FACULTY OF MEDICINE
Final Degree Project

CLASSIC VS SUPERIOR MESENTERIC ARTERY FIRST APPROACH IN CEPHALIC DUODENOPANCREATECTOMY FOR PANCREATIC CANCER

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La Dra. Laia Falgueras Verdaguer, de la Universitat de Girona,

DECLARO:

Que coneixent l'existència d'un estudi actual on es comparen les dues tècniques quirúrgiques, el treball titulat ***Classical vs Superior Mesenteric Artery First Approach in cephalic duodenopancreatectomy for pancreatic cancer,*** que presenta l'estudiant de medicina Gemma Domínguez Paredes com a treball de final de grau, ha estat realitzat íntegrament per l'alumna, amb objectius de treball i metodologia diferents i sense conèixer dades del protocol ja existent.

I, perquè quedi constància, signo aquest document.

Signatura: Laia Falgueres

Girona, 24 d'octubre de 2017

M'agradaria agrair a la unitat de cirurgia hepato-biliar-pancreàtica de l'Hospital Dr. Josep Trueta de Girona per a la seva acollida i pels coneixements adquirits gràcies a les seves ensenyances.

En especial vull agrair a la meva tutora Laia Falgueras per tota l'ajuda rebuda.

INDEX

1. ABBREVIATIONS

AP: Anatomical pathology

CA 19.9: Carbohydrate antigen 19-9

CT: computed tomography scan

DPC: Cephalic Duodenopancreatectomy

SMA: Superior Mesenteric Artery

SMAfa: Superior Mesenteric Artery first approach

SMV: Superior Mesenteric Vein

PC: Pancreatic Cancer

PH: Head of the Pancreas

PV: Portal Vein

WT: Whipple technique

2. ABSTRACT

Background: Surgery is the only curative treatment for head pancreatic cancer. The actual technique is the cephalic duodenopancreatectomy. Nowadays exist two different approaches for the pancreas resection, the classical technique also known as the Whipple intervention and the Superior Mesenteric Artery first approach. The SMA first approach remove more tissue from the surrounding area of the SMA and seems to be a more oncological technique. We are in need of a study that compares the survival without recurrences, the margins resection and the complications in both techniques to establish the approach with more benefits for the patients.

Objective: The aim of this study is to measure the disease-free time comparing the two different surgical techniques for pancreatic cancer. We will also evaluate the margins affectation and the early complications in each technique.

Design: A randomized, single-blinded, controlled clinical trial that will be performed in the *Hospital Universitari Josep Trueta* of Girona within the Hepatic-biliary-pancreatic unit, in the General Surgery Service, from January 2018 to June 2025.

Methods: 92 patients with head pancreatic tumor will be recruited with a consecutive method. This patients will be randomly placed in one of the two treatment groups, either WT or SMAfa. T-Student test will be used for statistical analysis of the primary objective. A chi-square test will analyse the secondary objectives with a confidence interval of 95%.

Key words: Whipple intervention, Superior mesenteric artery first approach, duodenopancreatectomy, pancreatic cancer, disease-free period.

3. INTRODUCTION

3.1 ANATOMY SUMMARY

The pancreas is an accessory digestive gland and it is a retroperitoneal structure that crosses the abdomen behind the stomach. The right limit is the duodenum and the left limit is the spleen.

The pancreas is divided in four parts: The head of is placed in the curvature of the duodenum, just right to the superior mesenteric vessels. In the inferior edge of the head there is the uncus, or uncinated process, that is spreading medially and passes posterior to the superior mesenteric artery (SMA). Posterior to the pancreas head there is the inferior cava vein, the right renal artery and the left renal vein. The neck of the pancreas is short and anterior to the superior mesenteric vessels and posterior to the pylorus. The body of the pancreas establishes contact with the aorta, the SMA, the left suprarenal gland and with the left kidney and its vessels in the posterior part and the anterior part is covered by the retroperitoneum and forms the gastric bed. The last part is the tail of the pancreas, it is next to the left kidney and in contact with the splenic hilium and left colic flexure.

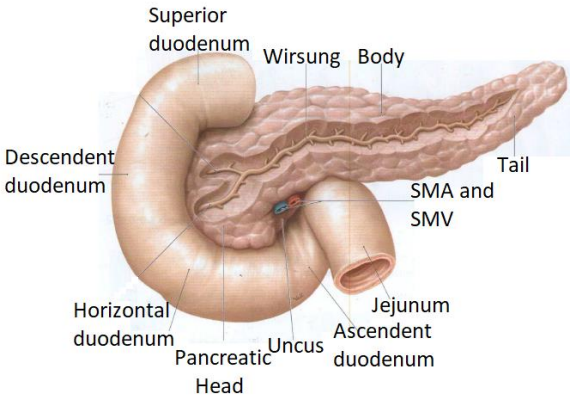


Figure 1 Anatomy of the Pancreas. Prometheus

The pancreatic duct, or Wirsung, starts at the tail and finishes at the pancreatic head (PH). The Wirsung together with the bile duct flows to the duodenum passing through the ampulla of Vater.

The blood supply proceeds from the branches of the splenic artery which forms arches with the gastroduodenal artery and the SMA. This blood drains to the pancreatic veins that go to the splenic vein. (1)

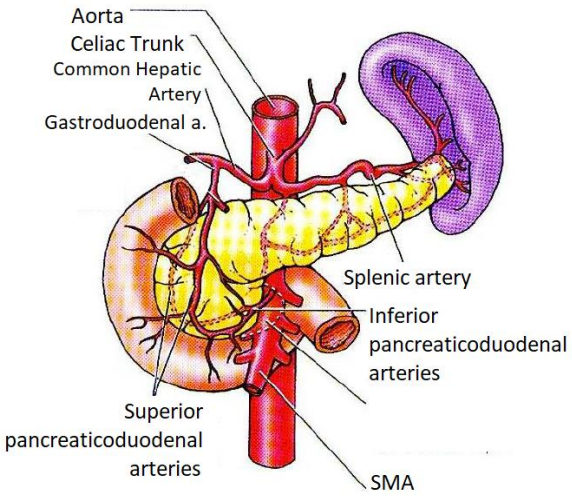


Figure 2 Pancreatic Vascularization (1)

3.2 EPIDEMIOLOGY

The pancreatic ductal adenocarcinoma is the most common tumor of the exocrine pancreas and the 4th lethal cancer. It is a severe and relevant disease because this tumor have bad prognosis and a high mortality rate, causing 227000 deaths per year worldwide.(2) In Catalonia during the 2016 there were 606 new cases of pancreatic cancer (PC) and 563 deaths in men and referred to the women there were 562 new cases and 498 deaths. Since 1994, the incidence of pancreatic cancer has increased 1,8% as well as the mortality rate.(3)

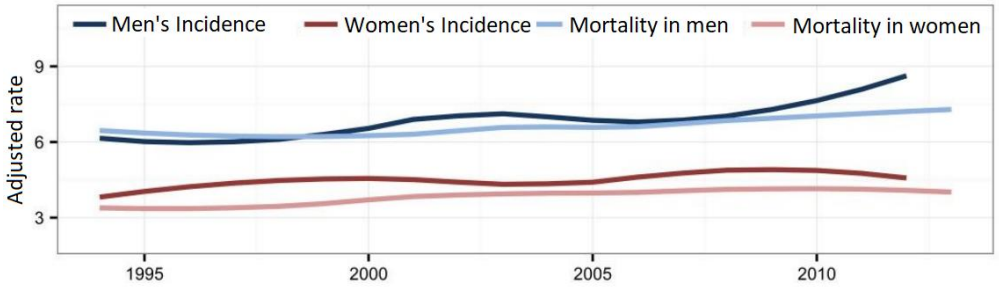


Figure 3 Epidemilogy of PC in Catalonia (3)

The 1-year survival rate is less than 20% and the 5-year rate does not exceed the 5%.(4,5) After the surgery, the 5-year survival rate can achieve to be 10 to 31%. (6)

The median age of PC diagnose is at 71 years and the majority of cases are diagnosed between 40 and 80 years. Of these, the 53% are diagnosed between the 65 and the 84 years of age.(7)

Of all the pancreatic cancer, between the 60 and 70% are located in the PH and only the 10-20% can be treated by surgery.(4,8) This, together with the fact that at the moment of the diagnose most of the patients are in an advanced stage, produces the poor prognosis in PC. Due to all these reasons it is essential to do and early diagnose and improve the surgical techniques, finding the best alternative.

3.3 AETIOLOGY AND RISK FACTORS

The causes of the PC are unknown but there is an evidence that tobacco use increases the PC risk from 2.5 to 3.6 times.(4) There are other factors that have been related but without a strong evidence: (9)

- People with diabetes mellitus have a 2.6 times higher risk of PC
- Alcohol consumption has an influence in daily drinkers of hard liquor, especially in those who drink >60ml of ethanol per day. The years of alcohol use do also affect.
- Some chronic medical conditions are related with a high risk of PC mainly in long-duration pancreatitis and recent cholecystectomy (less than 2 years ago).
- Family history of PC has been seen as a risk factor in first-degree relatives and in second-degree relatives. Other cancers also have a significant relationship with PC such as breast cancer with 60% more risk of PC in subjects with positive family histories and 80% more risk in colon cancer. In this patients is frequent a mutation of the BRCA.(10)

Risk Factor	Risk Estimate (95% CI)
Current Cigarette Smoking	OR= 2.20 (1.71–2.83)
Past Cigarette Smoking 1–10 years since quitting 15–20 years since quitting	OR=1.64 (1.36–1.97) OR=1.12 (0.86–1.44)
Diabetes Mellitus <3 years >10 years duration	RR=7.94 (95% CI, 4.70–12.55) OR 1.51 (95% CI=1.16–1.96)
BMI (>35 vs 18.9–24.9)	OR =1.55 (95%CI=1.16 – 2.07)
Heavy Alcohol (> 6 drinks/day)	OR 1.46 (95%CI=1.16–1.83)
Pancreatitits (>2 years)	2.71 fold (95% CI 1.96–3.74)

BMI= Body mass index; OR=odds ratio; RR=relative risk

Table 1 Risk Factors (10)

Sporadic mutations are involved in a percentage of ductal adenocarcinomas and the most common core gens are KRAS, 16/CDKN2A, TP 53 and SMAD4. (11)

3.4 CLINICAL PRESENTATION

The PC is mostly asymptomatic and the first symptoms are unspecific and they result from a mass effect.

When there is an obstruction of the common bile duct, the common symptoms are jaundice and obstructive cholestasis; and when the tumor obstructs the pancreatic duct are pancreatitis, dysglycemia or new-onset diabetes. Abdominal pain, nauseas and steatorrhoea are also common. (2)

At the diagnose, most patients have systemic manifestations such as weight loss, deep and superficial venous thrombosis, panniculitis, liver-function abnormalities, gastric-outlet obstruction, increased abdominal girth and depression. (4)

More rarely, when the tumor grows into the duodenum, it can cause upper gastroduodenal obstruction and bleeding.

3.5 DIAGNOSIS

The diagnosis of PC is established by different tests:

It is essential the realization of a General Blood Analysis with Tumoral Markers. Is common to find cholestatic pattern and mild anemia.

There are not specific tumor markers for the PC but the increase of CA 19.9 and carcinoembryonic antigen (CEA) are used in the clinical practice because when they increase are an alarm to the doctors. The CA 19.9 can be increased in diverse situations according that it has a low positive predictive value. In the follow-up of the postsurgical patients it has a huge importance since it allow us to know the evolution. The normal range of the CA 19.9 goes from 0 to 100 U/ml. The CEA is less used and the normal range goes from 0 to 3 ng/ml. It may be increased because of the tobacco use so in smokers it is considered normal to 5 ng/ml.

The second step are the Imaging Evaluations.

Computed tomography scan (CT) is the best-validated imaging modality for both diagnose and staging. Is performed a triphasic cross-sectional imaging that includes arterial, late arterial and venous phases. The difference between parenchyma and

adenocarcinoma are higher during the late arterial phase, seeing the lesion as a hypodense area. In the CT are also visualized the important arterial and venous structures to determine vascular invasion and decide the resectability, or not, of the tumor.(10,12,13) Of all the potential resectable tumors determined with CT, the 70-85% are able to undergo resection.(12)

When CT is contraindicated or to complement the extrapancreatic study, Magnetic Resonance Imaging (MRI) can be used. To examine the metastases disease and to do a better staging, Positron Emission Tomography/CT (PET/CT) has an increased sensitivity.

The Endoscopic Ultrasound (EUS) can be used to apport additional staging information. Is useful when the CT do not show lesion or there are questions about the involvement of the blood vessels and lymph nodes.(12)

The last option is to perform an Endoscopic Retrograde Cholangiopancreatography (ERCP) in the patients with no mass in the CT and no evidence of metastatic disease. This test can distinguish between benign and malignant lesions. The ERCP allows the examination of the pancreatic and bile ducts and a stent can be placed to decompress the bile duct.

After the imaging evaluation, there is the diagnostic staging laparoscopy but its use is controversial.

The need of a routine biopsy is not established because PC have an important inflammatory and desmoplastic component that makes the risk-benefit of the biopsy controversial. With the diagnose of the other tests is enough. The tissue diagnosis is mandatory when the patient is considered for neoadjuvant therapy.(14)

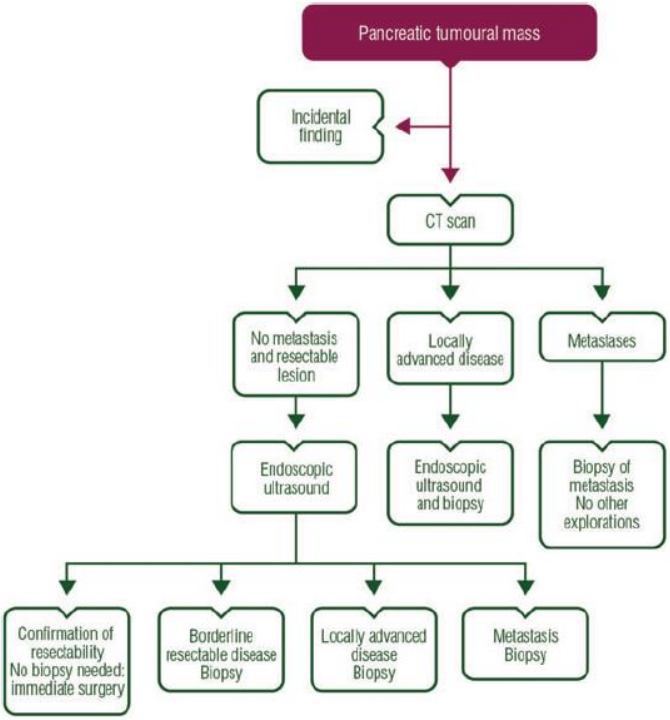


Figure 4. Diagnose work-up (2)

3.6 STAGING

After diagnose, the next step is the staging. The stage of the tumor will determine the treatment. Is used the staging system that includes the TNM classification described by The American Joint Committee on Cancer (AJCC). Resectable stages are Stage I and II and some tumors in Stage III are defined as borderline resectable, if Stage III is defined as locally advanced the tumor is unresectable. (10)

The AJCC describes the TNM values:(15)

- Primary Tumor **(T)**
  - Tx**:** Primary tumor cannot be assessed
  - T0: No evidence of primary tumor
  - Tis**:** Carcinoma *in situ*
  - T1: Tumor limited to the pancreas ≤ 2 cm
  - T2: Tumor limited to pancreas > 2 cm
  - T3**:** Tumor extends directly into the duodenum, bile duct or peripancreatic tissues
  - T4: Tumor extends directly into stomach, spleen, colon or adjacent large vessels
- Regional Lymph Nodes **(N)**
  - Nx**:** Regional lymph nodes cannot be assessed
  - N0**:** No regional lymph node metastasis
  - N1**:** Regional lymph node metastasis
    - pN1a: Metastasis in a single regional lymph node
    - pN1b: Metastasis in multiple regional lymph nodes
- Distant Metastasis **(M)**
  - Mx: Distant metastasis cannot be assessed
  - M0**:** No distant metastasis
  - M1: Distant metastasis

Stage	Tumor Grade	Nodal Status	Distant Metastases	Median Survival†	Characteristics
				mo	
IA	T1	N0	M0	24.1	Tumor limited to the pancreas, ≤2 cm in longest dimension
IB	T2	N0	M0	20.6	Tumor limited to the pancreas, >2 cm in longest dimension
IIA	T3	N0	M0	15.4	Tumor extends beyond the pancreas but does not involve the celiac axis or superior mesenteric artery
IIB	T1, T2, or T3	N1	M0	12.7	Regional lymph-node metastasis
III	T4	N0 or N1	M0	10.6	Tumor involves the celiac axis or the superior mesenteric artery (unresectable disease)
IV	T1, T2, T3, or T4	N0 or N1	M1	4.5	Distant metastasis

Table 2. Staging of PC according to the AJCC (4)

3.7 TREATMENT

The only potentially curative treatment of the PC is the surgery, therefore the main objective is to do an early diagnose to perform surgical treatment to more patients in order to increase the survival rate and the free-disease period.

The surgery performed is the cephalic duodenopancreatectomy (DPC) that consists in the resection in block of the PH, the duodenal marc, with or without the ante-pyloric area, the ductus choledocus and the gallbladder. (16) The DPC is a technique indicated in the treatment of tumors and non-neoplasic diseases of the PH. It is also performed in tumors of the common bile duct, of the Vater ampulla and of the duodenum. It is a complicated intervention that requires refined surgical skills.

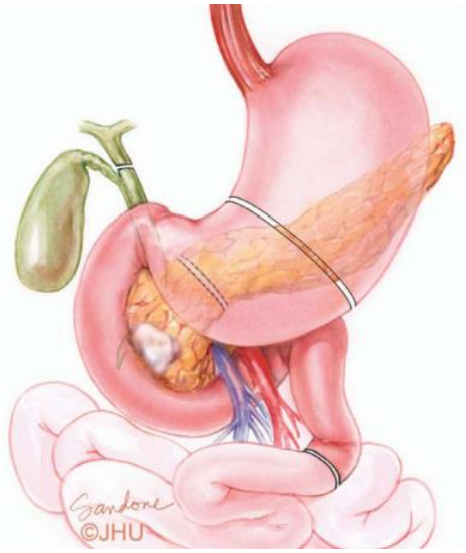


Figure 5 Cephalic duodenopancreatectomy (10)

Not all the patients can be operated and that is why there are some unresectability criteria. This criteria contain the situations where the patient does not benefit from the operation. In the DPC the unresectability criteria include: distant metastases, affectation of the SMA, affectation up to 180º of the celiac trunk, contact with the first jejunal branch of the superior mesenteric vein (SMV), infiltration or thrombosis in the SMV or portal vein (PV) that cannot be reconstructed and aorta invasion. (17)

The DPC have been the elected surgical treatment during decades using the Whipple technique but in the last years other variations related to the removal have been introduced. In the classical technique, the retro-portal lamina is approached in the last place and it makes impossible to know the state of the SMA and the celiac trunk, and the pancreas remains irrigated until the end of the surgery, a potential cause of haemorrhage. (16)

The Superior Mesenteric Artery First Approach (SMAfa) allows an early deliberate dissection of peripancreatic arteries and facilitates the identification and ligation of the superior and inferior pancreaticoduodenal arteries reducing intraoperative blood loss.(18) Starting with the approach of the SMA the surgeon can determine the tumor's resectability by analysing if there is tumoral invasion of the SMA or the celiac trunk. With the SMAfa is also possible to determine the invasion of the SMV and PV and facilitate the resection and reconstruction. (19)

The disease free survival and the overall survival have also been compared and the SMAfa obtains a better results than Whipple Technique (WT).

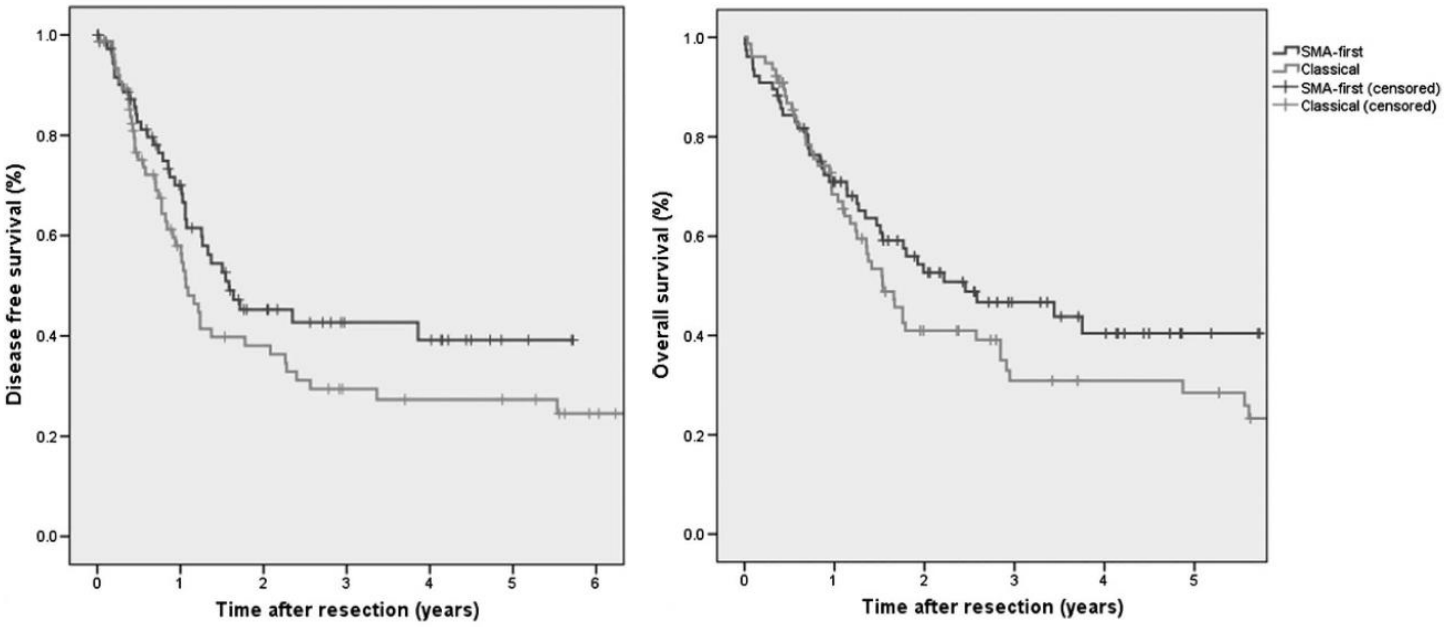


Figure 6 Disease free survival and overall survival in relation to technique (18)

Other important factor in the surgery is the affectation of the resection margins. As said before, only the 20% of the patients can opt to a curative treatment, and even in patients who undergo surgery the 5-year survival amounts only 7-25%.(20) This occurs because of the frequent tumor recurrence that is caused by R1 resections.

The margin resection are classified as R0, indicates complete resection; R1, meaning microscopic margin involvement and R2, macroscopic margin involvement. (21)

In the pancreatic cancer there are other treatments such as chemotherapy and radiotherapy that are used for the unresectable disease and the borderline tumors. They can be used as palliative treatment or otherwise as a neoadjuvant treatment to perform a posterior surgery. Is common that some patients after the DPC receive some sessions of radiotherapy. Since this study is aimed at the surgical treatment we will emphasize in the surgical treatment leaving the rest of the treatments aside.

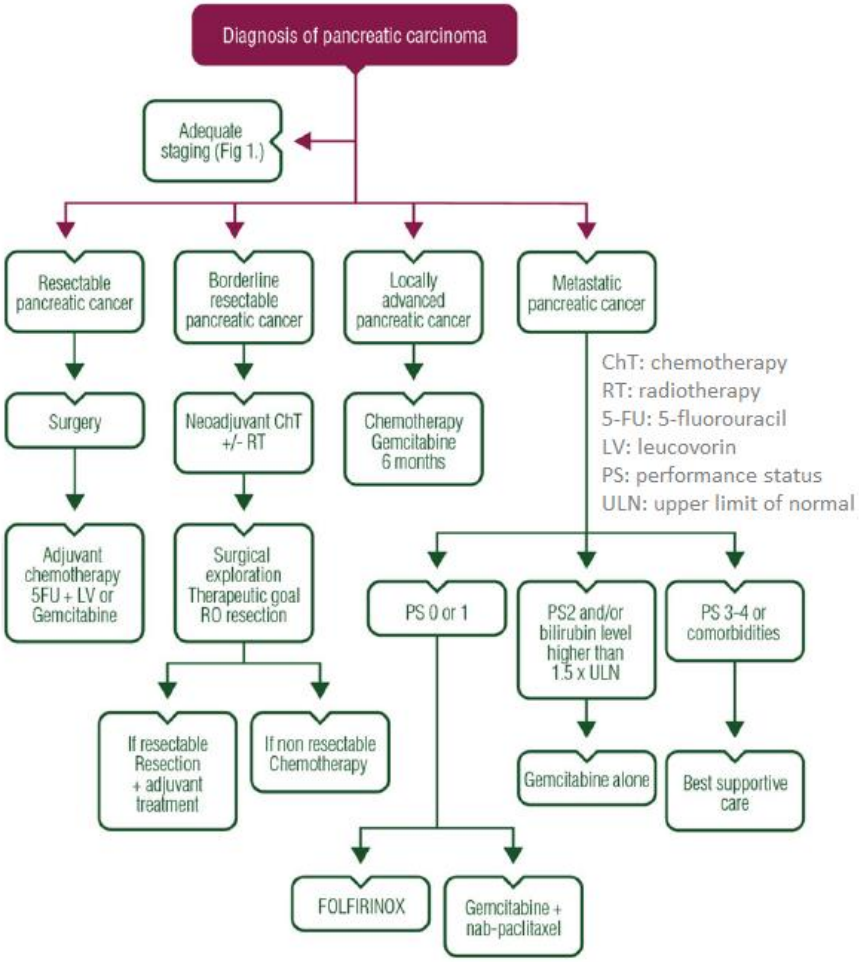


Figure 7 Treatment strategy (2)

3.8 COMPLICATIONS

Mortality rate after DPC has decreased to less than 3% but morbidity remains high, from 18% to 52%.(22) Most frequent complications are anastomotic insufficiencies, pancreatic fistulas, delayed gastric emptying and intraabdominal abscess.

Complication	n	%
Pancreatic fistula	54	10.8
Delayed gastric emptying	39	7.8
Hemorrhage	38*	7.6
Wound infection	38	7.6
Intraabdominal abscess	27	5.4
Biliary fistula	15	3.0
Pulmonary complication	12	2.4
Newly developed diabetes mellitus	31	6.2
Chyle leakage	5	1.0
Others	12	2.4
Total	162†	32.4

*Twenty-two patients (58%) developed delayed hemorrhage 5 days after surgery: 21 during hospital stay and 1 after discharge.
†Sixty-five patients developed 2 or more complications and death occurred in 6 cases.

Table 3 Postoperative complication after duodenopancreatectomy (25)

Pancreatic anastomosis are responsible of the majority of complications, in particular, pancreatic fistula. It is a persistent drainage of any measurable volume of drain fluid on or after the 3th day of the postoperative curse with any amylase content greater than 3 times upper the normal serum value.(23) To decrease the incidence, some studies propose a pancreaticogastrostomy that involves anastomosing the pancreas to the posterior wall of the stomach.(24)

Another complication is the haemorrhage after the DPC. The haemorrhage is a critical complication that has a prevalence of 5% to 12%(22) and a mortality rate of 10.5%. This is because the delayed hemostasis due to the diagnostic difficulties. Furthermore, most of the haemorrhage are from the major arterial system and there is an important bleeding. (25) There is a theory that indicates local sepsis resulting from a pancreatic fistula the main cause of haemorrhage. Also the skeletonization of the vessels during the lymphadenectomy may injure the arteries. It is important to discard this complication in patients with continuous abdominal pain.

Delayed Gastric Emptying is another frequent complication defined as:(26)

a. Nasogastric tube decompression for ≥ 10 days + 1 of the following criteria
    - Emesis after nasogastric tube removal
    - Postoperative use of prokinetic agents after postoperative day 10
    - Reinsertion of a nasogastric tub
    - Failure to progress with diet
b. Nasogastric tube decompression < 10 days + 2 of the criteria

To classify the different complications according to its risk, there is the classification adopted by the International Transplantation Society that consists of 5 grades depending on the treatment required and risk of the patient's life. (ANNEX 7)

After knowing the complications, for our study is important to know if there are differences between the WT and the SMAfa. Few studies show heterogeneity in the results and there are not clear differences. Also have been seen that the SMAfa has less incidence of pancreatic fistula, of delayed-gastric emptying and less hospitalization time while the incidence of postoperative diarrhoea that requires medication is higher. Referring to the haemorrhage, the reintervention rate and the in-hospital mortality rate remain the same for both techniques.(27)

4. JUSTIFICATION

Knowing that the PC is one of the most mortal cancers, with an aggressive behaviour and a poor prognosis and according that the only curative treatment for the PC is the surgery, it is very relevant to study about the different techniques and be able to use the best approach in every patient. To increase the survival rate as well as the time without recurrence, is important to know the relation between the margin resection, the free-disease period and the technique used. In this study we aim to see which surgical group live longer without recurrences and the relation between the surgical technique and the tumoral margins.

Some studies have started to show some survival differences between the two techniques and it is primordial to determine the approach that leads the patient to a longer free-disease survival without heterogeneity, obtaining significant results.

The affectation of the margins has an important relation with the recurrences. During some years there was not a consensus about how to treat the resected piece in the AP (anatomical pathology) analyses. At the moment that all the pathologists start using the same technique, the number of R1 resections increased a lot due to more exhaustive analyses. This leads us to believe that the results that we have, are not reliable. In this study, all the specimens will be treated with a standardized technique, following the European Study Group for PC protocol to obtain reliable results.(20,28)

With a standardized technique we will obtain the relation between the surgery and the affectation, or not, of the margins and this will allow us to compare it between the two techniques to know the more oncological approach.

In the other hand, this study will also be useful to know the complications that occur in the different techniques to compare them.

Some studies have compared both techniques but there are not any significant results due to an important heterogeneity between the different trials. With our study we will be able to compare the long-term evolution of the disease with the time without recurrence and the short-term aspects such as the margins of the resected piece and the surgical complications.

With this trial we want to have reliable results that make and impact into the treatment of the PC. Comparing the two techniques leads the surgical treatment to an important improvement. We want to validate our hypothesis to achieve an enlargement of the survival of the patients.

5. HYPOTESIS

Superior Mesenteric Artery Approach is an appropriate alternative to the classical resection in the surgical treatment of patients with resectable head pancreas tumor due to an increase of the disease-free period.

6. OBJECTIVES

6.1 MAIN OBJECTIVE

The main objective of this study is to measure the disease-free survival in patients with head pancreas tumor after the surgical intervention comparing the results between the two different surgical techniques of DPC: Superior Mesenteric Artery Approach vs Classical Approach.

6.2 SECUNDARY OBJECTIVES

- Quantify the number of resection RO after the AP exam in the two different techniques.
- Describe complications in patients due to the surgical intervention comparing them between the two different approaches.

7. METHODS

7.1 STUDY DESIGN

The most accurate design for the study would be a prospective randomized comparative trial. We have two randomized treatment groups that compare with each other to minimise selection bias and obtain reliable results. The control group will be the patients operated by classical approach. It will be a single-blind trial because the surgeon will know the technique used to be able to perform the intervention. The radiologist, pathologist and statistic expert will be blinded.

7.2 POPULATION OF STUDY

The study will take place in *Hospital Universitari Josep Trueta*, where the patients will be selected, operated and followed.

The population will be the patients diagnosed with head PC with resectable disease. Not all the patients are useful to be in the study and it is needed inclusion and exclusion criteria.

Concerning the inclusion criteria the patients must have been diagnosed with resectable head PC. All the patients with a non-resectable cancer do not fit into the trial because the interest is to evaluate the surgical treatment.

On the other hand, in the exclusion criteria there are:

- High-risk surgery patients that may distort the results:
  - Equal or up to ASA IV in preoperative work up
  - Patients older than 85 years old
- Non-resectable criteria founded during the surgery:
  - Affectation of celiac axis, SMA or hepatic artery.
  - Tumor growth towards the stomach, colon, mesocolon, inferior vena cava or aortic artery.
  - Liver metastases, peritoneal affectation or lymphadenopathies that are non-adjacent to the pancreas.
- Neoadjuvant treatment before the surgery because the results will be influenced by the effects of the chemotherapy.

7.3 SAMPLE

SAMPLE SELECTION

The patients will be recruited by a non-probabilistic consecutive method. When patients are diagnosed they will be potential candidates for the trial. If they meet the inclusion criteria the surgeons or residents of general surgery will inform the patients about the study and try to convince them to be part of it. All the participants must agree by giving their written consent. (ANNEX 2)

SAMPLE SIZE

The size of the sample needed will be of 92 subjects to have a sample that is representative of the population of study.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test 92 subjects are needed, 46 in each group, to recognize a statistically significant difference greater or equal to 3 months, considering that the follow-up after the surgery will be every 3 months. The common standard deviation is assumed to be 5 month about the average of the survival rate of 18 months in operated patients. It has been anticipated a drop-out rate of 5%.

The sample size has been calculated with the GRANMO application.

ESTIMATED TIME OF RECRUITMENT

According to the sample size calculation we need 92 patients. Taking into account that every year in the *Hospital Universitari Josep Trueta* are operated around 20 patients, in accordance with the data provided by the Hepatic-biliary-pancreatic department, we will need about five years to recruit the sample.

RANDOMITZATION MEHTODS AND MASKING TECHNIQUES

After recruiting the patients they will be randomized in order to avoid the selection bias, assigning them to one of the two groups of intervention, A or B.

Before beginning the study the investigators will decided which DPC technique will correspond to each group and with a simple 1:1 randomization the patients will be placed in group A or B. The patients won't know in which group they fit to respect the blinding.

In a trial that involves a surgical treatment is not possible to do a double-blind study and the patient will be blind in a simple-blind study.

It is important to blind the pathologist who analyse the specimen after the surgery and the radiologist who does the CT interpretation during the follow-up. The statistical expert who will analyse the results will also be blinded. The only specialist who knows which technique is used is the surgeon and this way the AP specialist and the radiologist do not get influenced finding results by the approach that was performed.

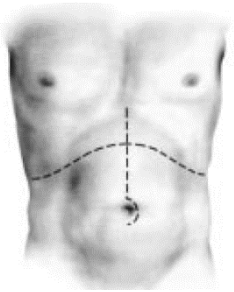
7.4 VARIABLES

INDEPENDENT VARIABLES

In this study there are two independent variables, the type of surgical technique.

The first one is the classical approach, the **Whipple intervention**: (29)

The WT is a block resection of the PH, the gallbladder and the common bile duct, the gastric antrum, the duodenum and the first portion of the jejunum.



The patient is positioned in supine position with the arms forming a cross. The operating area must be ample from the breast line to the pubis. The incision is transversal subcostal bilateral passing between the xifoides of the sternum and the navel.

Figure 8 Transversal subcostal bilateral incision (29)

First of all is performed **an evaluation of the resectability**:

1. Manual surgical examination is done in centripetal structure from the sides to the injury.
2. It is necessary to take samples mostly from the lymph nodes to a posterior histological exam.
3. It is also important to do a palpation searching suspicious lymph nodes or carcinomatosis signs in the diaphragmatic cupolae, liver, peritoneum, bowel and the pouch of Douglas.
4. Expose celiac region with and incision of the gastrohepatic ligament in the pars flaccida.

5. Search adenopathies in the interaortocaval sulcus and in the celiac axis by separating the Spiegel lobe to the right.
6. Introduce the thumb and the index finger in the Winslow hiatus to explore the hepatic pedicle.
7. Release the first centimetres of jejunum to explore the superior mesenteric pedicle.
8. Exploration of the pancreas and the tumor:
    a. Complete coloepiploic resection to access to the omentum transcavity and explore the superior part of the transverse mesocolon, mesenteric pedicle lymph nodes from the isthmus and the body of the pancreas, release de colonic right angle and descend it to not injure the VMS.
    b. Kocher manoeuvre, which consists in a dissection of the anterior plane of the cava vein medially rotating the duodenum and the PH, to expose the inferior infrahepatic cava vein where the potential metastatic adenopathies are located.

       With this procedure we get a mobile PH and is easier to evaluate the tumor location and characteristics.

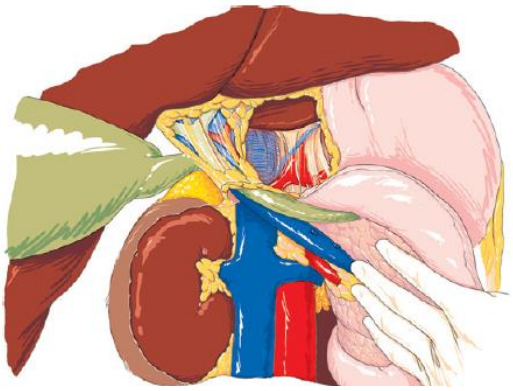


Figure 9 Kocher manoeuvre (16)

    c. Separation of the front face of the mesentericportal axis and the posterior plane of the isthmus of the pancreas. The VMS is exposed, the plane is dissected by following the adventitia layer. Locate the PV passing through the omentum cavity next to the pancreas. Continue the retroisthmic liberation with the finger and individualize the isthmus with bows.

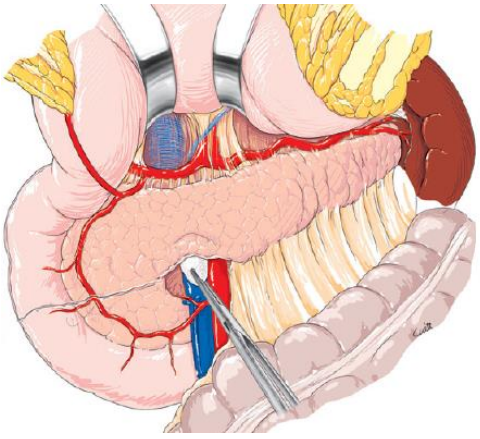


Figure 10 Retroisthmic liberation (16)

After the exploration we may find different situations where we can continue or not the surgery. If there are distant lymph nodes invaded or metastatic affectation in the AMS origin nodes the resection is not continued because it does not provide any benefits. If the tumor invades the PV a resection can be done but it will require a vascular reconstruction. When the tumor is limited to the pancreas, with or without invasion of the local lymph nodes, a curative resection will be performed.

The second step of the intervention is the **excision**:

1. <u>Dissection of the Hepatoduodenal Ligament</u>

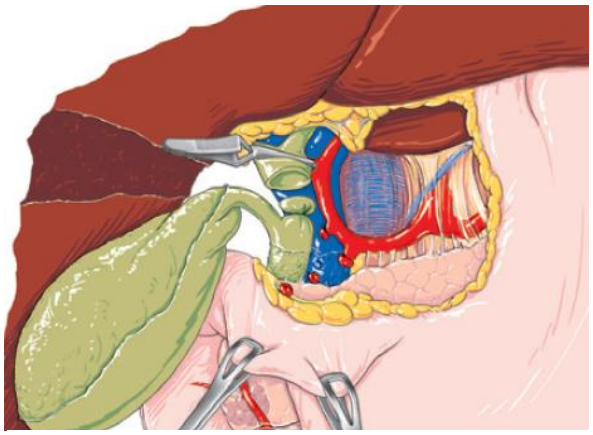


Figure 11 Cholecystectomy, dissection of bile duct and ligation of gastroduodenal artery (16)

   a. Perform a cholecystectomy, dissect the bile duct and the regional lymph nodes.
   b. Divide the bile duct at the level of the cystic duct to expose the PV in the hepatoduodenal ligament.
   c. Trace down the PV to the pancreas neck and ligate and divide the tissue around he vein to expose the suprapancreatic PV.
   d. Identify and excise the hepatic artery lymph nodes to see the hepatic artery. Follow the curse of the hepatic artery to find the gastroduodenal artery and ligate it.
   e. Dissect the posterolateral aspect of the PV.

2. <u>Gastric section</u>
   a. The gastric section described by Whipple involve a resection of the distal third of the stomach, ten centimetres above the pylorus. After the resection the stomach has to be close and moved to the right.
   b. Remove the right part of the mayor omentum, next to the antrum and covering the PH.
3. <u>Pancreatic section</u>
   a. Done in the left side of the PV.
   b. Control the haemorrhage with a continuous suture in the cephalic part and an X stitch in the caudal part. It is important not to injure the Wirsung duct.

c. Resection of a small part of the pancreas for a histological exam to verify the margins. If they are affected the resection has to be more extended.

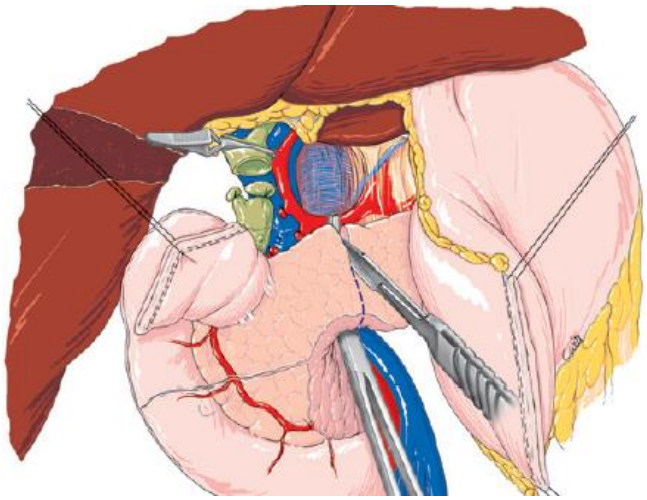


Figure 12 Gastric and pancreatic section (16)

4. Jejunal section
    a. Lift up the transverse mesocolon and expose the Treitz angle and the fourth portion of the duodenum.
    b. Expose the Treitz muscle by moving the inferior mesenteric pedicle through the left and section it to release the duodenojejunal angle.
    c. Section the duodenum 10 centimetres from the duodenojejunal angle.
5. Retroportal lamina section
    a. The retroportal lamina subjects the duodenalpancreatic block and contains the lymphatic vessels, the PH venules and the posterior arteries that drain to the AMS.
    b. It has to be sectioned protecting the AMS and expanding to the maximum the chain of lymph nodes removal.

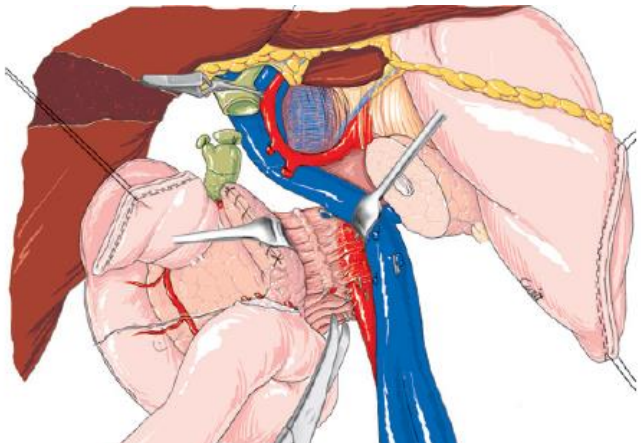


Figure 13 Retroportal lamina section (16)

The last step in the intervention is the **reconstruction**, following the Child assembly:

1. Pancreaticjejunal anastomosis or pancreaticogastric anastomosis
    a. According to the surgeon criteria.
2. Hepaticojejunal anastomosis
    a. Performed 20 or 30 centimetres away from the pancreaticjejunal anastomosis.
    b. Implant the common hepatic duct to the jejunal loop.
3. Gastrojejunal anastomosis
    a. The anastomosis has to be done in the front part of the transverse mesocolon
    b. The anastomosis is done 40 centimetres from the hepaticojejunal anastomosis.

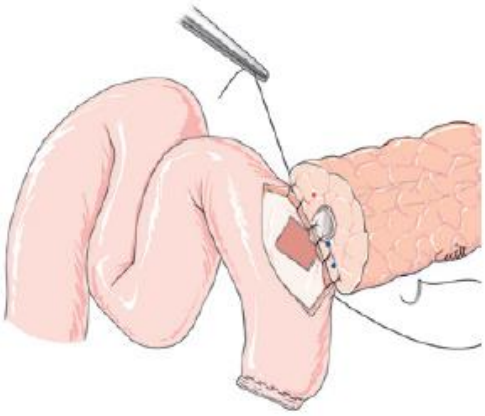


Figure 14 Pancreaticjejunal anastomosis (16)

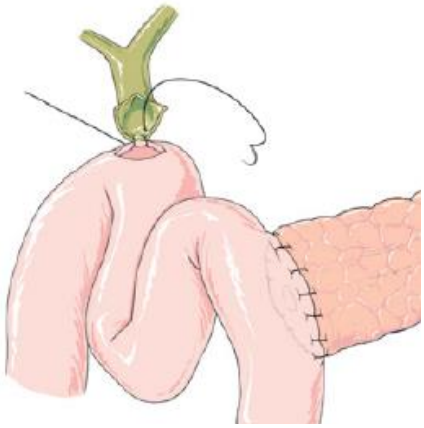


Figure 15 Hepaticojejunal anastomosis (16)

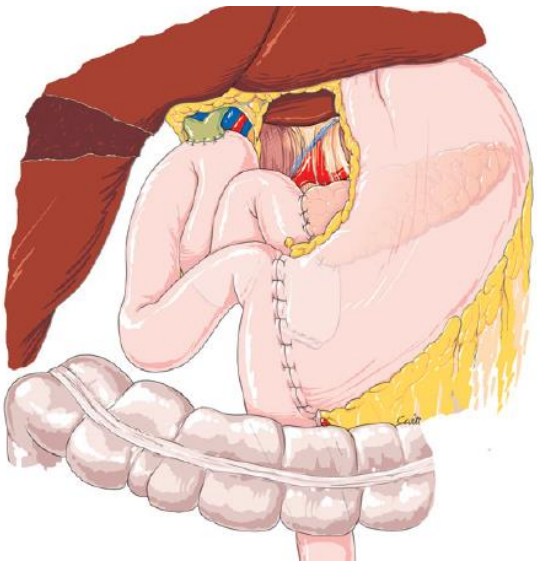


Figure 16 Reconstruction (16)

The second independent variable is the **Superior Mesenteric Artery First approach**: (30,31)

The preparation of the patient and the evaluation of the resectability is done in the same way that in the classical approach.

After confirming the absence of dissemination the dissection can start:

1. The first step is to attach the transverse mesocolon to the right perinephric area and bring down the rest of the transverse mesocolon to expose the cava vein.
2. Do a Kocher manoeuvre (explained in the classical approach technique) to expose the aortocaval region and be able to evaluate the lymph nodes. Any suspicious node is excised and sent to a histological exam. If the nodes are reported positive the intervention have to stop.
   With the Kocherization is also exposed the origin of the SMA.

Dissection of the SMA

1. Dissection following the SMA with a right-angle dissector and passing around the artery a vascular loop.
2. Incise longitudinally the perivascular tissue around the SMA.
3. After 1-2 cm from the origin of the artery the hepatic artery can be seen and must be looped and protected.
4. Continue the dissection until the third part of the duodenum.
5. It is important to divide all the connective tissue between the PV and the SMA. When performing the dissection the tumor invasion on the SMA or on an important portion of the PV can be seen, and if present the resection can be abandoned.

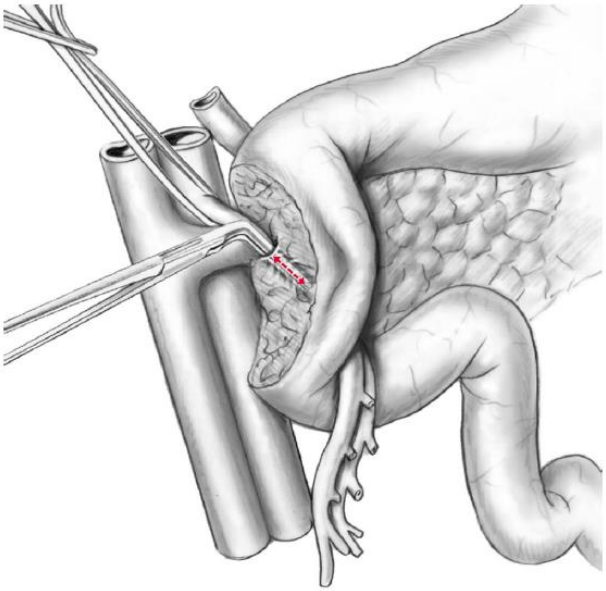


Figure 17 Origin of SMA and dissection of the perivascular tissue (30)

6. The dissection is done until you find the hepatoduodenal ligament.

Dissection of the Hepatoduodenal Ligament (explained in the Classical approach).

Dissection of the Uncinate Process and the Neck of the Pancreas:

1. Do some traction of the duodenum and the PH to expose the PV and continue the dissection down from the pancreas border.
2. In the posterolateral dissection of the PV some ligatures must be performed in the vessels. After the dissection the neck of the pancreas is exposed.
3. Separate the pancreas from the PV until the splenoportal junction is seen. In this point can be seen if there is invasion of the PV or the SMV.
    a. If there is invasion the SMV and the suprapancreatic PV are dissected and looped and the neck of the pancreas is dissected.
    b. If there is not invasion: control the splenic vein, dissect the neck of the pancreas and value if it is necessary to complete the resection with a part of the SMV or PV depending on the degree of involvement.

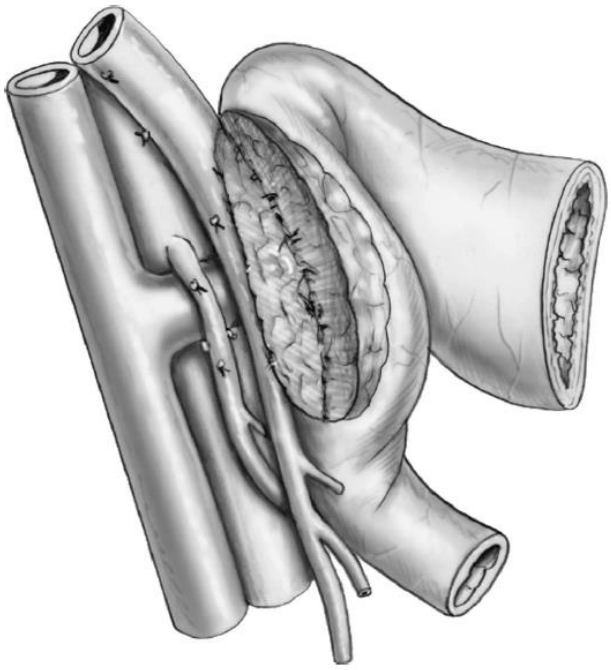


Figure 18 Exposure of the anterolateral aspect of PV, ligatures of the vessels and neck dissection (30)

4. After the separation and resection of the PH, divide the proximal jejunum and the stomach in the same way that is done in the classical technique.

The reconstruction of the gastrointestinal continuity is performed in the same way that in the WT.

DEPENDENT VARIABLE

According to the main objective of measuring the disease-free survival, the dependent variable are the number of months with no disease recurrence.

Every patient after the discharge from the hospital will have a follow-up every three months. Before the medical visit the patient needs to do:

- A blood analysis with the tumor markers CA 19.9 and CEA (32)
- An abdominal and thoracic CT scan

There are not specific tumoral markers of the PC but the serum levels of CA 19.9 increase in a high percentage. The main use of the CA 19.9 and the CEA is during the follow-up, when the values increase it is an alarm sign that indicates potential recurrence and requires a deepest study.

The abdominal CT enables us to see by image the alterations or modifications that suffers the operated zone. In the follow-ups we have to focus on the location of the lesion before the intervention because in the PC the recurrence use to be in the same place of the primary lesion. The CT is also useful to locate metastases. The thoracic CT is useful to located distant metastases.

To study the secondary objectives of examine the ressection margins, the piece is sent to AP. Is important that every piece is examined with a standardized technique, following the European Study Group for PC protocol: (20,28)

Specimens Preparation:

1. Fixe the DPC specimens overnight in 10% formalin.
2. Stain the circumferential soft tissue margins and surfaces accorded to a color code.

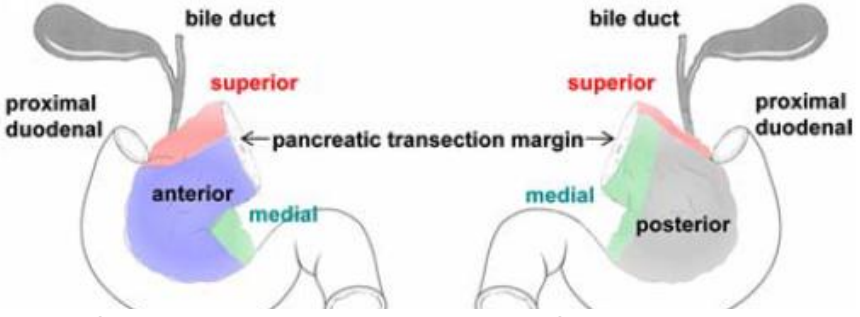


Figure 19 Vision of the margins. Color code: red, superior surface; blue, anterior; black, posterior; green, medial (28)

3. Identify and completely embed all the transection margins of the organs and the resection margins of the vessels.
4. Slice the specimen in 3 to 5 mm-thick slices following and axial plane perpendicular to the duodenal axis.

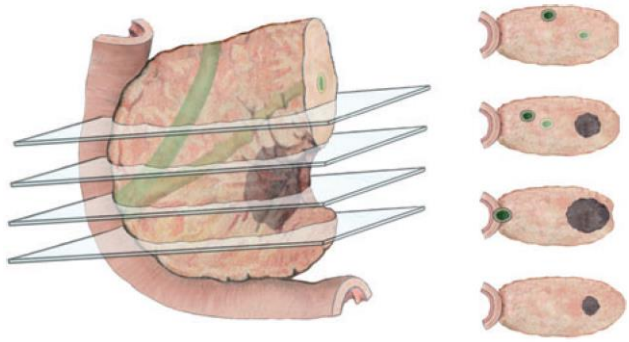


Figure 20 Slicing in an axial plane (20)

5. Divide the slices in two groups depending on above or below the ampulla.
6. Identify the tumor and measure the size and the relation with the anatomical structures and the margins.
7. Take the macroscopically infiltrated tissue samples from the PH and from the tumor with the closest margin or anatomical structure.
8. The non-macroscopically infiltrated pieces are largely sampled in a perpendicular fashion to the pancreatic parenchyma.
9. Embed the lymph nodes that are smaller than 0.5 cm. If the nodes are bigger and if they are not macroscopically infiltrated are sliced in thin sections.
10. Regional lymph nodes are labelled according to the TNM system.

The Histological Examination includes:

- PC subtype
- Grade of differentiation
- pTNM
- Presence or absence of peritumoral (at least 5 mm from the tumor) perineural, lymphatic and vascular spread
- Number of lymph nodes retrieved and the number and localization of the nodes that contained metastases
- Presence and grading of precursor lesions

Assessment of R Status:

R1 is defined when the distance of the tumor from the resection margin in equal or less than 1 mm. When the margin is infiltrated is defined as *direct extension of the primary neoplasm* or *locoregional spreading/metastasis* if there is affectation of other structures.

For the dependent variable of the secondary objectives that compares the complications, the surgeon have to register the data.(ANNEX 6) The surgical complications are those that appear during the first 90 days after the surgery. During the hospitalization the surgical team will control every day the patients and after the discharge from the hospital and after 90 days, concurring with the first follow-up visit, the doctor will ask about any complications. If the patient go to the emergency service the data will be registered in that moment. The aim of the complications is to separate them in the two groups of intervention to compare the percentage of complication in each group and which occur depending on the intervention. In every follow-up visit the doctor will ask for any newly developed complications. At the end of the follow-up we will calculate the number of patients and the percentage from the total of the different complications in WT group and the SMAfa group.

COVARIABLES

The covariables are other factors that can influence the relation between the independent and the dependent variables. It is important to know them to see if they make any influence in the results.

- Age: years
- Gender: male or female
- American Society of Anaesthesiologist risk score: ASA grades
- Affectation of the vein structures in the surgery: percentage

7.5 PROCEDURES

All the professionals involved in the Hepatic-biliary-pancreatic unit in the general surgery department have to be informed about the trial in order to fulfil the objectives. The study has a specific circuit that has to be followed by all the doctors:

First visit: The first step is to recruit the patients into the trial the day that they are diagnosed of resectable PC. The doctor have to explain the study and try to convince them. They have to agree by signing the informed consent after reading the informative paper. (ANNEX 1) (ANNEX 2) It is important that the patients understand they will not know which technique is used to maintain the simple-blind study.

Anaesthesiology visit: Before the surgical procedure the patients must have a visit with the anaesthesiologist who will decided if the patient can be operated and which is the operatory risk classifying he or she into the different stages of the ASA (American Society of Anaesthesiology) classification. (ANNEX 7)

Before the surgery the patient have to give the consent for the realization of the intervention. (ANNEX 3)

Surgery: The day of the intervention the surgeon team will receive a closed envelope with the technique that must be performed in the patient placing randomly the patient into one of the two groups of treatment.

After the surgery the resected piece is send to AP to do the margins examination.

Follow-up: After the discharge from the hospital every 3 months the patient will have a visit with the surgeon to control the recurrence of the cancer. (ANNEX 5) Before going to the visit they need to do an abdominal and thoracic CT and a blood analysis to complete the follow up and for being able to detect any recurrence.

8. STATISTICAL ANALYSIS

When the data collection is finished, the statistical analysis must be done. To analyse the dependent variable as the disease-free months will be done by using the Cox model. With the hazard risk we will be able to analyse how many time (in our case months) passes until the appearance of cancer recurrence. With this model we will compare the time to the clinical event in each group to know in which technique there is a longest time without recurrence.

We will assume a confidence interval of 95% and to be considered statistically significant we need a $p<0.05$.

The independent variable is defined as a dichotomic categorical variable. The dependent variable of the main objective is a quantitative continuous variable. About the secondary objectives the affectation of the margins classified in R0, R1 and R2 is an ordinal categorical variable. The different complications are a nominal categorical variable.

To evaluate the different variables we have different tests. For the categorical variables a Chi-squared test will be used and the quantitative variable will be evaluated by the T-Student test.

9. WORK PLAN AND CHRONOGRAM

This study is expected to last 7 years and 5 months from the protocol approval to the moment of the publishment and the dissemination.

1. **Preparation and coordination phase** (3 months)

After the approval we will review the protocol and present it to the CEIC of *Hospital Universitari Josep Trueta*. Once the CEIC agrees the main researcher will meet all the researchers, including surgeons, radiologists, pathologist, statistics and every person that have a roll in the study to explain the aims of the trial. Methods and design will be explained and discussed and the instructions required will be given. The clinical research associated will coordinate and explain the patients' recruitment and organize a meeting every 6 months in order to control and asses the progression of the study.

2. **Field work**

   - Sample recruitment (56 months): The patients that comply with the criteria to be part of the study will be recruited by a consecutive method (as explained before) and randomly placed in one of the two groups of treatment. Since we need 92 patients and in the *Hospital Univeritari Josep Trueta* the surgeons operate 20 patients per year the sample recruitment will last 56 months or 4.6 years. (20 patients/year means 1.7 patients every month and to complete the 92 patients recruitment we will need 56 months)
   - Intervention (56 months): Due to the consecutive recruitment of the patients the sample recruitment and the intervention period will coincide in time.
   - Follow-up (18 months): The follow-up for each patient is a year and a half according to average of 18 months of disease-free survival with a standard deviation of 5 months. The follow-up of all the patients have to start after surgical intervention of the first patient and finish 18 months after the last patient operated. This way the follow-up will coincide with the time of recruitment and intervention.

3. **Data collection** (74 months)

In this study the data collection will start with the sample recruitment and it will last untill the last day of the follow-up. This is because from the first patient we have to collect the data, also during the surgery, the AP result after the surgery, the information during the hospitalization and the data from the follow-up. (ANNEX 4)

4. **Data analysis and interpretation** (6 months)

After all the medical procedures and follow-up, the data will be analysed and the results will be materialized in the final article.

5. **Publication and dissemination** (6 months)

When the study is finished and the article is written, the researches will publish the scientific paper and will inscribe it to a different congresses to expand the trial results.

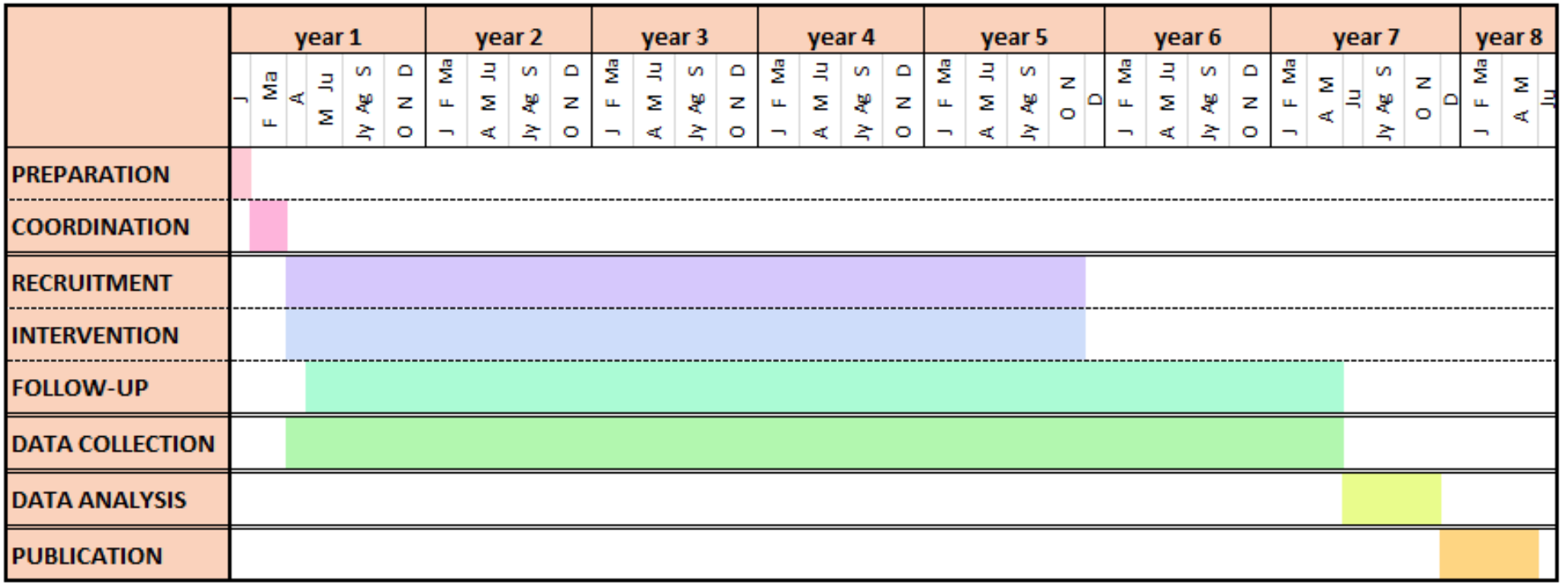


Table 4. Chronogram

J: January
F: February
Ma: March
A: April
M: May
Ju: June
Jy: July
Ag: August
S: September
O: October
N: November
D: Desember

10. ETHICAL AND LEGAL CONSIDERATIONS

This study will involve humans and must respect the principles of the Helsinki Declaration and have to be approved by the Clinical Research Ethical Committee (CEIC) of the *Hospital Universitari Josep Trueta*. This Committee will analyse the trial and the ethical aspects to be sure they are respected. Furthermore if the CEIC give additional indication will be respected. In addition to the CEIC, the management of the centre have to approve the trial too.

The protocol must follow the Spanish law 14/2007 of 3rd of July about Biomedical Investigation involving invasive procedures. Moreover, the privacy of the participants and the personal information have to be protected according to the Spanish law 15/1999 of the 13th of December about data protection, confidentially and protection of personal data.

All the principles of bioethics will be respected. First of all, the patients will be informed about the interventions and the procedures of the study providing them an information document. All the questions will be answered and the potential participants will agree to participate voluntarily. To express the accordance and the understanding they will have to sign the informed consent. This way the autonomy principle will be respected. Secondly, to respect the beneficence and non-maleficence principles, the study have an exclusion criteria to do not perform a surgical treatment to a patient that the risk-benefit relation is prejudicial. Finally, all the patients will receive the same conditions and will be equally treated and respect the justice principle. To achieve this principle every participant will remain anonymous and randomly placed to one of the different groups without any differences.

11. STRENGTHS AND LIMITATIONS

In our study there are some limitations that should be considered.

In first place, the main limitation is the impossibility of a double-blind. The fact that the trial studies surgical procedures makes impossible to blind the surgeon who performs the intervention. This means the surgical team will know in which group is placed every patient and a detection bias can be done. To overcome this limitation the surgeons will be the only professionals involved in the study who will know it; the pathologist, the radiologist and the statistician will be blinded. With this option in the specimen AP analyses, in the follow-up CT and in the study of the results the professionals will not be influenced by which surgical technique was used.

The second bias can be related in the recruitment of the sample. The consecutive method is a non-probabilistic and there is the risk of not obtain the most representative population. Trying to minimize this potential selection bias, very extensive inclusion criteria have been set to have a very similar sample to the reference population. With the exclusion criteria we try to reduce the confusing factors.

This study will be unicentric. This makes the recruitment and intervention period longer and during these years new studies can be carried out. Dealing with surgical treatments the human factor is really relevant. Every surgeon has a personal way and habits of performing the surgeries. Knowing that in the same department are found interpersonal differences, extending the number of surgeons involved makes the differences multiply. Such difficulties are amplified by the fact that in not all the hospitals the SMAfa is performed and must be added the lack of knowledge and experience to perform the technique. After evaluating all this factors, priority has been given to a good technique with the minimal differences sacrificing a shorter duration of the study. Seeing that the duration of the trial is 7 years and a half, is considered an allowable time considering the benefit obtained avoiding as much as possible the differences of execution.

Another limitation are losses and withdrawals in the duration of the study. Considering it is an oncological disease, the anticipated losses are a low percentage, 5% in this study, and have been taken into account in the sample size calculation. Losses will be

registered and quantified and deceased will also be registered with the causes of death and the belonging group.

One of the strengths of the trial is the randomization to distribute the patients into the two groups that allows the extrapolation of the future results on the general population.

12. FEASIBILITY

This trial will take place exclusively in the Hospital Universitari Josep Trueta de Girona. The hospital will provide everything that is necessary. The operating room costs and the involved surgeons and medical staff' salaries will be covered by the hospital. The posterior procedures such as the pathologist and the medical cares and follow-up will be also provided by the health system.

For the extra CT and blood analyses that are needed to complete the follow-up, which appears in the budget, will be carried on in the same hospital with an agreement of payment. This way is easier to the patients and at the same time we make sure that the radiologist who make the CT and its analyses are from the same team.

The surgeons from the hepato-biliary-pancreatic unit are used to perform both of the techniques, thing that allows to ensure the reliability and quality of the surgeries. The department just needs to meet to explain and optimise the performance of the study and make consensus of the technique to avoid as much as possible execution differences.

Using the same circuit that patients use in the everyday practice makes the study really feasible, avoiding problems with organization or payments.

13. BUDGET

For the realization of this study we will need an inversion of 122 410€.

The cost of the surgical intervention, the AP analyses, the blood analyses and the CT needed for the follow-up are include in our National Health System (NHS). A patient diagnosed with resectable PC is operated and followed up the same way that we propose in our study, this way there are not extra costs.

The two different surgical techniques are currently performed in the *Hospital Universitari Josep Trueta* consequently does not represent and additional cost.

After the surgical intervention the patients will be hospitalized during a period of time. The hospital includes hospitalization and the doctors' attention in the postoperative plan not affecting at the budget.

In the everyday clinic practice the patient have a follow-up visit every 3 months but the CT and the blood analyse are only done every 6 months and in our trial we need them every 3 months. This way one of every two CT and blood test will be under our budget. The follow-up will last one year and a half that means 6 CT and blood analyses. Of these we will have to pay for 3 CT scan (95€ the thoracic CT and 204€ the abdominal CT) and 3 blood tests with tumoral markers (40€ each). The total is 93564€ including 3 CT and 3 blood analyses for the 92 participants of the trial.

As we are working with invasive procedures is necessary to contract an insurance for the patients, whit a total of 9200€ (92 patients for 100€ each).

It will be necessary a statistical expert for the randomization of the patients and to analyse the results. We will hire him or her for an estimate number of 180 hours with a salary of 25 € per hour, that means a cost of 4500€.

A part from the statistical analyses we also need a clinical research associated who will be responsible of the data monitoring and control, give assessment and coordinate the medical staff involved and the patients. This will mean 7500€ for 300 hours in a salary of 25€ per hour.

After the study an important part is the publication and the dissemination. For the publication in national and international journals we have assigned 3000€. In the dissemination including two congresses, one in a national level and the other one in a international level with the travel and the food also computed, means a total of 4500€.

	Price	Quantity	Total
STAFF AND SERVICES			
Statistical expert	25€/h	180h	4500€
Clinical research associated	25€/h	300h	7500€
Meetings and Formation	100€	1	100€
Insurance	100€	92	9200€
MATERIAL AND FOLLOW-UP			
Informed consent printing	0.50€	92	46€
Abdomen CT	204€	276	56304€
Thoracic CT	95€	276	26220€
Blood Analyses	40€	276	11040€
PUBLICATION AND DISSEMINATION			
Publication expenses	3000€	1	3000€
Inscription to national congress	500€	1	500€
Inscription to international congress	1000€	1	1000€
Travel accommodation and food	1500€	2	3000€
TOTAL		**122 410€**	

Table 5. Budget

14. IMPACT

The main objective of the study is to increase the knowledge of both surgical techniques, specially the SMAfa, to observe improvements and be able to respond to the problems and complications that we have nowadays. The most important, considering an oncological disease such as PC, in to identify the technique with more oncological benefits about the free-disease survival together with the margins of the AP specimen. If possible we would like to establish a relation between the principal objective and the second ones getting to know the connection between the techniques used: which one achieve a better survival and oncological margins more ample.

In the last years the mortality rate caused by PC has not improved much, condemning the patients to a few months of life. By improving the surgical techniques used we can achieve an approach that enlarges the free-disease survival by a more wide margins.

If the results obtained are relevant and validate the hypothesis, for our population of study, we will be confident to implement the SMAfa as a main approach to perform the future surgeries to enlarge the time without recurrences in our patients. Furthermore the SMAfa allows to resect all the connective tissue between the PV and the SMA, improving the oncological results and allows to see the main mesenteric vessels, specially the arteries, which in a future could be repaired changing the unresectable criteria. This could be possible thanks to the SMAfa. This procedure, together with the oncological improvements of the technique, would have a huge impact in the treatment of the PC allowing the surgery to patients that nowadays are excluded from it.

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16. ANNEXES

16.1 ANNEX 1

FULL D'INFORMACIÓ AL PACIENT SOBRE L'ESTUDI

TÍTOL DE L'ESTUDI: *CLASSIC VS SUPERIOR MESENTERIC ARTERY FIRST APPROACH IN CEPHALIC DUODENOPANCREATECTOMY FOR PANCREÀTIC CANCER.*

"DUODENOPANCREATECTOMIA CEFÀLICA EN TUMORS DE CAP PANCREÀTIC: ABORDATGE CLÀSSIC VS ABORDATGE INICIAL DE L'ARTÈRIA MESENTÈRICA SUPERIOR."

PROPÒSIT I OBJECTIU DE L'ESTUDI

El seu metge el convida a participar a l'estudi clínic coordinat per l'Hospital Universitari Josep Trueta, ja que compleix els requisits per a participar-hi. Aquest estudi consisteix en la comparació de dues tècniques quirúrgiques en l'extirpació del tumor de cap de pàncrees.

Aquesta intervenció, anomenada duodenopancreatectomia cefàlica, consisteix en la resecció en bloc del cap del pàncrees juntament amb altres estructures properes: l'intestí que l'envolta, anomenat duodè; la via biliar i la bufeta biliar i en ocasions una part de l'estómac. Existeixen variacions de la tècnica quirúrgica amb la intenció d'aconseguir ampliar els marges de resecció i aconseguir una supervivència major. Aquest estudi vol compara dues tècniques: la tècnica clàssica i l'abordatge inicial de l'artèria mesentèrica superior. La diferència entre les tècniques consisteix en la manera com s'aborda la zona anatòmica, començant per l'artèria mesentèrica superior i tenint una millor visió dels vasos en la segona tècnica. En estudies realitzats fins al moment s'observa una lleu millora de la supervivència i menys complicacions però sense diferències significants.

Amb aquest estudi es pretén conèixer si la hipòtesi és vàlida i amb l'abordatge inicial de l'artèria mesentèrica superior hi ha una millora de la supervivència lliure de malaltia i menys complicacions. L'única manera de confirmar-ho es fer dos grups de pacients de característiques semblants i realitzar una tècnica a cada grup. A tots els participants se'ls tractarà igual, amb un estudi preoperatori i un seguiment igual amb l'única diferència de utilitzar l'abordatge clàssic o l'abordatge inicial de l'artèria mesentèrica superior.

PROCEDIMENTS DE L'ESTUDI

Es realitzarà un estudi preoperatori estàndard per determinar que es pot realitzar la intervenció.

En el moment de la cirurgia es decidirà de forma aleatòria, amb un 50% de possibilitats de rebre cada tècnica, a quin grup formarà part. Al acabar la cirurgia la peça extirpada s'enviarà a anatomia patològica per un estudi dels marges de la lesió.

Durant l'hospitalització rebrà les cures oportunes i es farà un seguiment exhaustiu per avaluar l'aparició de complicacions.

Després de l'alta hospitalària es farà un seguiment on tindrà visita cada tres mesos i s'haurà de realitzar una tomografia computeritzada (TC) i una analítica per estudiar l'aparició de nou de la malaltia.

INCONVENIENTS I BENEFICIS

Si es confirma la hipòtesi de treball, els pacients a qui se'ls realitzi l'abordatge inicial de l'artèria mesentèrica superior podrien tenir major supervivència lliure de malaltia amb millor resposta oncològica i menys complicacions derivades. En estudis realitzats fins al moment no s'han observat més inconvenients ens aquest grup respecte a l'abordatge clàssic.

PARTICIPACIÓ

La seva participació a l'estudi és totalment voluntària. Si decideix no participar la seva atenció mèdica no es veurà influenciada en cap nivell.

Si desitja abandonar l'estudi, en qualsevol moment, és lliure de fer-ho sense donar explicacions i sense que això afecti al seu tractament normal o a la qualitat de les cures que rebrà.

El seu metge també podrà retirar-lo de l'estudi en qualsevol moment. Aquesta situació es podria donar si vostè experimenta un efecte secundari o complicació greu i imprevist, si experimenta canvis en la seva situació clínica o si no compleix amb el pla establert per a l'estudi.

Se'l mantindrà infomat de qualsevol nova informació disponible o que pugui afectar a la seva decisió.

Aquest estudi ha estat analitzat i aprovat per el Comitè Ètic d'Investigació de l'Hospital Universitari Doctor Josep Trueta de Girona, que ha dictaminat que és ètic i que amb els resultats publicats fins al moment en cap moment se'l pot perjudicar, ni a vostè ni a la seva salut.

16.2 ANNEX 2

FORMULARI DE CONSENTIMENT INFORMAT DE PARTICIPACIÓ A L'ESTUDI DEL PACIENT

CONSENTIMENT ESCRIT

TÍTOL DE L'ESTUDI: *CLASSIC VS SUPERIOR MESENTERIC ARTERY FIRST APPROACH IN CEPHALIC DUODENOPANCREATECTOMY FOR PANCREATIC CANCER.*

"DUODENOPANCREATECTOMIA CEFÀLICA EN TUMORS DE CAP PANCREÀTIC: ABORDATGE CLÀSSIC VS ABORDATGE INICIAL DE L'ARTÈRIA MESENTÈRICA SUPERIOR."

Jo, _____, amb DNI _____:

He parlat amb el Dr/Dra _____

He llegit el full d'informació que se m'ha entregat

He pogut fer preguntes sobre l'estudi i s'han respòs de manera satisfactòria

He rebut suficient informació sobre l'estudi

Comprenc que la meva participació és voluntària

Comprenc que puc retirar-me de l'estudi:

- En qualsevol moment
- Sense donar explicacions
- Sense repercussions en la meva assistència mèdica.

En conseqüència dono lliurement el meu consentiment per entrar en aquest estudi

Signatura Participant

Signatura Investigador/metge

Data: _ _ / _ _ / _ _ _ _

Data: _ _ / _ _ / _ _ _ _

16.3 ANNEX 3

DOCUMENT DE CONSENTIMENT INFORMAT PER LA RESECCIÓ PANCREÀTICA

Jo, _____ amb el diagnòstic de TUMOR DEL CAP DEL PÀNCREES

DECLARO:

Que el Dr/Dra _____ m'ha explicat que es convenient procedir a una duodenopancreatectomia cefàlica.

1. Amb aquest procediment es pretén extirpar la part que conté el tumor del pàncrees, evitant les complicacions derivades d'aquest (com hemorràgia, infecció biliar o hepàtica, entre d'altres) que en cas de produir-se poden implicar una intervenció urgent.
2. El doctor o doctora m'ha advertit que el procediment requereix l'administració d'anestèsia general i que és possible que durant o després de la intervenció es necessiti l'ús de sang i/o hemoderivats, amb els riscos de transmissió d'infeccions o altres complicacions que això pot comportar.
3. Mitjançant aquesta tècnica s'extirparà el duodè, la vesícula biliar, el conducte biliar extrahepàtic. Entenc que en algunes ocasions, segons la localització del tumor es poden extirpar òrgans veïns afectats. El conducte biliar principal es reconstrueix amb un segment de l'intestí. El pàncrees restant es reconstrueix amb unió amb el jejú o l'estómac. També hi ha la possibilitat que durant la cirurgia es realitzin modificacions del procediment degut a troballes intraoperatòries per proporcionar el tractament més adequat.
4. Comprenc que, tot i la adequada elecció de la tècnica i la seva correcta realització, es poden presentar efectes indesitjats: tant els comuns derivats de tota intervenció quirúrgica i que poden afectar a tots els òrgans i sistemes, com els específics d'aquest procediment. Aquest poden ser poc greus i freqüents, com: Infecció o hemorràgia de la ferida quirúrgica, flebitis, trastorns temporals de les digestions, vessament pleural, dolor prolongat a la zona de la intervenció; o poc freqüents i greus, com: hemorràgia, insuficiència hepàtica, infecció intraabdominal, obstrucció intestinal, fístules biliars o pancreàtiques, colangitis i/o inflamació del pàncrees.

   El metge o metgessa m'ha explicat que les complicacions habitualment es ressolen amb tractament mèdic però que poden precisar una reintervenció, generalment d'urgència, incloent un risc de mortalitat.
5. També se m'ha indicat la necessitat d'informar de les meves al·lèrgies medicamentoses, alteracions de la coagulació, malalties cardiopulmonars, existència de pròtesis, marcapassos, medicació actual o qualsevol altre circumstància mèdica.
6. La realització del procediment pot ser filmat amb fins científics o didàctics respectant la confidencialitat d'acord amb la normativa vigent.
7. El metge o metgessa m'ha explicat que en el meu cas no existeix cap alternativa eficaç de tractament.

Comprenc les explicacions que se m'han facilitat en llenguatge clar i senzill i se m'ha permès realitzar totes les preguntes i observacions. Tots els dubtes han sigut solucionats.
També comprenc que, en qualsevol moment i sense necessitat de cap explicació, puc revocar el consentiment que ara dono.
Manifesto que estic satisfet amb la informació rebuda, que comprenc la intervenció i els riscos que comporta i en tals condicions:

DONO EL CONSENTIMENT a que se'm realitzi la intervenció a l'Hospital Universitari Doctor Josep Trueta de Girona.

Signatura Metge

Signatura Pacient

DNI:

16.4 ANNEX 4

FULL DE RECOLLIDA DE DADES

DADES GENERALS

Metge Responsable: _____

Núm Sobre d'aleatorització: ☐

Gènere: Home ☐ **Data de naixement**: _ _ / _ _ / _ _ _ _

Dona ☐

ANTECEDENTS PERSONALS

Hàbits tòxics: Enolisme ☐

Tabac ☐

Altres _____

IMC (kg/m^2): _____ **Pes:** _____ Kg

Diabetis Mellitus: Sí ☐

No ☐

Nivells CA 19.9: _____ U/ml

CEA: _____ ng/ml

Antecedents mèdics d'interès: _____

ANATOMIA PATOLÒGICA

Mida: _____ cm

Tumor primari: pT1 ☐

pT2 ☐

pT3 ☐

pT4 ☐

Nòduls limfàctics regionals: pN0 ☐

pN1 ☐

pN2 ☐

Afectació Marges: R0 ☐

R1 ☐

R2 ☐

Diferenciació: Diferenciat ☐

Moderat ☐

Indiferenciat ☐

DADES QUIRÚRGIQUES

Valoració anestèsica: ASA I ☐

ASA II ☐

ASA III ☐

Data de la cirurgia: _ _ / _ _ / _ _ _ _

Duració de la intervenció: _____ min

Pèrdues sanguínies: _____ ml

Transfusió intraoperatòria: Sí ☐ Concentrats: _____

No ☐

Diàmetre Wirsung: _____ mm

Consistència pàncrees: Tou ☐

Dur ☐

Preservació pilòrica: Sí ☐

No ☐

Resecció vascular: Sí ☐ Arterial ☐

Venosa ☐

No ☐

Observacions de la cirurgia o de la tècnica

EVOLUCIÓ POSTOPERATÒRIA

Ingrés UCI: Sí ☐ Dies: _____

No ☐

Transfusió postoperatòria: Sí ☐ Concentrats: _____

No ☐

Reintervenció: Sí ☐ Causa: _____

No ☐

Dia d'ingesta sòlida: _____

Dia de retirada del drenatge: _____

Dies ingrés: _____

Reingrés: Sí ☐ Causa:_____

No ☐

MORTALITAT (durant ingrés o primers 90 dies)

Sí ☐ Dies postoperatori: _____

Causa: _____

No ☐

16.5 ANNEX 5

FULL DE SEGUIMENT CADA 3 MESOS

ESTAT PACIENT

Bon Estat General ☐

Mal Estat General ☐

Èxitus ☐ Causa:_____

IMATGE (TC TORÀCIC I TC ABDOMINAL)

Recidiva Local: Sí ☐ Dies des de la cirurgia: _____

No ☐

Metàstasi a distància: Sí ☐ Dies des de la cirurgia: _____

No ☐

ANALÍTICA

CA 19.9: _____ U/ml

CEA: _____ ng/ml

16.6 ANNEX 6

FULL DE COMPLICACIONS

COMPLICACIONS DURANT HOSPITALITZACIÓ

Fístula Pancreàtica: Sí ☐ Volum drenatge:_____

Amilases drenatge:_____

Dies: _____

No ☐

Hemorràgia: Sí ☐ Causa:_____

No ☐

Retràs en el buidament gàstric: Sí ☐

No ☐

Infecció: Sí ☐
- Ferida ☐
- Abscés abdominal ☐
- Altres ☐

No ☐

Diabetis Mellitus de novo: Sí ☐

No ☐

Altres: _____

Clavien Classification: _____

COMPLICACIONS ALS 3 MESOS

Fístula Pancreàtica: Sí Volum drenatge:_____

Amilases drenatge:_____

Dies: _____

No ☐

Hemorràgia: Sí ☐ Causa:_____

No ☐

Retràs en el buidament gàstric: Sí ☐

No ☐

Infecció: Sí ☐
- Ferida ☐
- Abscés abdominal ☐
- Altres ☐

No ☐

Diabetis Mellitus de novo: Sí ☐

No ☐

Altres: _____

Clavien Classification: _____

REINGRÉS PER COMPLICACIONS

Sí ☐ Causa:_____

No ☐

Clavien Classification: _____

16.7 ANNEX 7

CLAVIEN-DINDO SCALE FOR COMPLICATION

Grade	Definition
I	Any deviation from the normal postoperative course without pharmacologic treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacologic treatment with drugs other than ones allowed for grade I complications. Blood transfusion and total parenteral nutrition* are also included.
III	Requiring surgical, endoscopic, or radiologic intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)† requiring IC/ICU management
IVa	Single-organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of the discharge, the suffix "d" (for disability) is added to the respective grade of complication (including resection of the pancreatic remnant). This label indicates the need for a follow-up to fully evaluate the complication.

*Note regarding DGE: The insertion of a central line for TPN or nasojejunal tube by endoscopy is a grade IIIa. However, if a central line is still in place or a feeding tube has been inserted at the time of surgery, then a TPN or enteral nutrition is a grade II complication.

†Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

CNS indicates central nervous system; IC, intermediate care; ICU, intensive care unit.

Table 6 Classification of surgical complications (26)

PREOPERATIVE STATUS ASSESMENT

(Grade)	ASA classification	(Grade)	Revised classification
1	class 1	1a	Normal healthy patient.
		1b	Patient with mild systemic disease. Normal health patient, with operative or anesthetic risk(s).
2	class 2	2a	Patient with moderate systemic disease. Patient with mild systemic disease, with operative or anesthetic risk(s).
		2b	Patient with moderate to severe systemic disease that does not limit activity. Patient with mild systemic disease, with operative and anesthetic risks. Patient with moderate systemic disease, with operative or anesthetic risk(s).
3	class 3	3	Patient with severe systemic disease that limits activity, but is not incapacitating. Patient with moderate systemic disease that does not limit activity, with operative and anesthetic risk(s). Patient with moderate to severe systemic disease that does not limit activity, with operative or anesthetic risks.
4	class 4	4	Patient with an incapacitating systemic disease that is a constant threat to life. Patient with severe systemic disease that limits activity, incapacitated.
5	class 5	5	Moribund patient no expected to survive 24 hours with or without operation.
In the event of emergency operation, precede the number with an E.			

Table 7 ASA Classification (33)