Complications in patients with POPF. *Extracted from (12).*

Complication	Incidence (%)
Respiratory complications	38
Intra-abdominal collections	26.5
Signs of sepsis	16.3
Postoperative hemorrhage	12.2
Biliary fistula	5.4
Cardiocirculatory complications	4.7
Enteric fistula	4
DGE	4
ARF	2.7
Hepatic insufficiency	2.7

DGE Delayed gastric emptying, *ARF* acute renal failure

Overall, POPF is the root cause of mortality after pancreaticoduodenectomy (5).

4.2. ETIOLOGY

During the last years, it has been seen that a POPF can be caused whether by a failure of healing or sealing of a pancreatic-enteric anastomosis in pancreas surgeries or it may represent a parenchymal leak not directly related to an anastomosis such as one originating from the raw pancreatic surface (e.g., for a trauma) (3,23).

The theory that hypoperfusion of the pancreatic stump and inadequate anastomotic vascular perfusion can lead to anastomotic failure has recently gained interest and been mentioned in different literature (3–5,7–9,27,29,30).

It is believed that hypoperfusion of the pancreatic remnant results in pancreas transection margin ischemia and inflammation, post pancreatectomy pancreatitis, shown with hyperamylasemia, and necrosis, with following failure of healing at the pancreatico-enteric anastomosis and resultant pancreatic leak (5–7,27,29).

We take as the definition of postoperative acute pancreatitis (POAP) the elevation of the serum pancreatic amylase levels above the upper limit of normal (52 U/L) on postoperative day (POD) 0 to 2 (6,7). Predicted severity is based on C-reactive protein with a cut-off of 180 mg/L at post-operative day 2 (6).

In addition, it has been detected that hyperlactatemia, a well-recognized hallmark of inadequate tissue perfusion and microcirculatory abnormalities, in the early post-operative period can be predictive of POPF (5).

However, the current published evidence is of poor quality and it does not support a causative link between hypoperfusion and POPF, needing further well-designed prospective studies to investigate it (5,8,9,30).

Other risk factors for POAP, which increases the likelihood of POPF are a soft pancreatic parenchyma, acinar cell density, a small pancreatic duct, a non pancreatic ductal adenocarcinoma (PDAC) pathology, and intraoperative blood loss (5,7,9,25,27,29).

Pancreas texture, pancreatic ductal diameter, PDAC or non PDAC pathology and intraoperative blood loss have been combined to create the pancreatic **fistula risk score**, having 4 risk levels: negligible risk (0 points); low risk (1 to 2); intermediate risk (3 to 6); high risk (7 to 10) (5,25).

Table 3: Fistula Risk Score for Prediction of Clinically Relevant Pancreatic Fistula After Pancreatoduodenectomy. *Extracted from* (25).

Risk factor	Parameter	Points*
Gland texture	Firm	0
	Soft	2
Pathology	Pancreatic adenocarcinoma or pancreatitis	0
	Ampullary, duodenal, cystic, islet cell	1
Pancreatic duct diameter, mm	≥5	0
	4	1
	3	2
	2	3
	≤1	4
Intraoperative blood loss, mL	≤400	0
	401–700	1
	701–1,000	2
	>1,000	3

*Total 0 to 10 points.

On the other hand, exocrine insufficiency, neoadjuvant therapy and additional resection of the pancreatic stump margin have been highlighted as factors protective of postoperative hyperamylasemia (POH) and POAP (7,29).

4.3. EPIDEMIOLOGY

Despite numerous trials aimed at reducing the incidence of POPF, its incidence still ranges between 3-45% of pancreatic operations, remaining largely unchanged over decades. This is likely due to poor understanding of its pathophysiology, with failure of current interventions to reduce POPF (3,5,6,8,12,23,24).

Some studies have tried to reduce the anastomosis failure using different techniques such as pancreaticogastrostomy over pancreaticojejunostomy (22), resulting with no advantages, total pancreatectomy which would lead to severe insulin-dependent

diabetes and potential effects of splenectomy, occlusion of the pancreatic duct by ligation or prolamine, and creation of a controlled fistula, but none have met with consistent success (3).

The mortality rate of POPF is 2,7%, highlighting the relevance of group C, with a rate of 30,7% (12).

4.4. DIAGNOSIS

As it has been said before, the suspicion of POPF can be done by a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase normal activity (12,23,24).

The aspect of the drained liquid can vary from a clear color that looks like pancreatic juice to a dark brown to greenish bilious fluid (if the anastomosis is near or aboard to a bilienteric anastomosis) (23).

In a patient with POPF we may also find abdominal pain and distention, impaired bowel function, delayed gastric emptying, fever (>38ºC), serum leukocyte count greater than 10,000 cells/mm^3, and increased C-reactive protein (23).

Imaging documentation is not mandatory to diagnose the pancreatic fistulas, but still, it may be useful for identifying further complications or other differential diagnosis (23).

However, it is important to know that signs of pancreatic necrosis can usually be observed by radiological imaging only more than 72 hours after the onset; nevertheless, an increase in serum amylase levels may represent the earliest sign of postoperative acute pancreatitis. This means hyperamylasemia can also be the early sign that can help us prevent POAP which increases the risk of POPF (6,7,29).

To sum up, POPF can be clinically suspected after the postoperative day 3 on the basis of the quality rather than the amount of drain output, but only a long-standing observation

will confirm the diagnosis because many patients will have an inflammatory serous output not related to anastomotic leak (23).

4.5. GRADING

The International Study Group of Pancreatic Fistula (ISGPF) proposed a grading system that allows a correct stratification of the complicated patients based on the clinical and economic impact (due to the difference of the associated complications and management) (12,23). This will allow to determinate whether the patient, once discharged, is capable of reestablishing a normal daily activity or needs an outpatient clinic and daily follow-up of the in situ drain (12).

Only after a long-standing observation, leading to a complete clinical recovery, discharge from the hospital or death, it is possible to differentiate and grade the POPF as grades A, B and C (23).

- **Biochemical leak (BL) (POPF grade A):** This grade is no longer considered a true pancreatic fistula or an actual complication because it doesn't have clinical impact (12,23,24). It implies no deviation in the normal postoperative pathway and therefore, does not affect the normal postoperative duration or stay (24).
    - *Etiology:* In this grade, patients with carcinoma of the ampullary region have a higher incidence of POPF compared to other tumor histotypes, such as ductal cancer (12).
    - *CT:* Normally peripancreatic fluid or other intra-abdominal collections are not present in the computed tomographic scan (23).
    - *Management:* The patient is fed orally and remains clinically well. Total parenteral nutrition, antibiotics or somatostatin analogues are not indicated (12,23,24). It is managed frequently by slow removal of the operatively placed drains (23).
    - *Hospital stay:* This grade does not always imply delay in hospital discharge (12,23,24), meaning a median hospital stay of 11 days (12).
    - *Economic impact:* BL implies a cost of 11,654 € (12).

- **POPF grade B:** This grade requires an adjustment in the management (23,24). It can be managed with conservative therapy or mini-invasive procedures including endoscopic, percutaneous, radiologic or angiographic interventions (12,24).
    - *CT:* It can show peripancreatic or intra-abdominal collections requiring repositioning of the peripancreatic drains through interventional image-guided means (23,24).
    - *Management:* Usually, the patient is kept with nothing by mouth (NPO) and is supported with partial or total parenteral or enteral nutrition, with Bengmark's tube positioned in the efferent loop of the duodenojejunal or the gastrojejunal anastomosis. Normally, the peripancreatic drains are maintained in place for an extended period, defined as 3 weeks/21 days after operation), with the exception of them not functioning to totally drain the fistula, which we would see in the CT. Antibiotics are usually required when the condition of the patient is stable but associated with abdominal pain, fever, and/or leukocytosis (12,23,24). Somatostatin analogues may also be used (23,24). If a POPF-related hemorrhage or pseudo-aneurism occurs, transfusions and/or angiography may be necessary. In the majority of cases, transfer to an ICU is not necessarily warranted but might be chosen (24).
    - *Hospital stay:* Grade B POPF often leads to a delay in discharge, or readmission after a previous discharge (12,23,24). The median hospital stay is 24 days (12). Many patients can be discharged with drains in situ and observed in the outpatient setting (12,23,24).
    - *Economic impact:* POPF B implies a cost of 25,698 € (12).

- **POPF grade C:** Whenever a grade B POPF leads to organ failure, clinical instability (for example caused by sepsis or hemorrhage) or when a reoperation is needed. If the patient results on death due to the fistula as the triggering factor, grade B POPF also shifts to a grade C. Obviously, reoperation potentially is associated with relevant morbidity and mortality, meaning the complications presented in grade C lead to a greater mortality (30,7%) (12,23,24).

- *CT:* It normally shows peripancreatic fluid collections that require percutaneous drainage (23). It can also show air bubbles near the anastomosis in case of complete dehiscence (12).
- *Management:* Clinical intervention is aggressive. The patient is kept with nothing by mouth (NPO) and total parenteral or enteral nutrition. It is also needed to provide intravenous antibiotics, and somatostatin analogues, normally in an intensive care unit setting (12,23). Often, stay in an ICU is necessary (24).

  A POPF grade C with deteriorating clinical status, together with sepsis and organ disfunction may require re-exploration for one of the following: 1) An attempt to repair the site of leakage with wide peripancreatic drainage, 2) Conversion to alternative means of pancreatic-enteric anastomosis (e.g., conversion of pancreaticojejunostomy to pancreaticogastrostomy) or 3) Completion of the pancreatectomy. (23)
- *Hospital stay:* The patient usually requires an extended hospital stay with a major delay in hospital discharge (12,23,24). The median hospital stay is 46 days (12).
- *Economic impact:* POPF C implies a cost of 59,492 € (12).

Pulmonary complications are statistically higher in the groups B and C rather than the group A (12).

We must be aware that increasing fistula grades not only imply a clinical and management repercussion, but also increases hospital costs (3,12). The total cost increase from a non-POPF duodenopancreatectomy (9,665 €) to grades A, B, and C POPF is 20,5%, 165% and 515% respectively (12).

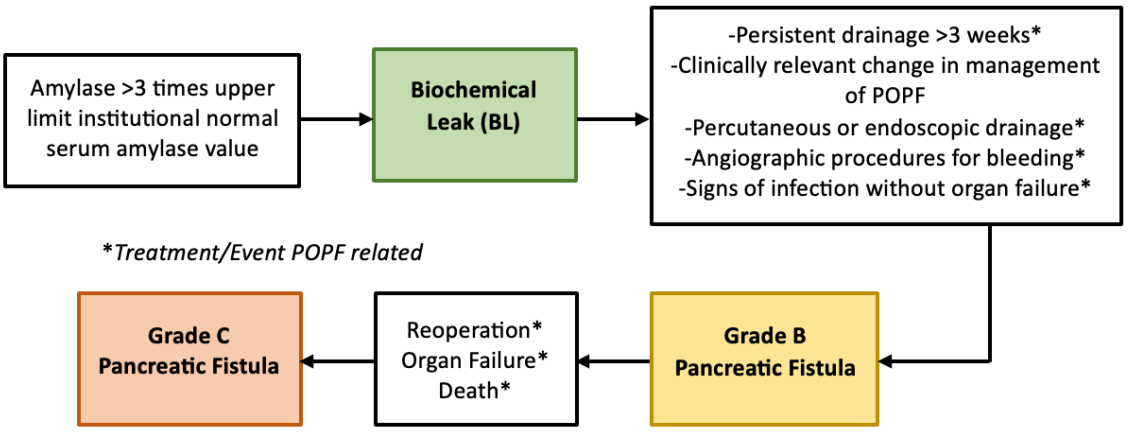


Figure 10: Flow Chart for BL, and POPF grade definition. BL, Biochemical leak; POPF, postoperative pancreatic fistula. *Adapted from* (24).

Event	BL (NO POPF)	Grade B POPF*	Grade C POPF*
Increased amylase activity > 3 times upper limit Institutional normal serum value	YES	YES	YES
Persisting peripancreatic drainage > 3 weeks	NO	YES	YES
Clinically relevant change in management of POPF#	NO	YES	YES
POPF percutaneous or endoscopic specific interventions for collections	NO	YES	YES
Angiographic procedures for POPF related bleeding	NO	YES	YES
Reoperation for POPF	NO	NO	YES
Signs of infection related to POPF	NO	YES, without organ failure	YES, with organ failure
POPF related organ failure^	NO	NO	YES
POPF related death	NO	NO	YES

Figure 11: The Revised ISGPS classification and grading of POPF: checklist for clinical use. *ISGPS*, International Study Group on Pancreatic Surgery; POPF, postoperative pancreatic fistula. *A clinically relevant POPF is defined as a drain output of any measurable volume of fluid with amylase level greater than 3 times the upper institutional normal serum amylase level, associated with a clinically relevant development/condition related directly to the POPF. #Suggests prolongation of hospital or ICU stay, includes use of therapeutic agents specifically employed for fistula management or its consequences (of these: somatostatin analogues, TPN/TEN, blood product transfusion or other medications). ^Postoperative organ failure is defined as the need for re-intubation, hemodialysis, and/or inotropic agents > 24 hours for respiratory, renal, or cardiac insufficiency, respectively. *Extracted from (24).*

Table 4. Economic impact of POPF. *Extracted from (12).*

Costs	No POPF	Grade A	Grade B	Grade C
Preoperative	*179,60*	*179,60*	*179,60*	*179,60*
Operating theatre	*3,567.58*	*3,567.58*	*3,567.58*	*3,567.58*
Postoperative				
Hospital Stay (mean)	*8 days*	*11 days*	*24 days*	*46 days*
Costs	*3,600*	*4,950*	*10,800*	*20,700*
Therapeutic interventions				
Antibiotics	-	-	*1,958.35*	*6,316.7*
Octreotide	-	-	*241.65*	*483.3*
TPN/EN	-	-	*1,540*	*3,700*
Blood transfusion	-	-	*70*	*280*
Hospital costs				
Radiology	*80*	*80*	*897*	*1,674*
Laboratory	*243.9*	*472.8*	*1,141.25*	*1,815.2*
ICU	-	-	-	*6,500*
Reoperation	-	-	-	*2,000*
Total	*7,671.08*	*9,249.98*	*20,395.43*	*47,216.38*
Total indirect costs (26%)	*1,994.48*	*2,404.99*	*5,302.81*	*12,276.25*
Total hospital costs	*9,665.56*	*11,654.97*	*25,698.24*	*59,492.64*
Total cost increase (%)		*20,5%*	*165%*	*515%*

5. INDOCYANINE GREEN

Indocyanine green (ICG) is a sterile, anionic, water-soluble, tricarbocyanine molecule. Once injected via the intravenous route, it binds to plasma proteins, such as albumin and lipoproteins. ICG fluoresces when excited by near infrared light (4,31), absorbing light from 790 to 805 nm and remitting it with an excitation wavelength of 800nm and longer (32–35).

Thus, with respect to technique, fluorescence imaging with ICG is fairly simple: the dye is administered and 30-120 seconds later its presence is visualized in the perfused organs under near infrared light (5,30,32,36).

The use of ICG imaging for real-time intraoperative organ perfusion assessment is well stablished in gastrointestinal surgery, specifically in assessing tissues prior to anastomosis (4,5,32,35–38). ICG has also been used in plastic surgery to assess flap viability (4,39), detect tumors and sentinel lymph nodes involving the breast (40,41), as well as in neurosurgery (42), surgery of the liver and biliary tree (34), vascular surgery (43), lungs surgery (44,45), and ophthalmology (33), among others (32), yet it is not widely used in pancreas surgery (5,33).

Some studies have used indocyanine green to see the viability of the pancreatic stump, helping to determinate the ischemic segment (7,27,31), needing further resection, avoiding ischemia and subsequent anastomotic failure. However, further studies should be done to prove its working (5,8,9).

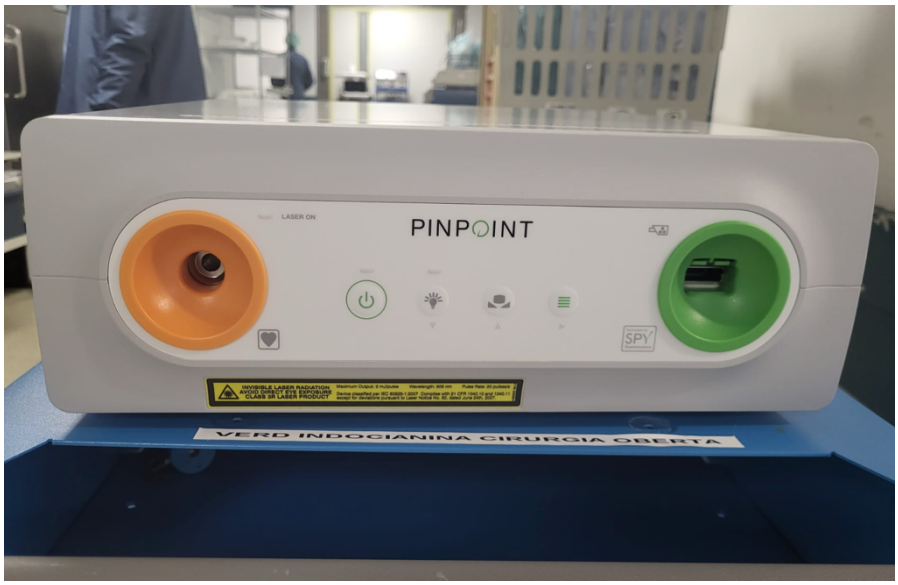


Figure 12: Control software and hardware for computing, input, and display.

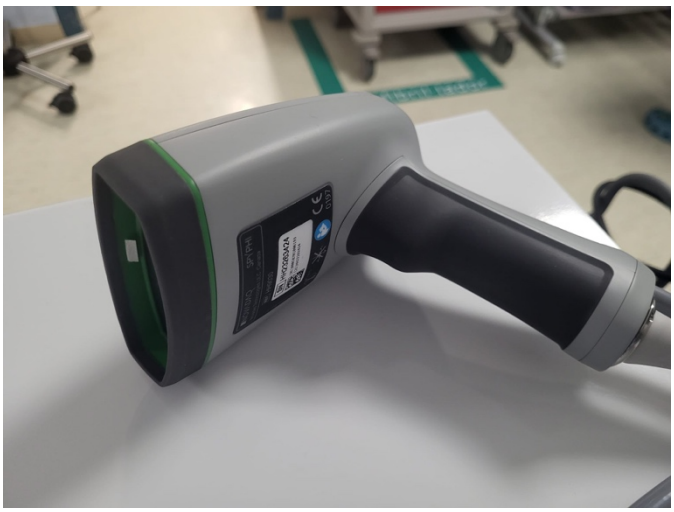


Figure 13 and 14: Probe that emits infrared light and receives the image in open surgery. The image will be seen through a screen, showing the organs stained with the ICG.

5.1. DOSE

Despite the rapidly expanding utilization of ICG, there is a lot of variability in the dose, concentration and administration of ICG during fluorescence-guided surgery (32).

However, we know that in the indocyanine green vials there are 25mg. These must be mixed with 10cc of sterile water, so that in each cc of distilled water there will be 2.5mg of indocyanine green.

Moreover, it has been seen that the perfusion of the pancreatic remnant could be visualized using intravenous injection of ICG dose of 0,1-0.2 mg/kg (30,31), meaning that the optimum total ICG dose, remaining within the safe spectrum, is from 5 to 10 mg (32,36).

In the event of failure to obtain a bright perfusion, the ICG dose can be repeated, but there is no consensus on how long surgeons should wait before administering a second dose, having heterogeneity, ranging from a waiting time of 3-5 min up to 10 min (36).

In any case, even if the entire vial of ICG is not used, it cannot be reused for another patient, necessitating a new vial for each individual.

5.2. CONTRAINDICATIONS AND ADVERSE REACTIONS

The most important contraindication to the use of ICG is iodine allergy. In addition, known or suspected shellfish allergy is a relative contraindication to fluorescence imaging with ICG (9,36,39).

It is also contraindicated in patients with clinical hyperthyroidism, autonomous thyroid adenomas and focal and diffuse autonomous alterations of the thyroid gland (46).

Although reactions to ICG are extremely rare, prior to administering it, patients should be asked about potential allergies, to avoid adverse reactions.

5.3. LIMITATIONS

The only major barrier to using Fluorescence Imaging (FI) is the equipment unavailability (36).

With respect to the effect of FI on intraoperative patient risks, it has been seen that it exerted no impact on the risk of hemorrhage or the time required to complete surgery (36).

It has also been considered false that inadequate fluorescence and the need for repeat dosing constitute a major limitation (36).

To sum up, even that there are some adverse effects of ICG, its use during fluorescence-guided surgery should be considered very safe (32).

Thus, prior to undergoing fluorescence imaging with ICG, there's no need for patients to provide written informed consent specific to its use, as it is considered as an additional medication during surgery (34,36).

5.4. COSTS

Talking to the general surgery and pharmacy service of the *Hospital de Girona Dr. Josep Trueta,* they have told us that the brand used in the hospital is XalabarderFarma.

This brand is priced at 17€/vial, knowing that each vial is 25 mg, and that in every patient a new one is required.

Overall, using fluorescence technology, with ICG decreases the cost of a patient's peri- and postoperative care because it facilitates many surgical procedures and reduces the risk of a patient's postoperative care (32,36,39).

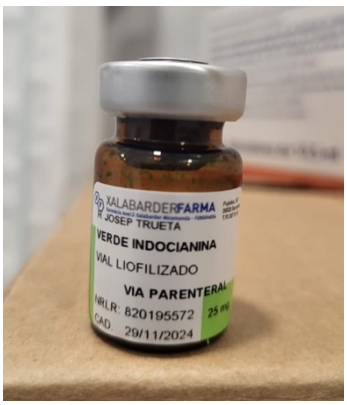


Figure 15: Indocyanine green vial of 25 mg.

JUSTIFICATION

The pancreatic fistula is the most common complication of the pancreaticoduodenectomy, being the main determinant of serious postoperative morbidity and mortality related to duodenopancreatectomy and playing a major role in terms of hospital stay and economic impact (4–9,11,12,23–27).

Despite numerous trials aimed at reducing the incidence of POPF, its incidence still ranges between 3-45% of pancreatic operations, remaining largely unchanged over decades (3,5,6,8,12,23,24).

The exact pathophysiology of fistulas and why they appear is not yet known, but several studies have begun to suggest that fistulas may be related to hypoperfusion of the pancreatic remnant after surgery, which would cause transection margin ischemia and inflammation, post pancreatectomy pancreatitis, and necrosis, leading to a failure of healing at the pancreatico-enteric anastomosis resulting in pancreatic leakage (3–5,7–9,27,29,30).

However, only a few studies have attempted to reduce anastomotic failure at duodenopancreatectomy focusing on issues related to perfusion of the pancreas. These studies suggest that ensuring adequate blood supply to the pancreas can result in a very low rate of anastomotic failure, but that further studies should be done (3,5,8,9,30).

On the other hand, indocyanine green is a technique already used in other surgical fields to assess organ perfusion, such us in gastrointestinal surgery, specifically in assessing tissues prior to anastomosis (4,5,32,35–38). ICG has also been used in plastic surgery to assess flap viability (4,39), detect tumors and sentinel lymph nodes involving the breast (40,41), as well as in neurosurgery (42), surgery of the liver and biliary tree (34), vascular surgery (43), lungs surgery (44,45), and ophthalmology (33), among others (32), yet it is not widely used in pancreas surgery (5,33).

This technique has made it possible to facilitate many surgical procedures, leading to a reduction of peri- and postoperative morbidity and mortality in other fields, thus reducing the hospital stay and overall cost of patient care (32).

The brand of ICG used in the *Hospital de Girona Dr. Josep Trueta* has a cost of 17€/vial, knowing that each vial is 25 mg, and that in every patient a new one is required. This price is not expensive and it is fully compensated with the economic benefits of the postoperative cost of the patient (32,36,39).

This raises the question of whether the use of ICG would significantly decrease the occurrence of pancreatic fistulas in patients who undergo duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta.*

In duodenopancreatectomy, the use of ICG would allow us to see if there is hypoperfusion of the pancreatic stump, leading us to an enlargement of the resection leaving a well perfused anastomotic zone.

The extent of the resection has been done in other studies 1,5 – 2 cm to the left, away from the vascular watershed of the neck of the pancreas. This extension is not technically demanding. It usually requires 10 – 15 minutes of additional operating time (3,8).

Furthermore, most of the general surgeons at the *Hospital de Girona Dr. Josep Trueta* are trained to perform this technique, so there would be no extra cost for teaching and explaining how indocyanine green works.

Overall, the use of ICG would allow us to decrease the incidence of pancreatic fistulas, along with their complications, morbidity and mortality, and also to reduce the hospital stay and economic cost of patient care.

HYPOTHESIS

Primary hypothesis

The use of indocyanine green significantly reduces the occurrence of pancreatic fistulas in patients who undergo duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta.*

Secondary hypothesis

- The use of indocyanine green modifies the extent of surgical resection of the pancreas during the duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta.*

- The use of indocyanine green significantly reduces the hospital stay in patients who undergo duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta*.

- The use of indocyanine green significantly reduces the 30-day mortality in patients who undergo duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta*.

OBJECTIVES

Primary objective

To assess whether the use of indocyanine green significantly reduces the occurrence of pancreatic fistulas in patients who undergo duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta*.

Secondary objectives

- To assess whether the use of indocyanine green modifies the extent of surgical resection of the pancreas during the duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta*.

- To assess whether the use of indocyanine green significantly reduces the hospital stay in patients who undergo duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta*.

- To assess whether the use of indocyanine green significantly reduces the 30-day mortality in patients who undergo duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta*.

METHODS AND MATERIALS

1. STUDY DESIGN

This project is designed as a **quasi-experimental study** to determine if the use of indocyanine green significantly reduces the occurrence of pancreatic fistulas in patients who undergo duodenopancreatectomy at the *Hospital de Girona Dr. Josep Trueta*.

Patients will be divided into two groups: patients who underwent CDP without the use of indocyanine green, and patients who will undergo CDP with the use of indocyanine green.

Therefore, the two groups will be created without doing randomization.

The study will be **unicentric**, as said before, as it will be conducted at the *Hospital de Girona Dr. Josep Trueta*.

2. STUDY POPULATION

The study population will be composed by those patients who underwent CDP without the use of indocyanine green, and patients scheduled for CDP at the *Hospital de Girona Dr. Josep Trueta*, which will undergo the intervention with the use of ICG. All patients must meet the following inclusion and exclusion criteria:

2.1. INCLUSION CRITERIA

- **Controls:**
    - Patients who underwent CDP without the use of indocyanine green.
    - Registered at the *Hospital de Girona Dr. Josep Trueta* existing database system with all the following information:
        - Age, sex and IMC.
        - Toxic habits (smoking or alcoholism)
        - If the patient has diabetes mellitus or not.
        - If the patient has exocrine insufficiency.
        - If the patient did neoadjuvant therapy.

        - If the patient did ERCP prior to surgery.
        - Surgical time.
        - Intraoperative blood loss.
        - Pancreas texture or consistency.
        - Pancreatic ductal diameter.
        - If there was associated venous/arterial resection or not.
        - Use of pancreatic duct stents or not.
        - PDAC or non PDAC pathology.
        - If there were post-operative complications and which ones.
    - ≥ 18 years old.
    - Patients operated since 2018.
- **Cases:**
    - Patients scheduled for CDP at the *Hospital de Girona Dr. Josep Trueta.*
    - ≥ 18 years old.

2.2. EXCLUSION CRITERIA

- **General:**
    - Those patients in whom it is / it was not possible to perform a Blumgart anastomosis.
    - Patients in whom an extra gesture has / had to be made during surgery, such as resection of other organs.
    - Patients in whom, during surgery, resection is / was ruled out:
        - Distant disease.
        - Local involvement.
        - Positive aorto-caval ganglia.
        - Ischemia and hemorrhage that do not allow the reconstruction, so that it has to be left for a second time.
- **Cases:**
    - Iodine or shellfish allergy.
    - Patients not fit to undergo surgery and/or general anesthesia.
    - Clinical hyperthyroidism, autonomous thyroid adenomas and focal and diffuse autonomous alterations of the thyroid gland.

2.3. WITHDRAWAL CRITERIA

Whenever possible, efforts should be made to ensure that the participants complete the study. Patients initiating the study should adhere to the follow-up schedule outlined in the protocol, unless there is a justified reason:

- Revocation of the informed consent requested by the patient.
- Pre-operatively death, intraoperatively death or death within the first few post-operatively days (72h) in which there is no time for a fistula to develop.
- Patient lost to follow-up: When the investigator tries to contact the patient to assess their health status within the first 30 post-operative days, and the patient does not attend scheduled visits. If after two documented calls, the investigator is unable to communicate with the patient, he/she will be considered lost to follow up.

3. SAMPLING AND SAMPLE

3.1. SAMPLE SELECTION

3.1.1. Patients who underwent CDP without the use of ICG

The data of the first group will be extracted from the existing database of patients who have undergone this operation since 2018 at the *Hospital de Girona Dr. Josep Trueta*.

The year 2018 has been chosen because in 2016 the definition of fistula developed by ISGPS was updated, so that if we include patients operated before the 2016 the risk of information bias due to differences in the definition would increase.

Moreover, in 2018 at the *Hospital de Girona Dr. Josep Trueta*, the surgeons started to perform CDP with the same anastomosis technique, the Blumgart, so choosing patients operated from 2018 onwards, also avoids the variable "type of anastomosis performed", which could cause confusion and intervene in the results.

These patients will be selected by performing a retrospective consecutive sampling, selecting them from the moment the study is started until the 66 patients we need are reached.

3.1.2. Patients who will undergo CDP without the use of ICG

This group will be selected according to a prospective consecutive sampling, in which all patients scheduled for CDP at the *Hospital de Girona Dr. Josep Trueta* between 1st May 2024 and 31st June 2026, meet the inclusion criteria and do not meet the exclusion criteria, will be offered to participate in the current study, and therefore, performed with the use of indocyanine green.

3.2. SAMPLE SIZE

According to several studies the incidence of POPF still ranges between 3-45% of pancreatic operations, remaining largely unchanged over decades (3,5,6,8,12,23,24).

If we look at the *Hospital de Girona Dr. Josep Trueta* data, where we are going to carry out the study, the incidence of POPF is 30%.

We estimated the sample size using GRANMO software, where accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 66 subjects are necessary in first group (patients who underwent CDP without the use of ICG) and 66 in the second (patients who will undergo CDP with the use of ICG) to find as statistically significant a proportion difference, expected to be of 0.3 in group 1 and 0.1 in group 2. It has been anticipated a drop-out rate of 10%.

3.3. ESTIMATED TIME OF RECRUITMENT

We asked some surgeons at the *Hospital de Girona Dr. Josep Trueta* the approximation of the number of CDP performed each year in this hospital. Over the last few years, about 35 CDP have been carried out annually.

To reach the number of participants required to carry out the study, being 66 in the second group (patients who will undergo CDP with the use of ICG), and considering a 90% participation in our study, a recruiting time of approximately 26 months will be needed.

At the *Hospital de Girona Dr. Josep Trueta* we already have a database with more than 100 patients operated for CDP without the use of ICG, so we will not need extra time to recruit patients from this group.

4. STUDY VARIABLES

4.1. INDEPENDENT VARIABLE

The independent variable is the **use of indocyanine green during the CDP.**

It is a dichotomous nominal qualitative variable since it has only two categories: to be used on the CDP or not.

4.2. DEPENDENT VARIABLE

4.2.1. Primary dependent variable

The primary dependent variable is the **occurrence of pancreatic fistulas.**

This is also a dichotomous nominal qualitative variable since it has only two categories: fistula appearing or not appearing.

We will consider that there is a fistula, according to the definition given by the ISGPS, when it appears an abnormal communication between the pancreatic ductal epithelium and another epithelial surface, which leads to a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase normal activity (12,23,24).

In addition, it has to be associated with a clinical relevant development/condition related directly to the postoperative pancreatic fistula, meaning that whenever an increased amylase activity is found in the fluid from an operatively placed drain, which does not impact on the clinical outcome of the patient, no fistula should be reported (24). Therefore, we will only take into account grade B/C POPF.

4.2.2. Secondary dependent variables

The secondary dependent variables are:

- **Modification of the extent of surgical resection of the pancreas.** This is also a dichotomous nominal qualitative variable since it has only two categories: it modifies the extent of surgical resection of the pancreas or it does not modify it.

  We will consider that the extent of the resection of the pancreas is modified when after analyzing it with the ICG, we see a hypoperfusion in the area where the anastomosis has to be performed, which leads us to extend the resection to the left, normally 1.5 - 2 cm, away from the vascular watershed of the neck of the pancreas.

- **Hospital stay.** This is a discrete quantitative variable. It will be evaluated according to the number of days the patient is hospitalized.

- **30-day mortality.** This is also a dichotomous nominal qualitative variable since it has only two categories: the patient died within the first 30 post-operative days or the patient survived.

4.3. COVARIABLES

We are going to consider several covariables since they could be confounding factors:

NAME OF THE VARIABLE	**MEASURE INSTRUMENTS**	**DESCRIPTION**	**CATEGORIES OR VALUES**
AGE	Quantitative discrete	Age of the patient	Years
SEX	Qualitative nominal	Sex as reported in the clinical story	0: Man 1: Woman
IMC	Quantitative continuous	Patient's weight in kilograms divided by the square of the height in meters	Numeric with decimal
SMOKING	Qualitative ordinal	According to WHO (2003) Non-smoker: 0 cigarettes/day Mild: <5 cigarettes/day Moderate: 6-15 cigarettes/day Severe: >16 cigarettes/day	Non-smoker, mild, moderate or severe smoker
ALCOHOLISM	Dichotomous qualitative nominal	Alcoholism if ≥4 UBEs/day in man or ≥2 UBEs/day in woman	0: No 1: Yes
DM	Dichotomous qualitative nominal	Glycemia ≥200mg/dL with clinical signs, or if there is no clinical signs and ≥2 pathological determinations in ≥1 of the following:	0: No 1: Yes

		-Fasting basal glycemia ≥126mg/dL (≥7mmol/L) -SOG glycemia (75g) >200mg/dL -HbA1c >6.5%.	
EXOCRINE INSUFFICIENCY	Dichotomous qualitative nominal	Exocrine insufficiency if fecal elastase test (FE-1) <200µg/g	0: No 1: Yes
NEOADJUVANT THERAPY	Dichotomous qualitative nominal	Neoadjuvant therapy before the surgery	0: No 1: Yes
*ERCP PRIOR TO SURGERY**	Dichotomous qualitative nominal	ERCP before the surgery	0: No 1: Yes
SURGICAL TIME	Quantitative continuous	Time between the beginning of the surgery, when the incision is made until it is completed and the abdomen is closed	Hours and minutes
INTRAOPERATIVE BLOOD LOSS	Quantitative continuous	The estimation of blood loss in each patient will be done by specialized nursing staff**	Numeric with decimal
PANCREAS TEXTURE OR CONSISTENCY	Dichotomous qualitative nominal	Intraoperatively determined by the operating surgeon	Soft or firm
PANCREATIC DUCTAL DIAMETER	Quantitative continuous	Intraoperatively using a ruler	Numeric with decimal (in mm)
ASSOCIATED VENOUS RESECTION	Dichotomous qualitative nominal	If during surgery the tumor invades the vein and resection is necessary	0: No 1: Yes
ASSOCIATED ARTERIAL RESECTION	Dichotomous qualitative nominal	If during surgery the tumor invades the artery and resection is necessary	0: No 1: Yes
PDAC OR NON PDAC PATHOLOGY	Dichotomous qualitative nominal	According to anatomopathological results	PDAC or non PDAC pathology
USE OF PANCREATIC DUCT STENTS	Dichotomous qualitative nominal	If the pancreatic ductal diameter is <3mm a pancreatic duct stent will be used	0: No 1: Yes
POSTOPERATIVE COMPLICATIONS	Non dichotomous qualitative nominal	Postoperative complications different from the POPF	Delayed gastric emptying, infection...

***ERCP prior to surgery:** it implies higher infection risk and more complications.

**Nursing staff will do the estimation of blood loss in each patient as it follows:

- The weight of dry compresses shall be measured before use and after being wet or soaked by blood.
- The difference between the total weight of used compresses – total weight of dry compresses will be made.
- The weight difference will be translated into the blood loss considering that 1 g Is equal to 1 ml of blood.

5. INTERVENTION

In this study, we will have the patients divided into two groups: patients who underwent CDP without the use of indocyanine green, and patients who will undergo CDP with the use of indocyanine green.

In the first group we will have the **patients who underwent CDP without the use of ICG** at the *Hospital de Girona Dr. Josep Trueta*. The data of these patients will be extracted from the existing database of patients who have undergone this operation since 2018.

At the time of their intervention, these patients were already provided with the information sheet and informed consent document to perform the CDP (see **Annex 2**), however, they will be contacted, and after an explanation, they will be given a protocol information sheet (see **Annex 3**) and an informed consent form (see **Annex 5**) to determine whether they allow to have their data used for this study.

On the other hand, we will have **patients scheduled for CDP** at the *Hospital de Girona Dr. Josep Trueta* that meet all the inclusion criteria and none of the exclusion criteria.

These patients will have their pathology explained, including the treatment and what the CDP consists of. Additionally, all details related to the study will be provided (objectives, intervention, duration of each phase, follow-up, confidentiality, implications it would have on the surgery, risks and benefits, etc.).

After a detailed description, they will be proposed to participate in the study as the group of patients **who will undergo CDP with the use of ICG**. If the patient agrees to participate in our study, he/she will receive the protocol information sheet (see **Annex 4**) and the informed consent document (see **Annex 5**).

Prior to the operation, as did in the other group, the patient will undergo:

- Multiphase abdominal CT and thoracic CT scan.
- CBC with blood count, liver profile, nutritional profile and tumor markers.
- Anesthesia evaluation.

Once the day of surgery arrives, CDP will be performed following the same steps as in the first group (See **Introduction**), with the difference that once the pancreas has been resected, the piece is already out and before performing the pancreatic-jejunal anastomosis, the ICG will be injected.

We will use an ICG dose of 0,1-0.2 mg/kg, remaining within the safe spectrum, from 5 to 10 mg.

Once the ICG is injected, surgeon will wait up to 120 seconds to assess whether there is hypoperfusion of the pancreatic stump or not.

In case we see hypoperfusion, it would lead us to an enlargement of the resection to the left (normally 1,5 – 2 cm), away from the vascular watershed of the neck of the pancreas, leaving a well perfused anastomotic zone. This extension is not technically demanding. It usually requires 10 – 15 minutes of additional operating time.

Once the pancreatic resection is completed, we will proceed to perform Blumgart anastomosis and complete the surgery.

To avoid infections, possible complications and to follow a unified procedure, the protocol established by the hospital will be followed for all patients during the period from pre-admission to post-operative (as did in the other group) (See **Annex 7**).

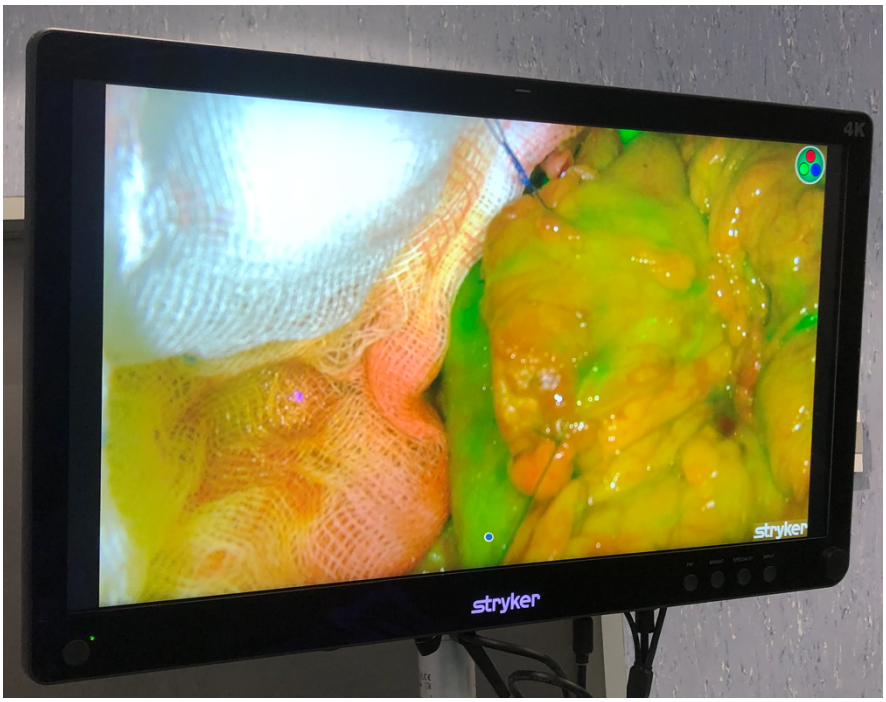
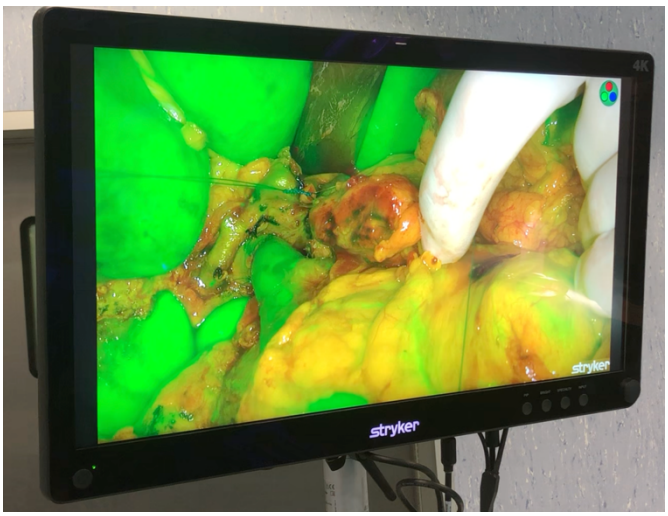


Figure 16: ICG administration during CDP. The anterior aspect of the pancreas is visualized.



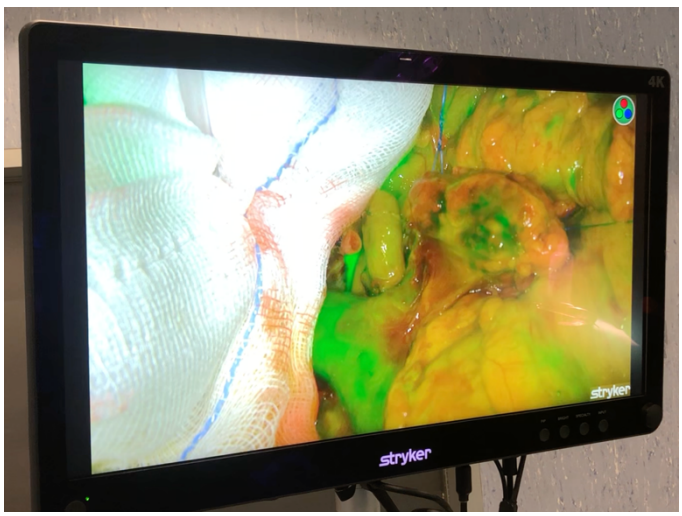


Figure 17 and 18: ICG administration during CDP. The surface of the pancreatic stump is visualized.

DATA COLLECTION

For the data collection, the data manager will create a computer-based database. All the information before, during and after the intervention will be recorded in a data record template, which will include the following information (see **Annex 6**). This information will be later transferred by the clinical coordinator in the database.

Also, the patient's identity will be codified in order to purse a pseoudonymization procedure.

To understand how the data collection will be carried out we have to take into account that there will be two groups:

- **Patients who underwent CDP without the use of ICG:** The data of the first group will be extracted from the already existing database of patients who have undergone this operation since 2018 at the *Hospital de Girona Dr. Josep Trueta*.

  The year 2018 has been chosen because in 2016 the definition of fistula developed by ISGPS was updated, so that if we include patients operated before the 2016 the risk of information bias due to differences in the definition would increase.

  Moreover, in 2018 at the *Hospital de Girona Dr. Josep Trueta*, the surgeons started to perform CDP with the same anastomosis technique, the Blumgart, so choosing patients operated from 2018 onwards, also avoids the variable "type of anastomosis performed", which could cause confusion and intervene in the results.

- **Patients who undergo CDP with the use of ICG:** The data for this second group will be collected in the same way in which the data for the first group has been collected. During the following post-operative days in which the patient is admitted, we will follow the protocol established by the *Hospital de Girona Dr.*

Josep Trueta (See **Annex 7**), making all the necessary tests at the time specified there, so that we can detect any pancreatic fistula that may present itself.
In addition, the use of ICG in these patients, the dose used and whether there was a need for repeat doses will also be specified in a section.

The clinical coordinator will be the responsible to review the data of the first group and fill out the data record template and the new database with their information.

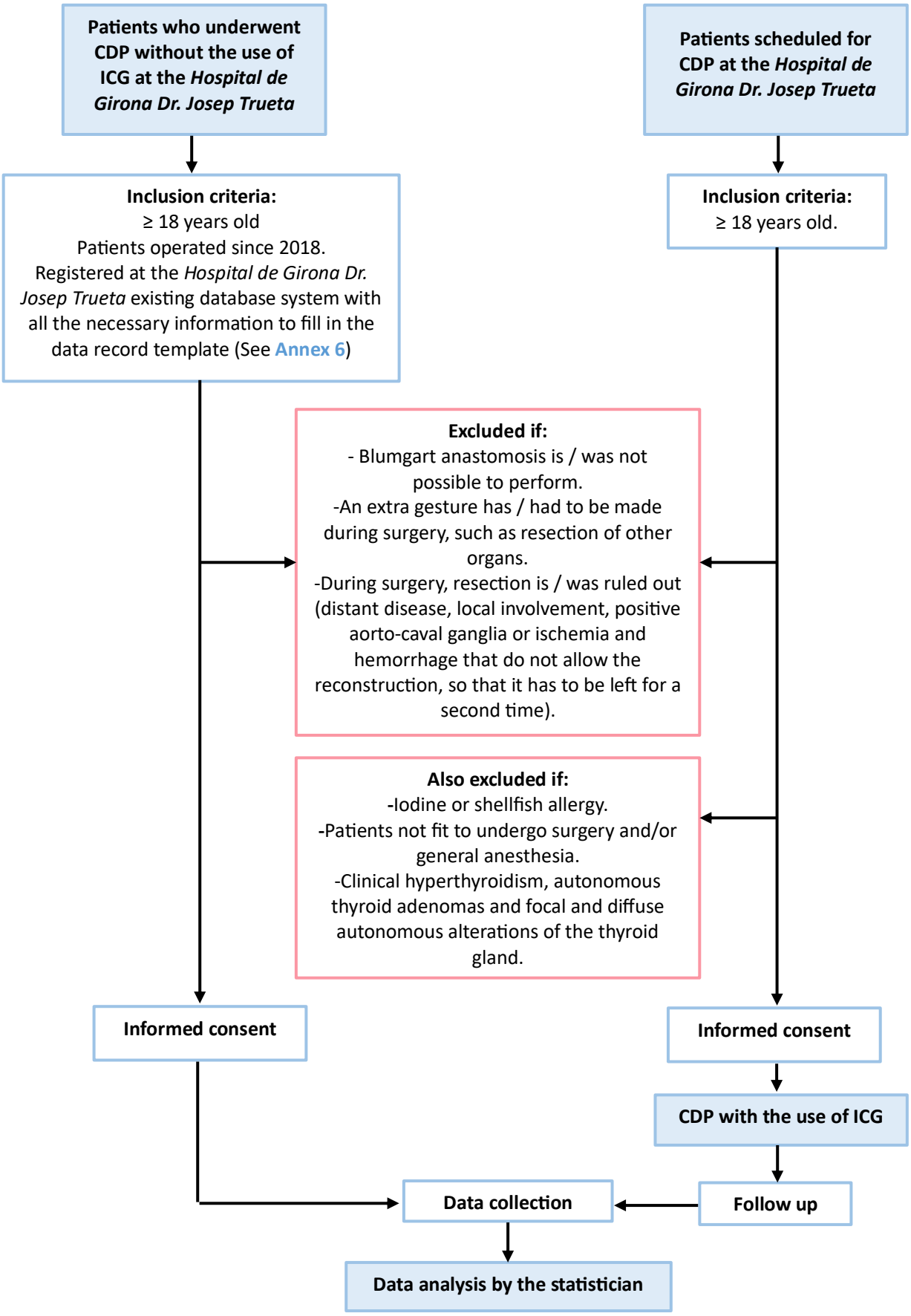
On the other hand, the data of the 2nd group will be collected by the surgeon in charge of each patient, who will fill in the new data record template. To facilitate the process, the data in this group will be entered and actualized in 3 moments:

- Once the intervention has been completed.
- Once after the discharge, occurrence of pancreatic fistula, or death of the patient.
- Once after the 30 post-operative day.

The clinical coordinator will be the one who will transfer all the data record template to the new computer-based database after the last data update by the surgeon. In case of any doubt, the clinical coordinator can always speak with the surgeon in charge and viceversa.

Once the data of every patient is collected, it will be sent to the statistician (stat) to analyze, which, to avoid a bias, will be blinded and she/he will not know whether indocyanine green was used in the patient's operation or not.

FLOW CHART


Patients who underwent CDP without the use of ICG at the *Hospital de Girona Dr. Josep Trueta*
Patients scheduled for CDP at the *Hospital de Girona Dr. Josep Trueta*
Inclusion criteria:
≥ 18 years old
Patients operated since 2018.
Registered at the *Hospital de Girona Dr. Josep Trueta* existing database system with all the necessary information to fill in the data record template (See Annex 6)
Inclusion criteria:
≥ 18 years old.
Excluded if:
- Blumgart anastomosis is / was not possible to perform.
-An extra gesture has / had to be made during surgery, such as resection of other organs.
-During surgery, resection is / was ruled out (distant disease, local involvement, positive aorto-caval ganglia or ischemia and hemorrhage that do not allow the reconstruction, so that it has to be left for a second time).
Also excluded if:
-Iodine or shellfish allergy.
-Patients not fit to undergo surgery and/or general anesthesia.
-Clinical hyperthyroidism, autonomous thyroid adenomas and focal and diffuse autonomous alterations of the thyroid gland.
Informed consent
Informed consent
CDP with the use of ICG
Data collection
Follow up
Data analysis by the statistician

SAFETY

Although mortality rate after CDP has decreased to less than 5%, the morbidity remains high (from 30 to 50%) even in high-volume centers (5,9,11–13,15,23).

The most common complication of the pancreaticoduodenectomy is the POPF, being the main determinant of serious postoperative morbidity and mortality related to pancreatic resection and playing a major role in terms of hospital stay and economic impact (4–9,11,12,23–27).

One of the most important determinants of safe CDP and to reduce the risk of POPF is the successful pancreatico-enteric anastomosis (3–5,8,9).

In this study we will use ICG to obtain a well vascularized pancreatic remnant. This will lead to an anastomosis in a well irrigated territory, thereby increasing the chances of a successful one and addressing this issue effectively.

Other complications of CDP include delayed gastroemptying, hemorrhage, and infections, which are among the most frequent. Additionally, complications such as sepsis, reoperation, insertion of a drain, malabsorption, steatorrhea, cardiovascular phenomena and death, among others, may also occur (11,16,17,28).

These complications would not be modified in our intervention, as the surgical technique and procedure will remain the same as in patients in whom ICG is not used.

In any case, during the post-operative period, as always done, the patient will stay in the hospital and will be cautiously guarded, so that if any of these complications appear, they can be treated as soon as possible.

In terms of ICG, we must be aware of the most important contraindication of its use: iodine allergy. In addition, known or suspected allergy to shellfish is a relative contraindication to fluorescence imaging with ICG (9,36,39).

ICG is also contraindicated in patients with clinical hyperthyroidism, autonomous thyroid adenomas and focal and diffuse autonomous alterations of the thyroid gland (46).

Although reactions to ICG are extremely rare, in this study we have included exclusion criteria to avoid possible harm to people with these conditions.

We should also consider allergies to medications such as analgesics or anesthesia. Prior to the operation, the patient will have a visit with the anesthesiologist to assess the potential risks of anesthesia and surgery and to determine if the patient can be operated on.

Additionally, before the operation, the patient will undergo other essential tests to ensure the safest possible surgery: Multiphase abdominal CT, thoracic CT scan, CBC with blood count, liver profile, nutritional profile and tumor markers.

To avoid infections, possible complications and to follow a unified procedure, the protocol established by the *Hospital de Girona Dr. Josep Trueta* will be followed for all patients during the period from pre-admission to post-operative, which increases the safety of the study (See **Annex 7**).

Concerning the impact of FI on intraoperative patient risks, it has been seen that it exerted no impact on the risk of hemorrhage or the duration of the surgery (36).

It has also been considered false that inadequate fluorescence and the need for repeat dosing constitute a major limitation (36).

Finally, we have to take into account that the surgeons of the *Hospital de Girona Dr. Josep Trueta* already use ICG for other purposes, so that they already have experience in this field, which further increases the safety of this study.

To sum up, even that there are some adverse effects of ICG, its use during fluorescence-guided surgery should be considered very safe (32), so that the benefits of this study far outweigh the risks.

STATISTICAL ANALYSIS

The analysis of the data obtained will be performed by a professional **statistician analyst**, who will do the investigation blinded to ensure he/she does not know which is the group where we used ICG and which is the group in which we didn't use it, representing the control group. By doing so, any potential bias is minimized, and the analyst's knowledge of the group allocation will not interfere with the final results.

The software used will be Statistical Package for Social Sciences (SPSS) software version 28.1. In all case, results will be considered statistically significant if value of p is <0.05, defining a confidence interval of 95%

1. DESCRIPTIVE ANALYSIS

In both groups (patients who underwent CDP without ICG and patients scheduled for CDP at the *Hospital de Girona Dr. Josep Trueta,* which will undergo CDP with ICG), the stat will summarize the **quantitative variable** (hospital stay) by using *means, standard deviation, medians and interquartile range (IQR).* **Qualitative variables** (use of indocyanine green during the CDP, occurrence of pancreatic fistulas, modification of the extent of surgical resection of the pancreas and 30-day mortality) will be described using *means of proportions.*

These descriptives will be stratified between patients who underwent CDP without ICG and patients scheduled for CDP at the *Hospital de Girona Dr. Josep Trueta,* which will undergo CDP with ICG, and additional stratification will be done by the covariates.

2. BIVARIATE ANALYSIS

Student's t test will be used to study if there are differences depending on the use of ICG or not with **quantitative variables** (hospital stay).

Chi-square or Fisher's exact test (if the expected number of cases in a cell will be lower than 5) will be used for the difference of proportions of the **qualitative variables** (use of indocyanine green during the CDP, occurrence of pancreatic fistulas, modification of the extent of surgical resection of the pancreas and 30-day mortality) between the two

groups (patients who underwent CDP without ICG and patients scheduled for CDP at the *Hospital de Girona Dr. Josep Trueta,* which will undergo CDP with ICG).

3. MULTIVARIATE ANALYSIS

It will be necessary to do a multivariate analysis adjusting the **independent variable** with the **dependent variables** according to the **covariates** that may interfere in the results, to avoid possible confusion.

To achieve this, a *COX model*, adjusted by a *Propensity Score*, will be used.

The *Propensity Score* will determine the probability of being in the pre- period (patients who underwent CPD without the use of ICG) and the probability of being in the post-period (patients who will undergo CPD with the use of ICG), considering all the covariables explained in this protocol.

This approach will enable the matching of patients in the pre- period with those in the post- period who have a similar *Propensity Score*, thus avoiding confusion.

This multivariate analysis will allow us to obtain a *Hazzard ratio* of the effect of ICG on pancreatic fistulas.

WORK PLAN AND CHRONOGRAM

1. RESEARCH TEAM MEMBERS

The essential personnel in the different stages of the quasi-experimental study include:

- **Main investigator (MI):** is the person leading the study, who is in contact with the coordinator of the hospital and makes sure that everything goes as it should.
- **Hospital coordinator (HC):** in the hospital there will be a hepatobiliary surgeon who will be the coordinator who collects the data into the data record template, together with the surgeon in charge of each patient, fills out the new computer-based database with this information, and ensures that the whole procedure is followed as specified. In addition, he/she is the one who communicates with the MI in case of any doubts. The clinical coordinator will meet once every 3 months with the MI.
- **Hepatobiliary surgeons:** will be the ones to perform the interventions.
- **Nurses:** nurses from the hospital who are present in the pre-operative process, in the intervention or in the post-operative process while the patient is admitted.
- **Data manager (DM):** person who creates the database.
- **Professional statistical analyst:** will do the analysis of the data obtained.
- **Other staff:** other physicians involved in the management of these patients, anaesthesiologists, anatomopathologists, digestologists, pharmacologists, radiologists, nutritionists…

2. STUDY STAGES

The whole study will have an estimated duration of 40 months (starting in November 2023 and finishing in February 2027). The steps done on this quasi-experimental study will succeed according the following order, grouped in 6 stages each consisting of different activities:

2.1. STAGE 1: ELABORATION OF THE PROTOCOL AND STUDY DESIGN (4 months: November 2023 – February 2024)

1) **First session** (November 2023, completed): in order to think about this project and what gaps of information there were in this area of study. The development

of this project was accorded by Dra. Laia Falgueras Verdaguer and Clàudia Vila Matamala.

2) **Bibliographic research and protocol elaboration** (November 2023 – January 2024, completed): an extensive bibliographic research has been done to soak up the latest evidence on CDP, POPF and ICG, as well as the redaction of the protocol.
3) **Hospital participating contact** (February 2024): the MI will propose to the *Hospital de Girona Dr. Josep Trueta* to participate in the study.
4) **Database creation** (February 2024): *Hospital de Girona Dr. Josep Trueta* already has a database where we already have more than 100 registered patients who have been operated on for CDP without the use of ICG and all the information we need for this study in these patients is being recorded.

   This database will be used to gather the information of the controls. However, a new one will be created by the data manager (10 hours are expected), to include other variables that are not taken into account in the first one, such as the use of the ICG, the dose used… (although we know that ICG has not been used in all patients so far), and that do not include other data that are not of interest for our study.

2.2. STAGE 2: ETHICAL APROVAL (3 months: February – April 2024)

5) **Ethical evaluation and approval:** the MI will present the protocol to the Ethics Committee of Clinical Investigation (CEIC) of *Hospital de Girona Dr. Josep Trueta* for its ethical approval. Any suggestions will be considered and consequently modified to achieve the CEIC's conditions.
6) **Contracting an insurance:** Carried out by the research team (RT).

2.3. STAGE 3: COORDINATION AND HEALTH PROFESSIONALS TRAINING (May 2024)

7) **Meeting** (May 2024): The MI will meet the research team of the *Hospital de Girona Dr. Josep Trueta* and the decision of who will be the HC will be made.
8) **Informative sessions** (May 2024): The surgeons in the hospital already know how to perform CDP and how to use indocyanine green, but there will be sessions to explain in detail how to follow the protocol properly, the doses of ICG, when to

inject it, how long to wait to assess hypoperfusion, and that in case of hypoperfusion, the pancreas resection should be extended to the left, so that it is done uniformly in all patients. They will also receive a copy of this protocol.

In these sessions they will learn how to use the data record template and the database correctly and it will be explained the sections to be filled out.

2.4. STAGE 4: SAMPLE RECRUITMENT, INTERVENTION, AND DATA COLLECTION (27 months: May 2024 – July 2026)

9) **Sample recruitment:** patients will be recruited by a non-probabilistic consecutive method for this study. They will have to meet all the inclusion and none of the exclusion criteria, as well as sign the informed consent. The recruitment will last until each group is formed of 66 patients, which is believed to take up to 26 months.

   The sample recruitment will take place in parallel with activities 9 and 10.

10) **Intervention:** as the patients reach the time of the surgery, the intervention, which is the CDP with the use of ICG, will take place. Data will be entered once the intervention has been completed.

11) **Follow up:** Once the intervention has taken place, the patient will remain in the hospital, and some tests will be ruled, according to the protocol established by the *Hospital de Girona Dr. Josep Trueta* (See **Annex 7**), so that any possible occurrence of fistulas can be assessed. The data will be updated once after the discharge, occurrence of pancreatic fistula, or death of the patient, and once again after the 30 post-operative day.

2.5. STAGE 5: DATA ANALYSIS AND INTERPRETATION (2 months: August – September 2026)

12) **Statistical analysis** (August 2026): performed by a statistician, who will analyze all the data collected through a descriptive, bivariate and multivariate analysis. Posteriorly, he/she will interpret the data obtained.

   He/she will do the investigation blinded to ensure he/she does not know which is the group where we used ICG and which is the group in which we didn't use it, representing the control group. This way any potential bias is minimized, and the

analyst's knowledge of the group allocation will not interfere with the final results.

13) **Results and conclusions** (September 2026): the statistician will present the results to the whole research team, who will discuss the outcomes and draw conclusions.

2.6. STAGE 6: RESULTS PUBLICATION AND DISSEMINATION (5 months: October 2026 – February 2027)

14) **Article writing, revision and publication** (October – November 2026): the MI will write the final article with the results and conclusions. It will be edited and supervised by an english corrector and published afterwards.

15) **Dissemination** (December 2026 – February 2027): the written study will be published as a journal article and the article will be presented to the *Asociación Española de Cirujanos (AEC)*. National and international congresses will be attended to present the results, including the *International Hepato-Pancreato-Biliary Association (IHPBA) World Congress* and *European-African Hepato-Pancreato-Biliary Association (E-AHPBA) Congress.*

ACTIVITIES	2023		2024												2025	2026												2027		Responsible personnel
	N	D	J	F	M	A	M	J	JL	A	S	O	N	D		J	F	M	A	M	J	JL	A	S	O	N	D	J	F	
STAGE 1: ELABORATION OF THE PROTOCOL AND STUDY DESIGN																														
First session																														MI
Bibliographic research and protocol elaboration																														MI
Hospital participating contact																														MI
Database creation																														DM
STAGE 2: ETHICAL APROVAL																														
Ethical evaluation and approval																														CEIC
Contracting an insurance																														RT
STAGE 3: COORDINATION AND HEALTH PROFESSIONALS TRAINING																														
Meeting																														MI, HC and hepatobiliary surgeons
Informative sessions																														
STAGE 4: SAMPLE RECRUITMENT, INTERVENTION AND DATA COLLECTION																														
Sample recruitment																														Hepatobiliary surgeons
Intervention																														Hepatobiliary surgeons and nurses
Follow up																														
STAGE 5: DATA ANALYSIS AND INTERPRETATION																														
Statistical analysis																														Stat.
Results and conclusions																														RT
STAGE 6: RESULTS PUBLICATION AND DISSEMINATION																														
Article writing, revision and publication																														MI
Dissemination																														

BUDGET

EXPENSES	UNIT COST	UNIT	TOTAL
PERSONNEL			
Data manager	40€/h	10h	400€
Hired statistician	40€/h	35h	1400€
SUBTOTAL			**1800€**
INSURANCE POLICY			
Liability insurance	30.000€	1	**30.000€**
MATERIAL			
ICG	17€/vial	70 vials	**1190€**
Cover to keep the probe sterile	20€	70 units	**1400€**
Protocol information sheet (controls)	0,01€/page	4 pages x 66 patients	**2,64€**
Protocol information sheet (cases)	0,01€/page	7 pages x 66 patients	**4,62€**
Informed consent document	0,01€/page	2 pages x 132 patients	**2,64€**
Study protocol	0,01€/page	105 pages	**1,05€**
PUBLISHING			
English correction			**150€**
Article publication and open access			**1500€**
DISSEMINATION COST			
Asociación Española de Cirujanos (AEC)	600€	1 inscriptions fees	**600€**
	350€	1 trip and accommodation	**350€**
E-AHPBA Congress	800€	1 inscription fees	**800€**
	700€	1 trip and accommodation	**700€**
IHPBA World Congress	925$ (853,82€)	1 inscription fees	**853,82€**
	800€	1 trip and accommodation	**800€**
TOTAL: 40.154,77 €			

The personnel participating in the research team will not receive additional compensation. It is considered that their motivations for joining the study should not be incentivized for any economic grounds, because researchers are rewarded by the scientific prestige and intellectual gains.

The informative sessions will be conducted by the main investigator, who will explain how to follow the protocol step by step. He/she will also not receive any financial reward. During these briefings, a paper copy of the study protocol will be provided to the hepatobiliary surgery service, which would have a cost of only 1,03€. In addition, the e-mail addresses of the session members will be collected to send each one of them a digital copy of the protocol so that they can consult it whenever they need to.

Moreover, the *Hospital de Girona Dr. Josep Trueta* already dispose of the materials for the surgery (CDP), so there will be no problems when ordering them as it is a common procedure, meaning that this material will not be considered in the study budget.

The only thing to be considered is the price of the vials and of the cover to keep the probe sterile. We only require 66 vials and covers, but we will purchase 70 as a precaution in case of breakage or other issues.

We must also have into account that these patients routinely undergo all the tests following the protocol established by the *Hospital de Girona Dr. Josep Trueta* (See **Annex 7**), so these processes are already implemented in the clinical practice of the hospital. Therefore, no additional material or goods will be required.

FEASIBILITY

First of all, the research team who has designed the study are well prepared to conduct it. This is a unicentric quasi-experimental study that will be carried out in the *Hospital de Girona Dr. Josep Trueta.* This center has a multidisciplinary team including general surgeons, anaesthesiologists, anatomopathologists, digestologists, radiologists, pharmacologists, nutritionists…

We have to take into account that hepatobiliary surgeons are already familiar with CDP surgery and know perfectly well how to use the ICG, meaning that they are already experienced and formed. This eliminates the need for additional training on its application.

However, to ensure uniformity in the execution of the surgical technique, informative sessions are planned to remind all surgeons of the procedure's protocol outlined in this document. Additionally, an online database will be made accessible to researchers.

In terms of the sample, the number of patients needed to perform this study is 66 in each group, which will be collected in 26 months, which is a reasonable time, from a logistical point of view.

We will not require much additional material since all the necessary equipment is routinely used in clinical practice at this hospital. Therefore, we will only need to buy the ICG, which is very economically priced (17€/vial), the cover to keep the probe sterile and contract an insurance. Together with the other expenses discussed in the budget section, we can see that the cost is fully compensated with the economic benefits of the postoperative cost of the patient. Consequently, the price of our study is low.

Finally, the planning and timing are well defined in our work plan and follow adequate timelines so that all activities can be carried out properly.

Summarizing all this information, it is concluded that this study has a **feasible realization.**

ETHICAL AND LEGAL CONSIDERATION

The study will be performed under the requirements established by the World Medical Association (WMA) in the **Declaration of Helsinki** of *Ethical Principles for Medical Research Involving Human Subjects* (last revision in the 64th General Assembly, Fortaleza, Brazil, in October 2013) (47). This quasi-experimental study obeys the Principles of Biomedical Ethics from Beauchamp and Childress, more commonly known as the four fundamental ethical principles:

- **Beneficence:** it is the moral obligation to act for the benefit of others. In this study this principle is fulfilled since all patients are treated with CDP, which is the curative treatment for their pathologies. Furthermore, the surgeries will be performed by expert hepatobiliary surgeons with experience in this technique.
  In addition, the implementation of ICG in surgery involves very few risks compared to all the benefits it can have, such as the non-occurrence of pancreatic fistula, which would mean a faster recovery.
- **Non-maleficence:** consists of not doing to others what is rationally inappropriate for humans. To meet the non-maleficence, exclusion criteria have been used to avoid harm to patients who could be at risk in this study, such as those with potential allergies to iodine or shellfish. In addition, doses of 0.1 - 0.2 mg/kg will be administered and may reach up to 10 mg, which would be the limit established to guarantee the maximum possible safety and avoid toxicity. Furthermore, CDP continues to be performed so that we are not depriving patients of their appropriate treatment for their disease. Also, to avoid infections and possible complications the protocol established by the *Hospital de Girona Dr. Josep Trueta* will be followed for all patients during the period from pre-admission to post-operative, which increases the safety of the study (See **Annex 7**). Moreover, in the event of a complication, the hospital has available personnel to solve the problem as efficiently as possible. Finally, if any inconvenient occurs, the insurance coverage of our patients will be guaranteed.

- **Justice:** an equitable distribution of health resources will be respected in the study, and any discrimination to any group of patients will be avoided to guarantee the principle of justice.

  All the patients who meet the inclusion criteria and do not have any exclusion criteria will have the same possibility to enter in the study. From those, everyone will be informed of the details of the study.

- **Autonomy:** it means recognizing patient's capacity to make certain choices about actions related to them, based on their values and preferences.

  The patients will be given a **protocol information sheet** (see **Annex 3** and **4**) in an understandable language to provide the knowledge and understanding of the study. In addition, **written informed consent** (see **Annex 5**) must be obtained from each participant before taking part in the study, assuring that they understand what it entails, have freedom to refuse entry and can withdraw whenever they wish without prejudice. In consequence, the decision whether or not to participate in the study will be respected as it indicates *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 (48).*

1. PRIVACY AND CONFIDENCIALITY

All patient data will be anonymous, preserving the confidentiality and privacy of the patient according to:

- *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales* (49)
- *Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos y por el que se deroga la directiva 95/46/CE (Reglamento general de protección de datos) (50).*

All data collected will only be used for the intended purpose of this study.

2. COMITÈ D'ÈTICA D'INVESTIGACIÓ CLÍNICA (CEIC)

The present project will be submitted to the CEIC from *Hospital de Girona Dr. Josep Trueta*. Suggestions given will be considered and its approval will be compulsory before starting the study.

The system of checks to be carried out during the course of the research shall be in accordance with the *Ley 14/2007, de 3 de julio, de Investigación biomédica* (51).

Furthermore, as indocyanine green is not yet indicated for visualization of pancreatic perfusion, our study will also stick to the regulations for clinical drug trials, in accordance with:

- *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 (52).*
- *Documento de instrucciones de la AEMPs para la realización de ensayos clínicos a España. V13:30/11/2020 (53).*
- *Reglamento (UE) no 536/2014 del parlamento europeo y del consejo de 16 de abril de 2014 sobre los ensayos clínicos de medicamentos de uso humano (54).*
- *Normas de Buena Práctica clínica del ICH (International Conference on Harmonization): Institutional Reveiw Board / Independent Ethics Committee (1996) (55).*

3. TRANSPARENCY

All the investigators will have to declare no conflict of interest, and they will also have to agree to publish all data and results with total transparency, including unfavorable data or events.

LIMITATIONS OF THE STUDY

The greatest disadvantage of **the quasi-experimental design** is that randomization is not used when creating the two groups, limiting the study's ability to conclude a causal association between an intervention and an outcome.

As the groups are non-equivalent, and the sampling method is a consecutive non-probabilistic one, it is possible to encounter a selection bias, when a sample does not resemble the reality of the population, obtaining unrepresentative results. However, these problems will be minimized in the multivariate analysis, when the effects of potential confounding factors will be adjusted, and thus interval validity of the study will increase.

The other main limitation is that patients know which group they belong to and therefore whether ICG is used in their operation. In addition, surgeons, having to administer and use the ICG, also cannot be blinded, so that it cannot be double blind. In any case, we have to keep in mind that the presence or not of fistula is evaluated in a very objective way and therefore, even if the surgeon who evaluates it is not blinded, it will be reliable. Moreover, to avoid the bias, statistical analysist will be blinded, so she/he will not know which patient receives each technique.

On the other hand, we think that for many people the fact that the study is unicentric can be a limitation, but in our case, we have prioritized obtaining results with high internal validation in order to determine exactly the problem and how to solve it.

Another limitation could be the equipment unavailability to for using FI and ICG, but the *Hospital de Girona Dr. Josep Trueta* already has this equipment as they use the ICG for other type of surgeries.

Finally, we have to consider withdrawals and losses of patient for different reason. We have anticipated this problem by calculating a drop-out rate of 10% when we calculate our sample size.

CLINICAL AND HEALTHCARE IMPACT

The pancreatic fistula is the most common complication of the pancreaticoduodenectomy, being the main determinant of serious postoperative morbidity and mortality related to duodenopancreatectomy and playing a major role in terms of hospital stay and economic impact (4–9,11,12,23–27).

Despite numerous trials aimed at reducing the incidence of POPF, its incidence still ranges between 3-45% of pancreatic operations, remaining largely unchanged over decades (3,5,6,8,12,23,24).

The exact pathophysiology of fistulas and why they appear is not yet known, but several studies have begun to suggest that fistulas may be related to hypoperfusion of the pancreatic remnant after surgery, which would cause transection margin ischemia and inflammation, post pancreatectomy pancreatitis, and necrosis, leading to a failure of healing at the pancreatico-enteric anastomosis resulting in pancreatic leakage (3–5,7–9,27,29,30).

In this study we strongly believe that the use indocyanine green during the duodenopancreatectomy would allow to see if there is hypoperfusion of the pancreas, leading to an extension of the pancreatic resection to the well perfused area, and thus avoiding the appearance of a pancreatic fistula.

Overall, the use of ICG would allow us to decrease the incidence of pancreatic fistulas to a 10%, along with their complications, morbidity and mortality, and also to reduce the hospital stay and economic cost of patient care.

Conducting this study would provide our healthcare system with the knowledge that would lead to future benefits for the patients and for the hospital, in the hope of improving the health outcomes of these patients.

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ANNEXES

ANNEX 1 - Intraoperative images of the CDP

All images have been kindly provided by the hepatobiliary surgery service of the *Hospital de Girona Dr. Josep Trueta* or taken during the internship period in this hospital.

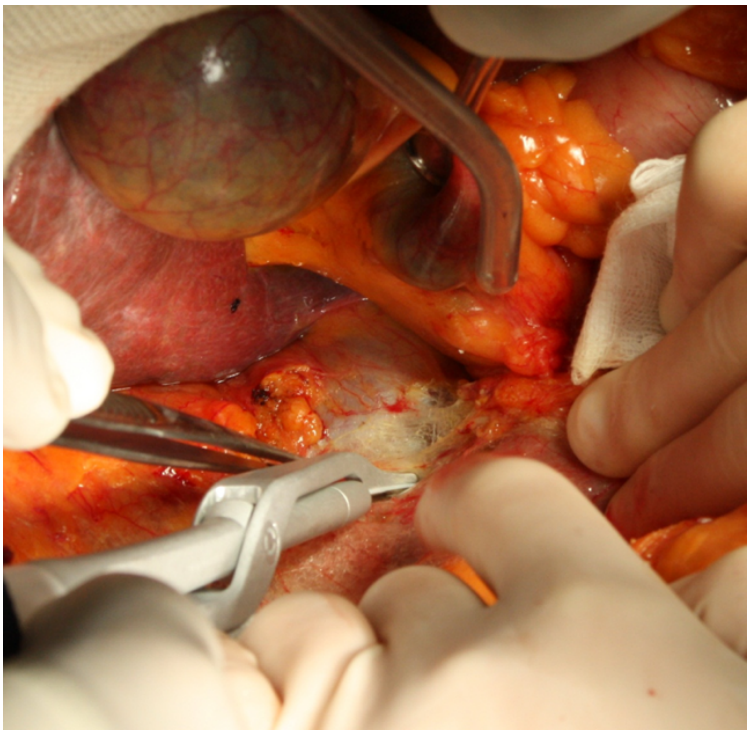


Figure 21: Kocher's maneuver.

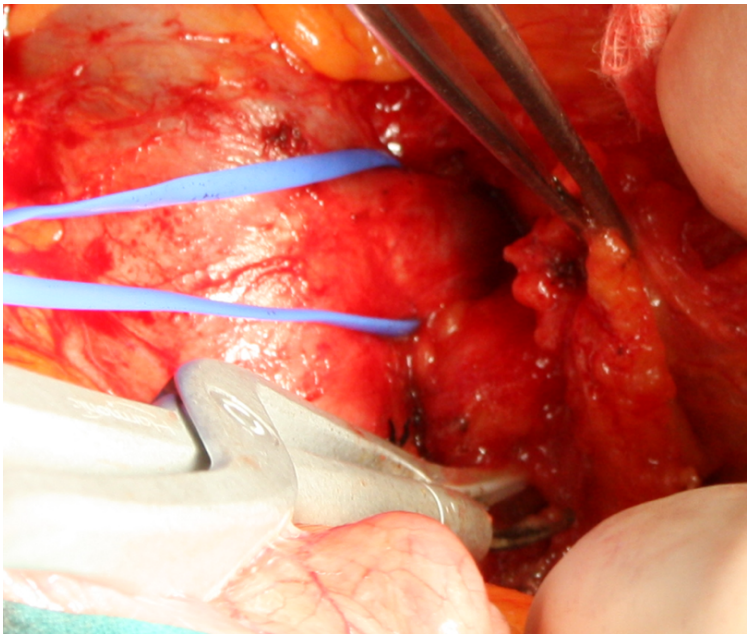


Figure 22: Inter aorto-caval lymphadenectomy. If there is lymph node metastasis to the interaorto-caval area, surgery is not continued because it is considered distant disease (metastatic).

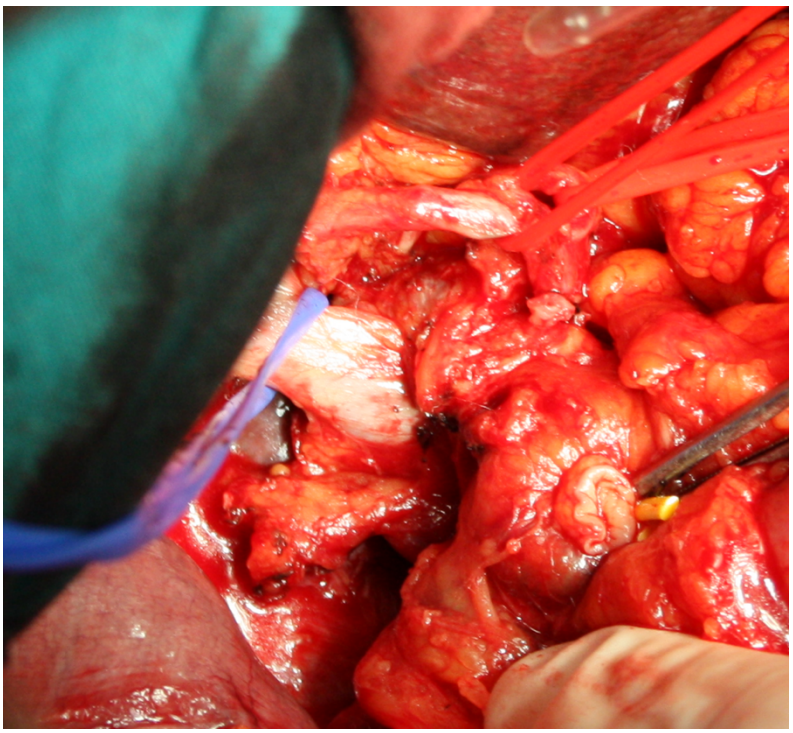
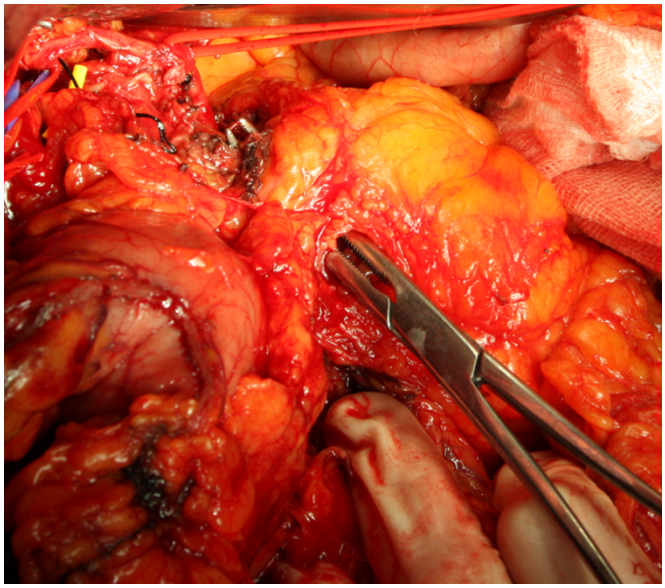


Figure 23: Hepatic hilum dissection and lymphadenectomy.
Red vessel-loop, Hepatic artery; *Blue vessel-loop,* Portal vein; *Yellow vessel-loop,* Severed bile duct.



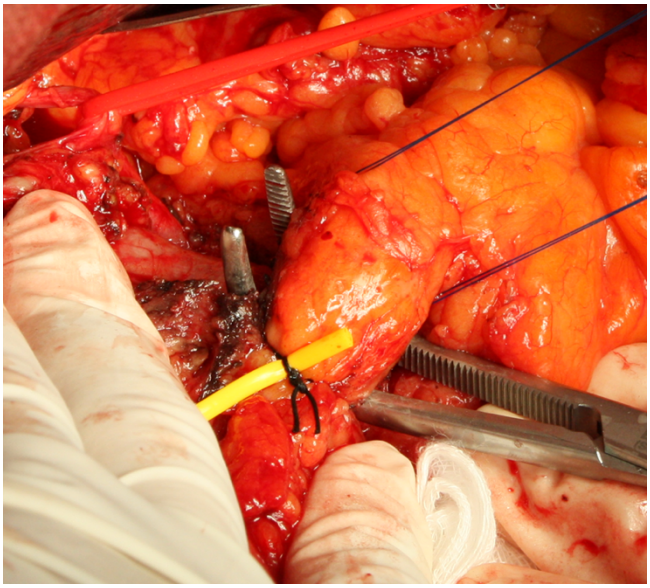
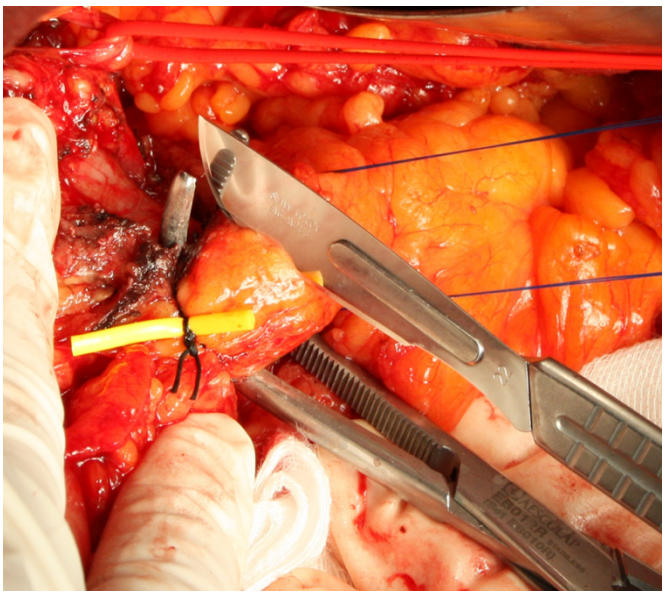


Figure 24 and 25: Dissector passing the retropancreatic sulcus over the anterior aspect of the SMV – portal vein.



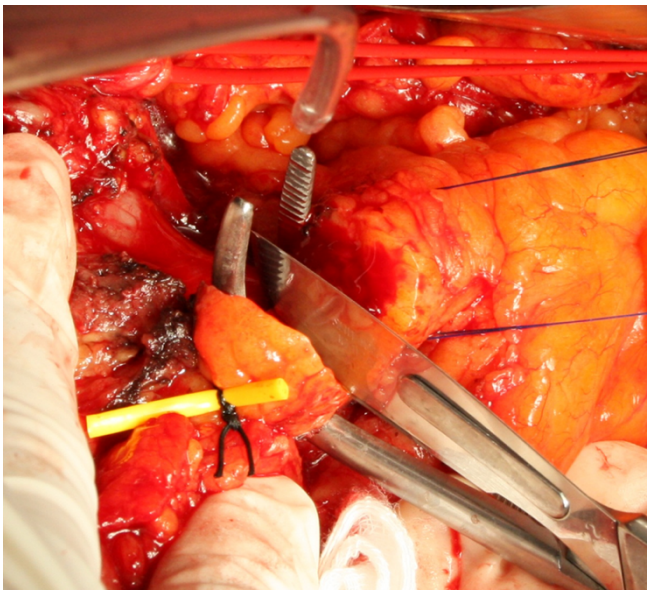
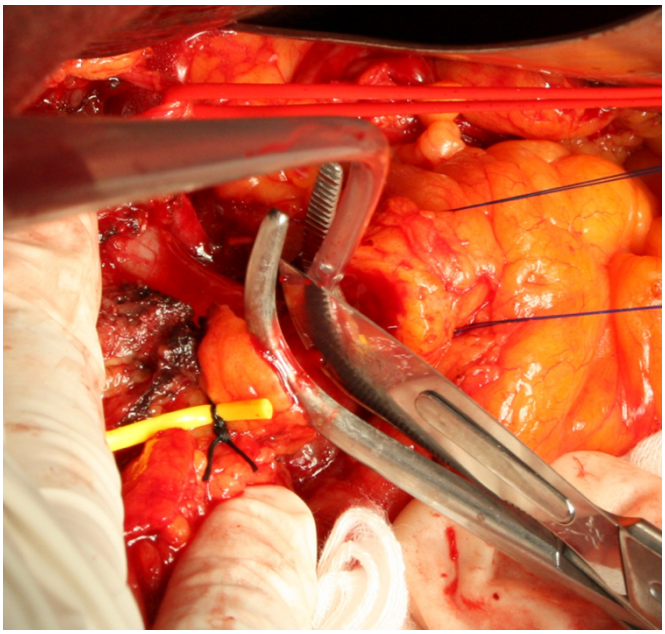


Figure 26 and 27: Section of the pancreatic neck (step 1 and 2)



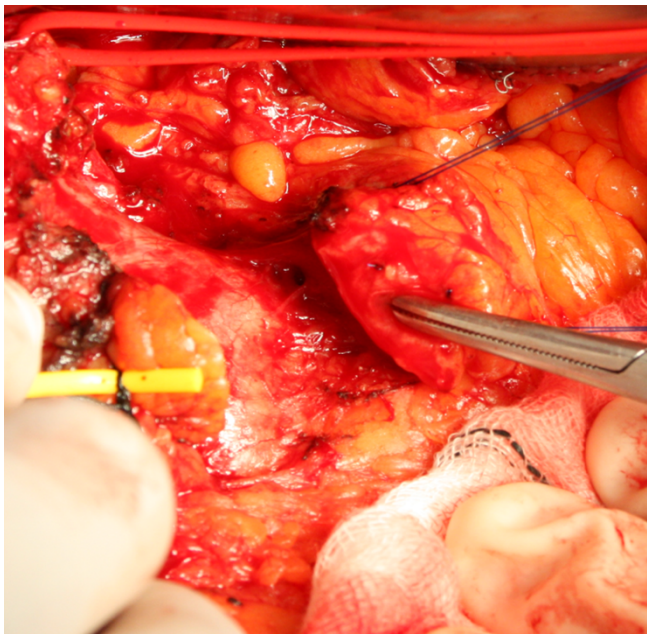


Figure 28 and 29: Section of the pancreatic neck (step 3 and 4)

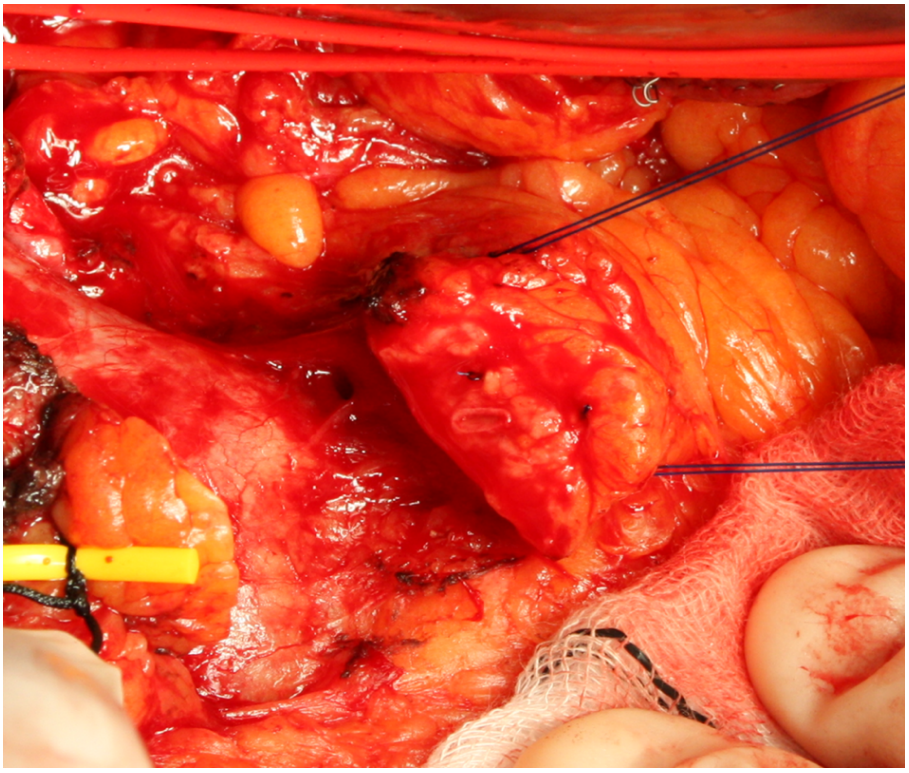


Figure 30: Surface of the pancreatic stump.
That is the moment we would inject ICG in our study.

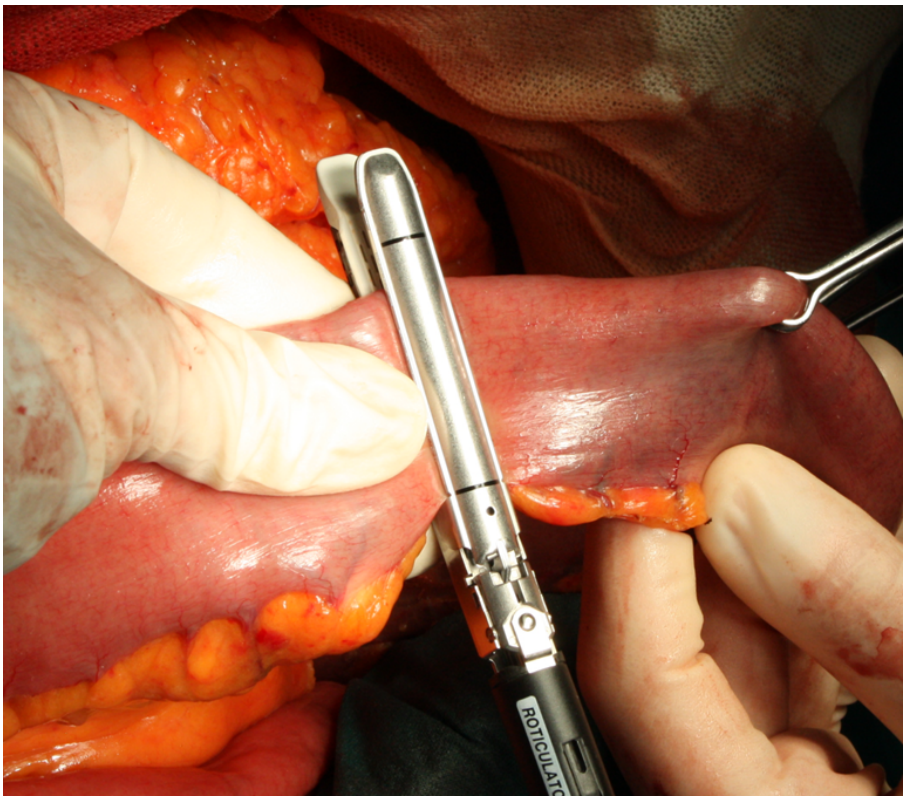


Figure 31: Section of the jejunum.

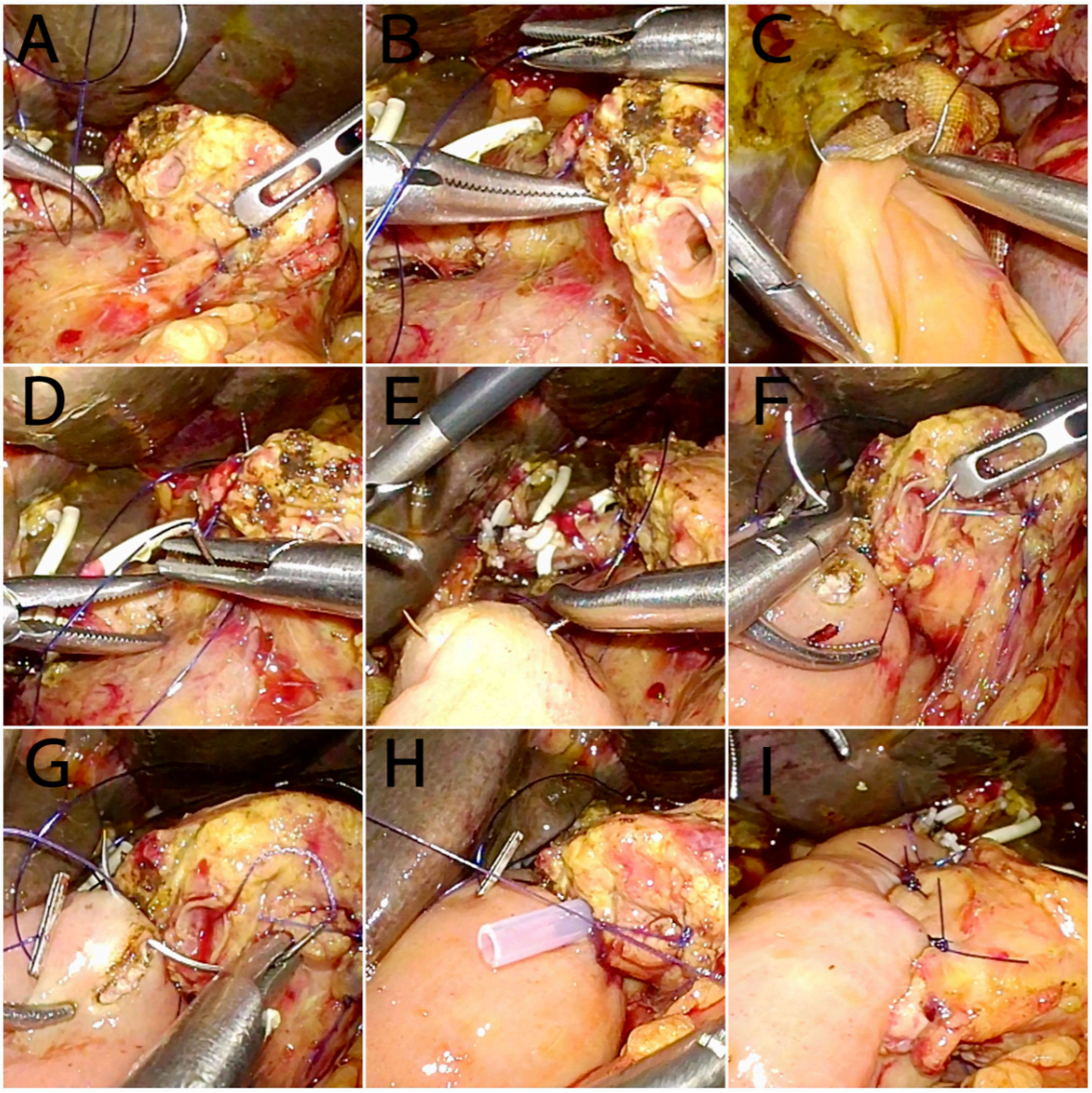


Figure 32: Reconstruction. Pancreatic duct connected to the jejunum with Blumgart anastomosis. Intraoperative images of the modified Blumgart pancreaticojejunostomy procedure. (A) The specimen has been removed; pancreaticojejunostomy proceeds next. (B) At 1.5 cm from the edge of the pancreatic stump, a 3-0 large needle penetrates the pancreas. (C) Stitching of the posterior wall of the jejunum. (D) At 0.5 cm from the edge of the pancreatic stump (at the same level as the previous stitch), the needle penetrates the pancreas. (E) Stitching of the anterior wall of the jejunum. (F,G) Stitching of the pancreatic duct and jejunal mucosa. (H) An internal pancreatic stent is placed, and the duct-to-mucosa anastomosis is continued. (I) After suturing using 4–5 needles, all sutures were tied. *Extracted from (56).*

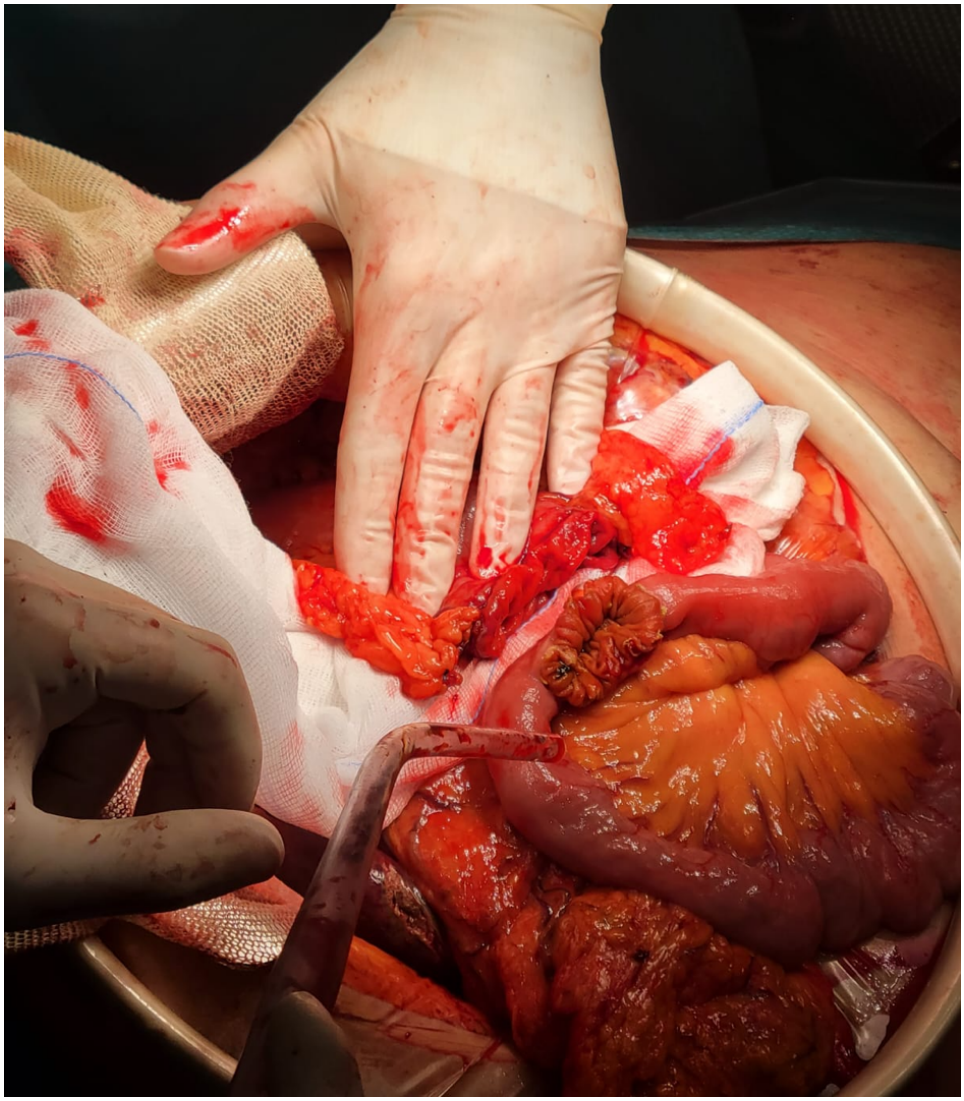


Figure 33: Sectioned antrum. Gastrojejunal anastomosis.

ANNEX 2 – Information sheet and informed consent document to perform the CDP

Hospital Universitari de Girona Doctor Josep Trueta
Institut Català de la Salut

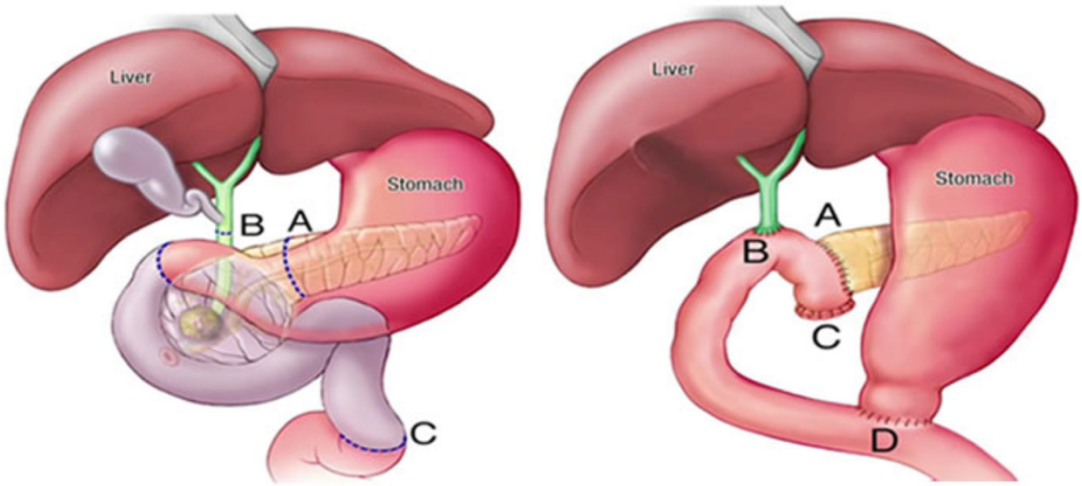
CONSENTIMENT INFORMAT per duodenopancreatectomia cefàlica

DADES D'IDENTIFICACIÓ
Nom i cognoms:
NHC:
Nom i cognoms del representant (si escau): .....

SOL·LICITUD D'INFORMACIÓ
Desitjo ser informat sobre la meva malaltia i la intervenció que se me'n va a realitzar:
Sí No
Desitjo que la informació de la meva malaltia i intervenció li sigui proporcionada a: .....

DESCRIPCIÓ DEL PROCEDIMENT
El cirurgià m'ha explicat que tinc el diagnòstic de ..... per el que se'm realitzarà una duodenopancreatectomia cefàlica (eliminació de part de pàncrees que subministra sucs digestius a l'intestí juntament amb la porció duodenal adjacent i els conductes biliars).
Hi ha la possibilitat que durant la cirurgia calgui realitzar modificacions del procediment per les troballes intraoperatòries, per tal de proporcionar-me el tractament més adequat. El conducte biliar principal i el pancreàtic cal reconstruir-los mitjançant sutura amb l'estómac o un segment d'intestí. Entenc que en ocasions, segons la localització de la malaltia, cal extirpar altres òrgans veïns afectats.

El procediment requereix d'anestèsia general, dels riscos de la qual seré informat per l'anestesiòleg, i és possible que durant o després de la intervenció sigui necessària la utilització de sang i/o hemoderivats.
Es podrà utilitzar part dels teixits obtinguts amb caràcter científic, en cap cas comercial, excepte que jo manifesti el contrari.
Les dades de la cirurgia i perioperatori seran registrades en una base de dades amb finalitats científiques.
La realització del meu procediment pot ser filmat amb fins científics o didàctics, llevat que jo manifesti el contrari.



BENEFICIS DEL PROCEDIMENT

El cirurgià m'ha explicat que mitjançant aquest procediment, es pretén la curació o millora de la meva malaltia, evitant les complicacions derivades de la mateixa.

ALTERNATIVES AL PROCEDIMENT

Si és el cas que pensem que no hi ha una alternativa eficaç de tractament per la seva malaltia com a tractament pal·liatiu del tumor de pàncrees hi ha la quimioradioteràpia.

Existeix la petita possibilitat que la seva malaltia, tot i les proves realitzades anteriorment, tingui un diagnòstic diferent un cop analitzada la peça d'anatomia patològica. El tractament que se li ofereix és el millor en aquest moment en el benentès de la interpretació pel nostre equip mèdic d'aquestes.

RISCOS GENERALS I ESPECÍFICS DEL PROCEDIMENT

Comprenc que, tot i l'adequada elecció de la tècnica i de la correcta realització, poden presentar-se efectes indesitjables, tant els comuns derivats de tota intervenció i que poden afectar tots els òrgans i sistemes com altres específics del procediment, que poden ser:

1. **Generals:**
    a. Col·lapse de petites àrees dels pulmons, augmentant el risc d'infecció al pit. Això pot precisar antibiòtics i fisioteràpia.
    b. Coàguls a les cames (trombosi venosa profunda) amb dolor i inflor. Poques vegades part d'aquest coàgul pot trencar-se i dirigir-se als pulmons, el que pot ser fatal.
    c. Un atac cardíac, a causa d'un sobreesforç al cor o una embòlia.
    d. Mort intraoperatòria.
2. **Específics:** Hi ha alguns riscos / complicacions, que inclouen:

a. El problema més seriós és la fugida de sucs pancreàtics, biliars o gàstrics a la cavitat abdominal, a causa del trencament de l'anastomosi. Això pot requerir reintervenció o un període prolongat d'alimentació intravenosa.
b. Sagnat profund en la cavitat abdominal. Pot necessitar des de reposició de líquids i transfusió fins arteriografia urgent o cirurgia addicional.
c. Dany de l'intestí, que pot causar fuites de líquid intestinal. Això pot requerir reintervenció.
d. Infeccions com acumulacions de pus a la cavitat abdominal. Això pot necessitar cirurgia i/o drenatge.
e. El moviment intestinal pot estar paralitzat o bloquejat després de la cirurgia i això pot causar acumulació de líquid a l'intestí amb inflor de l'abdomen i vòmits.
f. Especialment en un home pot haver dificultat per orinar i pot ser necessari col·locar un tub inserit en la bufeta.
g. Una dehiscència en la ferida completa o incompleta, en el postoperatori o una hèrnia a llarg termini. Això pot requerir reintervenció.
h. En algunes persones, la curació de la ferida pot ser anormal i la ferida pot engrossir-se i formar queloides o pot ser dolorosa.
i. Poden formar-se adherències (bandes de teixit cicatricial) i causar obstrucció intestinal. Això pot ser en breu o a llarg termini i pot necessitar reintervenció.
j. Sensació inusual després dels àpats anomenada "dúmping".
k. Problemes nutricionals com pèrdua de pes o anorèxia a causa de l'extirpació de part de l'estómac, o males digestions causa de la insuficiència pancreàtica (diarrea, malnutrició).
l. Major risc en persones obeses d'infecció de ferida, pneumònia complicacions i trombosi.
m. Major risc en fumadors d'infecció de ferida, pneumònia, infeccions, complicacions cardíaques i pulmonars i trombosi.

Aquestes complicacions habitualment es resolen amb tractament mèdic (medicaments, sèrums, etc.), però poden arribar a requerir una reintervenció, generalment d'urgència, i excepcionalment pot produir-se la mort.

RISCOS PERSONALITZATS I ALTRES CIRCUMSTÀNCIES:

.....

CONSEQÜÈNCIES DE LA CIRURGIA

Insuficiència pancreàtica, diabetis, possible .....

VOLEU FER ALGUNA MANIFESTACIÓ EN RELACIÓ AMB LA INTERVENCIÓ?:

.....

Declaracions i signatures:

DECLARO:

- Que he estat informat amb antelació i de forma satisfactòria pel metge, del procediment (duodenopancreatectomia cefàlica) que se'm realitzarà així com dels seus riscos i complicacions.
- Que he comprès les explicacions que se m'han facilitat en un llenguatge clar i senzill, i el facultatiu que m'ha atès m'ha permès realitzar totes les observacions i m'ha aclarit tots els dubtes que li he plantejat
- Que he llegit i comprès aquest escrit. Estic satisfet amb la informació rebuda, he formulat totes les preguntes que he cregut convenient i m'han aclarit tots els dubtes plantejats.
- Que entenc que el procediment pot incloure una transfusió de sang.
- Que entenc que un metge que no sigui el signant pugui intervenir-me així com un especialista en formació.
- Que conec i assumeixo els riscos i/o seqüeles que poguessin produir-se per l'acte quirúrgic pròpiament dit, per la localització de la lesió o per complicacions de la intervenció, malgrat que els metges posin tots els mitjans al seu abast.
- Que se m'ha informat de la possibilitat d'utilitzar el procediment en un projecte docent o d'investigació sense que comporti risc addicional sobre la meva salut i d'analitzar les meves dades.
- Que entenc que si s'extreuen òrgans o teixits durant la cirurgia, que aquests poden ser retinguts durant un període de temps i després rebutjades per l'hospital.
- També comprenc que, en qualsevol moment i sense necessitat de donar cap explicació, puc revocar el consentiment que ara prest, amb només comunicar-ho a l'equip mèdic.

Signatura del metge que informa **Signatura del pacient**

Dr/a: **D./Dª:**

Col·legiat nº
Data:

D./Dª: ....., amb DNI: ……..
en qualitat de ..... a causa d'.....
dono el meu consentiment a què se li realitzi el procediment proposat.
Signatura del representant:

Data: .....

Revocació del consentiment:

D./Dª: ....., amb DNI: ……
REVOCO el consentiment anteriorment donat per a la realització d'aquest procediment per voluntat pròpia, i assumeixo les conseqüències derivades d'això en l'evolució de la malaltia que pateixo / que pateix el pacient.
Signatura del representant:

Data .....

ANNEX 3 - Protocol information sheet: Control group

FULL D'INFORMACIÓ AL PARTICIPANT: GRUP CONTROL

TÍTOL DE L'ESTUDI: Use of Indocyanine green to reduce postoperative pancreatic fistula, the most common complication of cephalic duodenopancreatectomy.
INVESTIGADORS PRINCIPALS:
CENTRE ASSISTENCIAL:
Facultatiu especialista de l'Àrea de Cirurgia General i Digestiva. Unitat de Cirurgia Hepatobiliopancreàtica. Hospital Universitari Dr. Josep Trueta de Girona.

INTRODUCCIÓ

Ens dirigim a vostè per informar-lo sobre un estudi de recerca en el que se'l convida a participar. L'estudi ha estat aprovat pel Comitè D'Ètica i Investigació Clínica (CEIC) de l'Hospital Universitari Josep Trueta de Girona d'acord amb la legislació vigent, i amb respecte als principis enunciats en la declaració de Hèlsinki i a les guies de bona pràctica clínica.

La nostra intenció és que vostè rebi la informació correcta i suficient per tal que pugui avaluar si vol o no participar en aquest estudi. Per això llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir després de l'explicació. A més, pot consultar amb les persones que consideri oportú.

Participació voluntària

Ha de saber que la seva participació en aquest estudi és voluntària i que pot decidir no participar o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que això alteri la relació amb el seu metge ni es produeixi cap perjudici en el seu tractament.

OBJECTIUS

L'objectiu de l'estudi és determinar si el verd d'indocianina pot ajudar a reduir la incidència de fístules pancreàtiques en pacients que s'intervenen de duodenopancreatectomies cefàliques a l'Hospital de Girona Dr. Josep Trueta.

A més a més, també es vol determinar si amb aquesta tècnica es modifica la resecció del pàncrees i si es redueix l'estància hospitalària i mortalitat als 30 dies després de l'operació.

DESCRIPCIÓ DE L'ESTUDI

Per què és necessari aquest estudi?

Les fístules pancreàtiques postoperatòries són la complicació més freqüent de la duodenopancreatectomia cefàlica, sent el major determinant de morbiditat i mortalitat post-operatòria i tenint un gran rol en termes d'estància hospitalària i impacte econòmic.

Encara que alguns estudis han intentat reduir la incidència de fístules pancreàtiques postoperatòries, encara es donen entre el 3-45% de les operacions.

Recentment, han sorgit estudis on valoren la hipoperfusió del monyó pancreàtic com una de les principals causes de l'aparició d'aquestes fístules. Aquesta falta de perfusió faria que no arribés sang suficient al pàncrees, creant un seguit de processos que porten a una fallida de l'anastomosi (sutura entre el pàncrees i el jejú), resultant en una fístula pancreàtica, en la qual els sucs pancreàtics surten cap a la cavitat abdominal.

D'altra banda, sabem que el verd d'indocianina ja s'utilitza en altres camps quirúrgics per valorar la perfusió dels òrgans, és a dir, per veure si arriba suficient sang.

Així doncs, aquest fet ens porta a pensar que l'ús del verd d'indocianina durant la duodenopancreatectomia cefàlica ens ajudaria a veure si queda un romanent pancreàtic ben perfós o no, per així poder determinar si cal ampliar la resecció pancreàtica abans de realitzar l'anastomosi i així evitar futures fístules, juntament amb les seves complicacions, mortalitat i impacte econòmic.

Que implicarà la seva participació en l'estudi?

Si se li ofereix participar en aquest estudi i accepta, les seves dades registrades durant la seva estància hospitalària, quan es va realitzar la duodenopancreatectomia cefàlica el ..... (data), seran utilitzades amb el fi de comparar-les amb les dades dels pacients que participin en el mateix estudi i se'ls realitzi la operació amb l'ús de verd d'indocianina.

Quants centres participen i quant temps dura?

En aquest estudi hi participa només l'Hospital Universitari Dr. Josep Trueta de Girona i està previst que tingui una duració de 40 mesos (començant el Novembre de 2023 i acabant el Febrer de 2027).

BENEFICIS I RISCOS DERIVATS DE LA SEVA PARTICIPACIÓ EN L'ESTUDI

La seva participació en l'estudi no suposa cap risc, ja que la cirurgia ja es va realitzar anteriorment i per tant només s'utilitzarien les seves dades.

Gràcies a la seva participació podríem valorar si l'ús del verd d'indocianina, podria disminuir el risc d'aparició de fístules pancreàtiques postoperatòries, si amb aquesta tècnica es modifica la resecció del pàncrees i si es redueix l'estància hospitalària i mortalitat als 30 dies després de l'operació, ajudant així a ampliar el coneixement científic en aquest àmbit i podent beneficiar a altres persones en un futur.

DESPESES I COMPENSACIÓ ECONÒMICA

La seva participació en l'estudi no li suposarà despeses addicionals, ni s'ofereix compensació econòmica per la seva participació a l'estudi.
Si està d'acord en participar en aquest estudi se li entregarà una còpia d'aquest document i el formulari de Consentiment Informat, que haurà de firmar d'acord amb les normatives vigents.

CONFIDENCIALITAT

La confidencialitat del pacient estarà protegida i la informació recollida en aquest estudi estarà tractada segons estableix la *Llei Orgànica 03/2018, del 5 de desembre* i del *Reglament (UE) 2016/679 del Parlament Europeu de 27 d'abril de 2016 de protecció de dades (RGPD).*

Les dades recollides es tractaran de forma confidencial i només seran utilitzades amb la finalitat d'investigació.

Totes les dades recollides durant l'estudi, així com els seus resultats, s'identificaran mitjançant un codi, de manera que no s'inclogui informació que permeti la seva identificació, i només el seu metge/col·laboradors podran relacionar-les amb vostè i amb la seva història clínica. Per tant, la seva identitat no serà desvetllada a cap altra persona llevat a les autoritats sanitàries, que així ho requereixi o en casos d'urgència mèdica.

L'accés a la seva informació personal quedarà restringit al metge de l'estudi / col·laboradors, autoritats sanitàries (Agencia Española del Medicamento y Productos Sanitarios) i al Comitè Ètic d'Investigació Clínica, ho precisin per comprovar les dades i procediments de l'estudi, però sempre mantenint la confidencialitat d'acord a la legislació vigent.

Es podran compartir les meves dades?

Les seves dades no seran cedides a terceres entitats, llevat en aquells casos expressament previstos per la llei.

No obstant, podran ser comunicades les informacions i els resultats, amb prèvia pseudonimització de les dades, als seus col·laboradors de conformitat amb la seva estricta necessitat de conèixer-los per a la realització de l'estudi/investigació.

En el cas que les seves dades pseudonimitzades siguin transferides fora de la UE a centres que realitzen serveis o altres grups d'investigació col·laboradors, la confidencialitat de les dades es garantirà mitjançant contractes o convenis específics i serà pels mateixos fins de l'estudi descrit o per el seu ús en publicacions científiques.
Així mateix, qualsevol dels resultats de la investigació realitzada seran anònims. Si fos precisa la publicació dels resultats que incloguin dades de caràcter personal, sol·licitarem el seu consentiment exprés.

Quins drets tinc?

En tot moment, pot exercir els seus drets d'accés, rectificació, supressió, oposició, limitació del tractament i portabilitat de les dades, així com retirar el seu consentiment prèviament prestat, en el seu cas, remetent una comunicació escrita, amb còpia del seu D.N.I en vigor a les adreces de contacte indicades més endavant.

També pot presentar una reclamació davant l'Agencia Espanyola de Protecció de dades o davant l'Agencia Catalana de Protecció de dades, si considera que els seus drets no han estat convenientment atesos.

Puc retirar-me de l'estudi?

Pot revocar en qualsevol moment aquest consentiment exprés. En cas de revocació, les dades facilitades i recollides no podran ser eliminades per tal de garantir la validesa de la investigació, si bé no es recolliran noves dades.

ALTRA INFORMACIÓ RELLEVANT

Té dret a ser informat de les dades rellevants per la seva salut que s'obtinguin en el curs de l'estudi. Aquesta informació se li comunicarà si vostè hi està d'acord. En el cas que prefereixi no ser informat, es respectarà la seva decisió.

CONTACTE AMB L' INVESTIGADOR

Per qualsevol dubte o informació addicional que precisi, o sobre els seus drets com a participant en un assaig clínic, estem sempre a la seva disposició i pot posar-se en contacte amb l'equip investigador, al telèfon ..... o al correu electrònic .....

ANNEX 4 - Protocol information sheet: Intervention group

FULL D'INFORMACIÓ AL PARTICIPANT: GRUP D'INTERVENCIÓ

TÍTOL DE L'ESTUDI: Use of Indocyanine green to reduce postoperative pancreatic fistula, the most common complication of cephalic duodenopancreatectomy.
INVESTIGADORS PRINCIPALS:
CENTRE ASSISTENCIAL:
Facultatiu especialista de l'Àrea de Cirurgia General i Digestiva. Unitat de Cirurgia Hepatobiliopancreàtica. Hospital Universitari Dr. Josep Trueta de Girona.

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La nostra intenció és que vostè rebi la informació correcta i suficient per tal que pugui avaluar si vol o no participar en aquest estudi. Per això llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir després de l'explicació. A més, pot consultar amb les persones que consideri oportú.

Participació voluntària

Ha de saber que la seva participació en aquest estudi és voluntària i que pot decidir no participar o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que això alteri la relació amb el seu metge ni es produeixi cap perjudici en el seu tractament.

OBJECTIUS

L'objectiu de l'estudi és determinar si el verd d'indocianina pot ajudar a reduir la incidència de fístules pancreàtiques en pacients que s'intervenen de duodenopancreatectomies cefàliques a l'Hospital de Girona Dr. Josep Trueta.

A més a més, també es vol determinar si amb aquesta tècnica es modifica la resecció del pàncrees i si es redueix l'estància hospitalària i mortalitat als 30 dies després de l'operació.

DESCRIPCIÓ DE L'ESTUDI

Per què és necessari aquest estudi?

Les fístules pancreàtiques postoperatòries són la complicació més freqüent de la duodenopancreatectomia cefàlica, sent el major determinant de morbiditat i mortalitat post-operatòria i tenint un gran rol en termes d'estància hospitalària i impacte econòmic.

Encara que alguns estudis han intentat reduir la incidència de fístules pancreàtiques postoperatòries, encara es donen entre el 3-45% de les operacions.

Recentment, han sorgit estudis on valoren la hipoperfusió del monyó pancreàtic com una de les principals causes de l'aparició d'aquestes fístules. Aquesta falta de perfusió faria que no arribés sang suficient al pàncrees, creant un seguit de processos que porten a una fallida de l'anastomosi (sutura entre el pàncrees i el jejú), resultant en una fístula pancreàtica, en la qual els sucs pancreàtics surten cap a la cavitat abdominal.

D'altra banda, sabem que el verd d'indocianina ja s'utilitza en altres camps quirúrgics per valorar la perfusió dels òrgans, és a dir, per veure si arriba suficient sang.

Així doncs, aquest fet ens porta a pensar que l'ús del verd d'indocianina durant la duodenopancreatectomia cefàlica ens ajudaria a veure si queda un romanent pancreàtic ben perfós o no, per així poder determinar si cal ampliar la resecció pancreàtica abans de realitzar l'anastomosi i així evitar futures fístules, juntament amb les seves complicacions, mortalitat i impacte econòmic.

Que implicarà la seva participació en l'estudi?

Si se li ofereix participar en aquest estudi i accepta, el cirurgià li explicarà el seu diagnòstic (.....) pel qual se li realitzarà una duodenopancreatectomia cefàlica (eliminació de part de pàncrees que subministra sucs digestius a l'intestí juntament amb la porció duodenal adjacent i els conductes biliars).

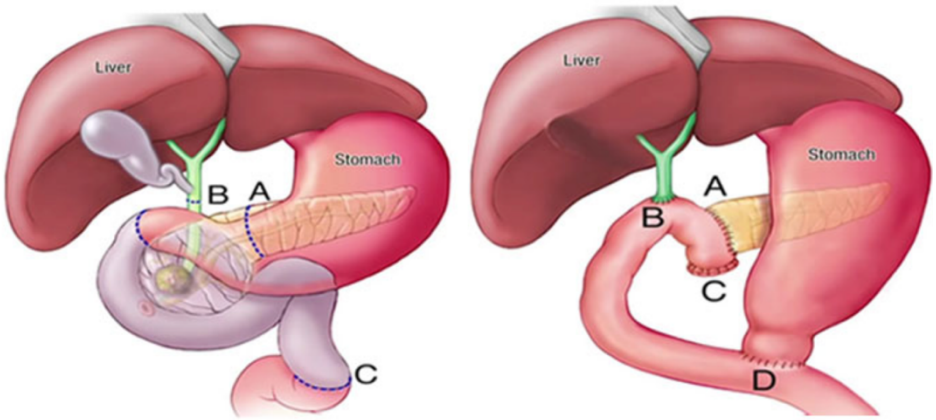
A l'igual que en aquesta cirurgia quan es realitza de forma rutinària fora de l'estudi, hi ha la possibilitat que durant l'operació calgui realitzar modificacions del procediment per les troballes intraoperatòries, per tal de proporcionar-li el tractament més adequat. El conducte biliar principal i el pancreàtic caldrà reconstruir-los mitjançant sutura amb l'estómac o un segment d'intestí. En ocasions, segons la localització de la malaltia, cal extirpar altres òrgans veïns afectats.

A més a més, en un moment determinat de la cirurgia se li injectarà una dosi de 0,1-0,2 mg/kg de verd d'indocianina per valorar la possible hipoperfusió del romanent pancreàtic. En cas de que aquest estigui hipoperfós, s'estendrà la resecció fins la zona

ben perfosa, que acostuma a ser uns 1,5-2cm més cap a l'esquerra. Seguidament el procediment seguirà de la mateixa forma que es realitza normalment.

El procediment requereix d'anestèsia general, dels riscos de la qual serà informat per l'anestesiòleg, i és possible que durant o després de la intervenció sigui necessària la utilització de sang i/o hemoderivats.
Es podrà utilitzar part dels teixits obtinguts amb caràcter científic, en cap cas comercial, excepte que vostè manifesti el contrari.
Les dades de la cirurgia i perioperatori seran registrades en una base de dades amb finalitats científiques i posteriorment seran comparades amb dades ja existents d'altres pacients que van realitzar, en un passat, la duodenopancreatectomia cefàlica sense l'ús del verd d'indocianina.

La realització del seu procediment pot ser filmat amb fins científics o didàctics, llevat que vostè manifesti el contrari.



Quants centres participen i quant temps dura?
En aquest estudi hi participa només l'Hospital Universitari Dr. Josep Trueta de Girona i està previst que tingui una duració de 40 mesos (començant el Novembre de 2023 i acabant el Febrer de 2027).

BENEFICIS DERIVATS DE LA SEVA PARTICIPACIÓ EN L'ESTUDI
Mitjançant aquest procediment, es pretén el tractament de la patologia que presenta, evitant les complicacions derivades del mateix.

A més a més, gràcies a la seva participació podríem valorar si l'ús del verd d'indocianina, podria disminuir el risc d'aparició de fístules pancreàtiques postoperatòries, si amb aquesta tècnica es modifica la resecció del pàncrees i si es redueix l'estància hospitalària i mortalitat als 30 dies després de l'operació, ajudant així a ampliar el coneixement científic en aquest àmbit i podent beneficiar a altres persones en un futur.

POSSIBLES RISCS DE LA DUODENOPANCREATECTOMIA CEFÀLICA:

Així com passa en la duodenopancreatectomia cefàlica rutinària sense l'ús del verd d'indocianina, tot i l'adequada elecció de la tècnica i de la correcta realització, poden presentar-se efectes indesitjables, tant els comuns derivats de tota intervenció i que poden afectar tots els òrgans i sistemes com altres específics del procediment, que poden ser:

1. **Generals:**
    a. Col·lapse de petites àrees dels pulmons, augmentant el risc d'infecció al pit. Això pot precisar antibiòtics i fisioteràpia.
    b. Coàguls a les cames (trombosi venosa profunda) amb dolor i inflor. Poques vegades part d'aquest coàgul pot trencar-se i dirigir-se als pulmons, el que pot ser fatal.
    c. Un atac cardíac, a causa d'un sobreesforç al cor o una embòlia.
    d. Mort intraoperatòria.
2. **Específics:** Hi ha alguns riscos / complicacions, que inclouen:
    a. El problema més seriós és la fugida de sucs pancreàtics, biliars o gàstrics a la cavitat abdominal, a causa del trencament de l'anastomosi. Això pot requerir reintervenció o un període prolongat d'alimentació intravenosa.
    b. Sagnat profund en la cavitat abdominal. Pot necessitar des de reposició de líquids i transfusió fins arteriografia urgent o cirurgia addicional.
    c. Dany de l'intestí, que pot causar fuites de líquid intestinal. Això pot requerir reintervenció.
    d. Infeccions com acumulacions de pus a la cavitat abdominal. Això pot necessitar cirurgia i/o drenatge.
    e. El moviment intestinal pot estar paralitzat o bloquejat després de la cirurgia i això pot causar acumulació de líquid a l'intestí amb inflor de l'abdomen i vòmits.
    f. Especialment en un home pot haver dificultat per orinar i pot ser necessari col·locar un tub inserit en la bufeta.
    g. Una dehiscència en la ferida completa o incompleta, en el postoperatori o una hèrnia a llarg termini. Això pot requerir reintervenció.
    h. En algunes persones, la curació de la ferida pot ser anormal i la ferida pot engrossir-se i formar queloides o pot ser dolorosa.
    i. Poden formar-se adherències (bandes de teixit cicatricial) i causar obstrucció intestinal. Això pot ser en breu o a llarg termini i pot necessitar reintervenció.
    j. Sensació inusual després dels àpats anomenada "dúmping".
    k. Problemes nutricionals com pèrdua de pes o anorèxia a causa de l'extirpació de part de l'estómac, o males digestions causa de la insuficiència pancreàtica (diarrea, malnutrició).

l. Major risc en persones obeses d'infecció de ferida, pneumònia complicacions i trombosi.
m. Major risc en fumadors d'infecció de ferida, pneumònia, infeccions, complicacions cardíaques i pulmonars i trombosi.

Aquestes complicacions habitualment es resolen amb tractament mèdic (medicaments, sèrums, etc.), però poden arribar a requerir una reintervenció, generalment d'urgència, i excepcionalment pot produir-se la mort.

POSSIBLES RISCS DERIVATS DE LA SEVA PARTICIPACIÓ EN L'ESTUDI

Els riscs de l'estudi seran els mateixos que en la duodenopancreatectomia cefàlica rutinària sense l'ús del verd d'indocianina (explicats en l'apartat anterior), amb l'afegit de reaccions adverses per al·lèrgia al iode o al marisc, les quals intentem descartar abans de realitzar la intervenció.

ALTERNATIVES AL PROCEDIMENT

Si és el cas que pensem que no hi ha una alternativa eficaç de tractament per la seva malaltia com a tractament pal·liatiu del tumor de pàncrees hi ha la quimioradioteràpia.

Existeix la petita possibilitat que la seva malaltia, tot i les proves realitzades anteriorment, tingui un diagnòstic diferent un cop analitzada la peça d'anatomia patològica. El tractament que se li ofereix és el millor en aquest moment en el benentès de la interpretació pel nostre equip mèdic d'aquestes.

DESPESES I COMPENSACIÓ ECONÒMICA

La seva participació en l'estudi no li suposarà despeses addicionals, ni s'ofereix compensació econòmica per la seva participació a l'estudi.
Si està d'acord en participar en aquest estudi se li entregarà una còpia d'aquest document i el formulari de Consentiment Informat, que haurà de firmar d'acord amb les normatives vigents.

CONFIDENCIALITAT

La confidencialitat del pacient estarà protegida i la informació recollida en aquest estudi estarà tractada segons estableix la *Llei Orgànica 03/2018, del 5 de desembre* i del *Reglament (UE) 2016/679 del Parlament Europeu de 27 d'abril de 2016 de protecció de dades (RGPD).*

Les dades recollides es tractaran de forma confidencial i només seran utilitzades amb la finalitat d'investigació.

Totes les dades recollides durant l'estudi, així com els seus resultats, s'identificaran mitjançant un codi, de manera que no s'inclogui informació que permeti la seva

identificació, i només el seu metge/col·laboradors podran relacionar-les amb vostè i amb la seva història clínica. Per tant, la seva identitat no serà desvetllada a cap altra persona llevat a les autoritats sanitàries, que així ho requereixi o en casos d'urgència mèdica.

L'accés a la seva informació personal quedarà restringit al metge de l'estudi / col·laboradors, autoritats sanitàries (Agencia Española del Medicamento y Productos Sanitarios) i al Comitè Ètic d'Investigació Clínica, ho precisin per comprovar les dades i procediments de l'estudi, però sempre mantenint la confidencialitat d'acord a la legislació vigent.

Es podran compartir les meves dades?

Les seves dades no seran cedides a terceres entitats, llevat en aquells casos expressament previstos per la llei.

No obstant, podran ser comunicades les informacions i els resultats, amb prèvia pseudonimització de les dades, als seus col·laboradors de conformitat amb la seva estricta necessitat de conèixer-los per a la realització de l'estudi/investigació.
En el cas que les seves dades pseudonimitzades siguin transferides fora de la UE a centres que realitzen serveis o altres grups d'investigació col·laboradors, la confidencialitat de les dades es garantirà mitjançant contractes o convenis específics i serà pels mateixos fins de l'estudi descrit o per el seu ús en publicacions científiques.
Així mateix, qualsevol dels resultats de la investigació realitzada seran anònims. Si fos precisa la publicació dels resultats que incloguin dades de caràcter personal, sol·licitarem el seu consentiment exprés.

Quins drets tinc?

En tot moment, pot exercir els seus drets d'accés, rectificació, supressió, oposició, limitació del tractament i portabilitat de les dades, així com retirar el seu consentiment prèviament prestat, en el seu cas, remetent una comunicació escrita, amb còpia del seu D.N.I en vigor a les adreces de contacte indicades més endavant.

També pot presentar una reclamació davant l'Agencia Espanyola de Protecció de dades o davant l'Agencia Catalana de Protecció de dades, si considera que els seus drets no han estat convenientment atesos.

Puc retirar-me de l'estudi?

Pot revocar en qualsevol moment aquest consentiment exprés. En cas de revocació, les dades facilitades i recollides no podran ser eliminades per tal de garantir la validesa de la investigació, si bé no es recolliran noves dades.

ALTRA INFORMACIÓ RELLEVANT

Té dret a ser informat de les dades rellevants per la seva salut que s'obtinguin en el curs de l'estudi. Aquesta informació se li comunicarà si vostè hi està d'acord. En el cas que prefereixi no ser informat, es respectarà la seva decisió.

CONTACTE AMB L' INVESTIGADOR

Per qualsevol dubte o informació addicional que precisi, o sobre els seus drets com a participant en un assaig clínic, estem sempre a la seva disposició i pot posar-se en contacte amb l'equip investigador, al telèfon ..... o al correu electrònic .....

ANNEX 5 - Informed consent document

PACIENT – CONSENTIMENT INFORMAT

TÍTOL DE L'ESTUDI: Use of Indocyanine green to reduce postoperative pancreatic fistula, the most common complication of cephalic duodenopancreatectomy.
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CENTRE:
Facultatiu especialista de l'Àrea de Cirurgia General i Digestiva. Unitat de Cirurgia Hepatobiliopancreàtica. Hospital Universitari Dr. Josep Trueta de Girona.

Jo (nom i cognoms):....., amb DNI:.....

He llegit el full d'informació que se m' ha entregat.
He pogut fer preguntes sobre l'estudi i s'han respost de forma satisfactòria.
He rebut suficient informació sobre l'estudi.
He parlat amb (nom de l'investigador):.....

Comprenc que la meva participació és voluntària.
Comprenc que puc retirar-me de l'estudi:
1º Quan vulgui
2º Sense haver de donar explicacions.
3º Sense que això repercuteixi en els tracte mèdic.

Rebré una còpia signada i datada d'aquest consentiment informat. Dono lliurement la meva conformitat per participar en l'estudi i dono el meu consentiment per l'accés i utilització de les meves dades en les condicions detallades en el full d'informació.

Signatura del pacient:
Nom:
Data:

Signatura de l'investigador:
Nom:
Data:

Desitjo que em comuniquin la informació derivada de la investigació que pugui ser rellevant per a la meva salut:

☐ SI ☐ NO

Signatura del pacient:
Nom:
Data:

Signatura de l'investigador:
Nom:
Data:

REVOCACIÓ DEL CONSENTIMENT INFORMAT

D./Dª: ....., Amb DNI: …….
REVOCO el consentiment anteriorment donat per participar en l'estudi anteriorment mencionat.

Signatura del representant:

Data .....

ANNEX 6 - Data record template

PATIENT DATA

Patients code:
Age:
Sex:
DM: Yes / No
IMC:
Surgeon in charge:
Alcoholism: Yes / No
Exocrine insufficiency: Yes / No
Smoking: Non-smoker / Mild / Moderate / Severe

PREOPERATORY DATA

Neoadjuvant therapy: Yes / No
ERCP prior to surgery: Yes / No

OPERATORY DATA

Date:
Surgical time: ….. h ….. min
Intraoperative blood loss: ….. ml
Pancreas texture or consistency: Soft / Firm
Pancreatic ductal diameter: ….. mm
Associated venous resection: Yes / No
Associated arterial resection: Yes / No
Use of pancreatic duct stent:
Use of ICG: Yes / No
Dose of ICG: ….. mg
Repetition of the ICG dose: Yes / No
Mortality: Yes / No

ANATOMOPATHOLOGY DATA

PDAC or non PDAC pathology: PDAC / Non PDAC

POSTOPERATORY DATA

POPF: Yes / No
Grade: B / C
Other complications:
Hospital Stay: ….. days
Mortality: Yes / No → If Yes: in …. post-operative day

ANNEX 7 – Perioperative protocol for pancreatic surgery

<table>
<tr><th>TIEMPO</th><th>PROTOCOLO</th><th>RESPONSABLE</th></tr>
<tr><td>Previo al ingreso</td><td>- Información completa de proceso asistencial a pacientes y familiares.
- Valoración preoperatoria. Prehabilitación, optimización nutricional y cardiológica.
- Corrección de anemia y otras comorbilidades. Protocolo de ahorro de sangre si Hb < 12 g/dl (valorar hierro iv, EPO).
- Si hiperbilirrubinemia de larga evolución y/o superior a 20 mg/dL valorar drenaje biliar.
- Iniciar vitamina K.
- Firma de consentimientos informados. Entrega de documentación.
- Cuestionario calidad de vida.</td><td>Cirujano
+
Anestesiólogo
+
Fisioterapeuta</td></tr>
<tr><td>Día previo a la intervención</td><td>- Iniciar profilaxis tromboembólica con enoxaparina 0,5 mg/kg/día a las 20 horas
- Ayuno a sólido las 6 horas previas a la cirugía y a líquido claro las 2 horas previas a la cirugía.</td><td>Cirujano
+
Anestesiólogo
+
Enfermería</td></tr>
<tr><td>Peroperatorio</td><td>Preoperatorio
- Baño o ducha completo previo a la cirugía.
- Ingreso el mismo día de la cirugía.
- Suplemento de bebida carbohidratada 12.5% maltodextrinas 250 cc 2 horas antes de intervención.
- Colocación de medias compresivas o de compresión neumática intermitente según riesgo tromboembólico.
- Control de glucemia capilar.
- Profilaxis enfermedad péptica. Omeprazol 40 mg/iv/24 horas.
- Administración profiláctica de antibiótico 30-60 minutos antes de la incisión quirúrgica. Antibiótico según protocolo del hospital (valorar si portador o no de prótesis biliar para indicar el antibiótico).

Intraoperatorio
- Inserción de catéter epidural torácico T6-T8. Iniciar anestesia epidural tras inducción e iniciar perfusión continua tras una hora de inicio.
- Inducción anestésica.
- Oxigenación FiO2 0.6-0.8
- Fluidoterapia guiada por objetivos con soluciones balanceadas en perfusión continua 5-7 ml/kg/h. Monitorización del volumen sistólico y del índice cardíaco. Mantener IC >2,5 l/min/m2.
- Sondaje vesical.
- Control glucémico. Objetivo glicemia < 150 mg/dl.
- Calentamiento activo con manta térmica y calentador de fluidos.
- Profilaxis náuseas y vómitos según escala Apfel.
- Preparación del campo quirúrgico con clorhexidina alcohólica para la piel.
- Utilizar incisión subcostal bilateral.
- Redosificación intraoperatoria de antibiótico si indicada.
- Según técnica quirúrgica:

<table><tr><th colspan="2">Duodenopancreatectomia cefálica</th><th rowspan="2">Pancreatectomia corporocaudal</th></tr><tr><th>Anastomosis pancreatogástrica</th><th>Anastomosis pancreaticoyeyunal</th></tr><tr><td>Colocar SNG</td><td>No colocar SNG</td><td>No colocar SNG</td></tr><tr><td>Drenaje</td><td>Drenaje</td><td>Drenaje</td></tr></table>
Postoperatorio inmediato
- Mantenimiento activo de temperatura. Objetivo: mantener > 36º todo el periodo perioperatorio.
- Mantenimiento de FiO2 0.5 2 horas tras finalizar la intervención. Fisioterapia respiratoria (inspiron 10/h).
- Fluidoterapia restrictiva.
- Analgesia pautada epidural en perfusión continua. Mínima administración de mórficos.
- Analgesia iv: Paracetamol 1 g/ 8 h y metamizol 2 g/ 8 h alternos.
- Profilaxis tromboembolismo: enoxaparina 40mg a las 6h de finalizar la cirugía. Mantener medias compresivas hasta deambulación.
- Profilaxis y tratamiento de náuseas y vómitos. Ondansetron 4 mg/8 h iv.
- Control analítico.
- Control glucémico. Objetivo glicemia < 150 mg/dl.
- Inicio de movilización a las 8 horas tras cirugía tras comprobación de bloqueo motor.
- Según técnica quirúrgica:

<table><tr><th colspan="2">Duodenopancreatectomia cefálica</th><th rowspan="2">Pancreatectomia corporocaudal</th></tr><tr><th>Anastomosis pancreatogástrica</th><th>Anastomosis pancreaticoyeyunal</th></tr><tr><td>Mantener SNG
No iniciar dieta</td><td colspan="2">Iniciar dieta a las 6h post-cirugía.</td></tr></table></td><td>Enfermería

Cirujano
+
Anestesiólogo
+
Enfermería

Cirujano
+
Anestesiólogo
+
Intensivista
+
Enfermería</td></tr>
</table>

<table>
<tr><td>1º día postoperatorio</td><td>
- No prolongar la profilaxis antibiótica más allá de las 24 h de la intervención.
- Limitación de la estancia en reanimación. Alta el día 1 postoperatorio.
- Profilaxis tromboembolismo con enoxaparina 0.5mg/kg/día. Continuar diariamente hasta el alta hospitalaria.
- Mantener la profilaxis mecánica antitrombótica si se ha iniciado en el preoperatorio.
- Profilaxis enfermedad péptica con omeprazol 40mg/24h iv. Continuar diariamente hasta el alta hospitalaria. En caso de anastomosis pancreatogástrica omeprazol 40mg/12h iv.
- Control glucémico estricto. Continuar diariamente hasta el alta hospitalaria.
- Analgesia endovenosa. No mórficos.
- Retirar sonda vesical.
- Continuar analgesia epidural (se puede mantener 2-3 días).
- Movilización activa (cama / sillón /inicio deambulación).
- Fisioterapia respiratoria. Continuar diariamente hasta el alta hospitalaria.
- Reintroducción medicación domiciliaria oral.
- Control analítico.
- Según técnica quirúrgica:
<table>
<tr><th colspan="2">Duodenopancreatectomia cefálica</th><th rowspan="2">Pancreatectomia corporocaudal</th></tr>
<tr><th>Anastomosis pancreatogástrica</th><th>Anastomosis pancreaticoyeyunal</th></tr>
<tr><td colspan="3">Determinación de amilasas del drenaje</td></tr>
<tr><td>Mantener SNG
No iniciar dieta</td><td colspan="2">Dieta líquida - semilíquida
Valorar suplementos nutricionales.</td></tr>
</table>
</td><td>Cirujano
+
Enfermería
+
Fisioterapeuta</td></tr>
<tr><td>2º día postoperatorio</td><td>
- Valorar disminución analgesia epidural hasta pararla (se puede mantener 2-3 días). Retirar catéter según coagulación.
- Movilización activa (deambulación).
- Según técnica quirúrgica:
<table>
<tr><th colspan="2">Duodenopancreatectomia cefálica</th><th rowspan="2">Pancreatectomia corporocaudal</th></tr>
<tr><th>Anastomosis pancreatogástrica</th><th>Anastomosis pancreaticoyeyunal</th></tr>
<tr><td colspan="3">Determinación de amilasas del drenaje</td></tr>
<tr><td>Mantener SNG
No iniciar dieta</td><td colspan="2">Iniciar semilíquida- fácil digestión
Parar sueroterapia
Valorar suplementos nutricionales</td></tr>
</table>
</td><td>Cirujano
+
Enfermería
+
Fisioterapeuta</td></tr>
<tr><td>3r día postoperatorio</td><td>
- Valorar disminución analgesia epidural hasta pararla (se puede mantener 2-3 días). Retirar catéter según coagulación.
- Movilización activa (deambulación).
- Control analítico.
- Según técnica quirúrgica:
<table>
<tr><th colspan="2">Duodenopancreatectomia cefálica</th><th rowspan="2">Pancreatectomia corporocaudal</th></tr>
<tr><th>Anastomosis pancreatogástrica</th><th>Anastomosis pancreaticoyeyunal</th></tr>
<tr><td colspan="3">Determinación de amilasas del drenaje: si valores de amilasa inferiores a 3 veces la amilasa en suero*, valorar retirada del drenaje.</td></tr>
<tr><td>*Retirar la SNG
Iniciar dieta y progresar</td><td colspan="2">Dieta normal</td></tr>
</table>
</td><td>Cirujano
+
Enfermería
+
Fisioterapeuta</td></tr>
<tr><td>Durante el resto de hospitalización</td><td>
- Dieta normal.
- Analgesia oral.
- Movilización activa (deambulación).
- Hemograma y determinación de amilasas al 5º día postoperatorio, en caso de que el paciente siga hospitalizado.
- Valorar alta a domicilio, criterios generales de alta: No complicaciones quirúrgicas, no fiebre, correcta tolerancia dieta oral, buen control del dolor con analgésicos orales, deambulación completa, aceptación por parte del paciente.
</td><td>Cirujano
+
Enfermería
+
Fisioterapeuta</td></tr>
<tr><td>Al alta</td><td>
- Mantenimiento de tromboprofilaxis 28 días tras cirugía.
- Analgesia oral.
- Seguimiento al alta / continuidad asistencial.
- Apoyo domiciliario – Coordinación con Atención Primaria.
</td><td>Cirujano
+
Enfermería
+
MAP</td></tr>
</table>