Universitat de Girona
Facultat de Medicina

EFFECT OF ENDOSCOPIC ULTRASOUND-GUIDED RADIOFREQUENCY ABLATION, ON OVERALL SURVIVAL, IN PATIENTS WITH LOCALLY ADVANCED PANCREATIC ADENOCARCINOMA: A multicenter randomized controlled clinical trial

Gastroenterology Department

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1. ABBREVIATIONS

5-FU: 5-fluorouracil

AEMPS: Agencia Española de Medicamentos y Productos Sanitario

CA 19.9: Carbohydrate antigen 19.9

CA: Coeliac axis

CEIC: Comité Ético de Investigación Clínica

CHA: Common hepatic artery

CT: Computed tomography

ECOG: Eastern Cooperative Group

EUS-RFA: Endoscopic ultrasound-guided radiofrequency ablation

FNA: Fine needle aspiration

FNI: Fine needle injection

GLM: General linear model

HDJT: Hospital Dr. Josep Trueta

ICV: Inferior cava vein

LOS: Length of stay

MRCP: Magnetic Resonance Cholangiopancreatography

MRI: Magnetic Resonance Imaging

NPV: Negative Predictive Value

PFS: Progression-free survival

PS: Performance status

PV: Portal Vein

QT: Chemotherapy

RFA: Radiofrequency ablation

RT: Radiotherapy

SMA: Superior Mesenteric Artery

SMV: Superior Mesenteric Vein

VAS: Visual Analogue Scale

2. ABSTRACT

Background: Pancreatic cancer is the fourth leading cause of cancer related death in the Western world. At time of diagnosis, 20% of patients present with a resectable tumour, 40% with an irresectable locally advanced tumor (without metastases) and 40% with metastatic disease. The median survival of patients with irresectable locally advanced pancreatic cancer is only 6 months. Currently, there is no effective treatment for these patients

Importance: There is an urgent need for new therapeutical options in pancreatic adenocarcinoma. Radiofrequency ablation (RFA) is a technique that has been demonstrated to be effective in the treatment of several irresectable tumours such as liver and lung neoplasms. RFA produces local tumour destruction from an electrode implanted directly into the tumour causing frictional heating.

Objective: To evaluate whether endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) plus conventional treatment (chemotherapy ± radiotherapy) improves overall survival in patients with non-resectable locally advanced pancreatic adenocarcinoma in comparison to protocolised treatment. The overall survival will be analysed 2 and 5 years after finishing the treatment. It will be also determined the safety of the procedure. So, complications after the intervention will be registered. Moreover, a pain score, length of hospital stay, type of chemotherapy received, radiotherapy, and progression free survival will be determined.

Design: A multicenter open-labelled randomized interventional clinical trial will be carried out. Patients with pancreatic cancer, confirmed anatomopathologically, will be introduced into the study performed in universitary centers such as: Dr. Josep Trueta Hospital, Vall d'Hebron Hospital, Bellvitge Hospital and Hospital Clinic of Barcelona.

Methods: A total of 274 patients are needed to complete the study. Group A (137 patients), will be treated with chemotherapy ± radiotherapy (QT±RT). Group B (137) EUS-RFA will be performed before starting the protocolised treatment (QT±RT). For this procedure, it will be necessary the Habib ™ catheter, a monopolar radiofrequency system, connected to a generator. Also, a linear ecoendoscope will be used to guide the intervention and visualize the surrounding anatomy.

Participants: Patients with non-metastatic locally advanced pancreatic cancer confirmed by citology or biopsy without previous treatment and performance status between 0-2.

3. INTRODUCTION

3.1. PANCREATIC CANCER

3.1.1. Incidence and epidemiology

Pancreatic cancer is the 4th most lethal cancer in humans causing 227 000 deaths per year worldwide (1). In Europe, pancreatic cancer is the 8th most prevalent (2). Taking into account that it only involves 3% of all new diagnosed cancers, it entails a bad prognosis.

In Spain, during 2014 there were 6 588 new cases registered in men and 3 405 in woman (3). During 2016, Cataluña has registered a total of 1168 new cases (606 for men and 562 for women) (4).

The 5-year survival rate of pancreas cancer in Europe is 6% (5). In Spain, the overall survival rate estimated between 2000-2007 was 5.2% for men and 7.0% for women (2).

It is important to emphasize that it prognosis has not improved over the last 20 years (1). According to the predicted number of deaths in 2013, compared to the real deaths of 2009, mortality caused by pancreatic cancer has increased by 19% (6). Since 1994, in Cataluña, the incidence of pancreatic cancer has increased 1.8% per year, with also an increase of mortality rate (0.9% - 1.8% per year, for men and women, respectively) (4).

Over 95% of pancreatic cancer growth within the exocrine portion, at least 80% of it is a ductal adenocarcinoma. Other type of exocrine pancreatic cancer arises from acinar cell or connective tissue.

The median age of diagnosis is 71 years for men and 75 years for women. Less than 3% are diagnosed before the age of 44 but more than half of pancreatic cancer cases are found between 65 and 84 years old (7).

Most of ductal adenocarcinoma progress to metastatic stage or locally advanced pancreatic cancer (1). The main reasons are due to long asymptomatic phase; delayed diagnosis; and also as a consequence of the early vascular, lymphatic and perineural dissemination.
Approximately, 40% have metastatic disease at the time of diagnosis.

Another fact that contributes to high mortality rates is that surgical resection is the unique curative option but, unfortunately, it can only be applied in 15-20% of patients, achieving 20% of 5-year survival rate after excision (1).

For all these reasons, it is essential to diagnose pancreatic cancer in early stages and to investigate new alternative therapeutic options.

3.1.2. Risk factors

Most pancreatic cancers are due to sporadically mutations, and only a few are caused by germline mutations. The core genes and pathways involved in ductal adenocarcinomas are KRAS, 16/CDKN2A, TP 53 and SMAD4 (8).

Familial pancreatic cancer, defined as at least two-first degree relatives with pancreatic cancer, accounts for only 5-10% of all cases (6) and BRCA may be the most common disorder in this context.

Cigarette smoking is the most well studied risk factor in pancreatic cancer (with overall relative risk of 1.74) (9) and it is the suspected preventable etiological cause of 20–30% of cases. Tobacco exposure and environmental tobacco smoke are also related to this neoplasm.

Obesity, is the second most modifiable risk factor. Also type 1 and 2 diabetes mellitus are associated with pancreatic cancer but the causal relationship between diabetes and tumor induction is not known (7).

Chronic pancreatitis and alcohol are both related to an increased risk. The excess consumption of alcohol is the most common cause of chronic pancreatitis so, sometimes the factor in pancreatic cancer is not clear.

3.1.3. Signs and symptoms

Early pancreatic cancer usually does not cause any symptomatology (10) or it may not be very specific. When symptomatic, pancreatic cancer has already spread outside the pancreas or has generated metastases.

60%-70% of pancreatic cancers are situated in the head of the pancreas, and the rest in the body or in the tail.

Early symptoms may occur because of a mass effect, especially if the tumor is in the head of the pancreas. Those which are diffusely involved in the pancreas, are normally diagnosed at a more advanced stage (1).

Jaundice, is one of the first symptoms, present in over 50% of patients. It is caused by the obstruction of the common bile duct and/or pancreatic duct. Jaundice, can be accompanied with choluria, acholia and pruritus.

Abdominal pain can be present in 80%-85% of patients with locally advanced pancreatic cancer, primarily due to invasion of the celiac or superior mesenteric arterial plexus. It is described as a dull epigastric pain that can irradiate to the back.

Patients with concomitant obstruction of the pancreatic duct may also show pancreatic exocrine insufficiency in the form of **steatorrhea** and **malabsorption**.

Diabetes and **pancreatitis** of varying severity can occur in pancreatic cancer. New-onset diabetes mellitus may herald pancreatic cancer in one quarter of patients, particularly in patients over 50.

If the tumor infiltrates the duodenum, it can produce an **upper gastroduodenal obstruction**.

3.1.4. Anathomopathology and molecular biology

According to the cellular differentiation, pancreatic cancers can arise from ductal cells in 90% (pancreatic adenocarcinoma), acinar cells or neuroendocrine cells.

Microscopically, these neoplasms can be classified as well-differentiated or poorly differentiated, with a mitotic rate greater than 10 high power fields.

Macroscopically the typical form of pancreatic adenocarcinoma is a solid lesion.

Different genetic mutations are found. On one hand, the activation of the oncogene KRAS; on the other hand the inactivation of tumour suppressor genes, like TP53, and finally the inactivation of those genes which control the repair of DNA damage (1).

3.1.5. Diagnosis

The improvement of the early diagnosis of pancreatic cancer means that these tumors should be detected when they are small and located within the pancreas, with no vascular invasion of other structures. Unfortunately, most pancreatic cancers are greater than 3 centimetres in diameter at the time of diagnosis, that is when it normally becomes symptomatic (11).

What should be done with a suspected pancreatic cancer?

- **A general blood analysis**: it can be found a cholestatic pattern and mild anemia. It is recommended to perform a basis biochemistry and coagulation (12).
- **Tumoral markers**: carbohydrate antigen 19-9 (CA 19.9)

  Although many biochemical markers have been examined in pancreatic cancer, none are definitive for pre-operative diagnosis (13).

  An increase in CA 19.9 serum levels is seen in a high percentage of patients with advanced disease, but it also can be elevated in obstructive jaundice, not originated by a tumoral cause (false-positive).

  CA 19.9 are not enough reliable as a population screening tool (12), but levels of if this tumoral marker higher than 500UI/ml, indicates a worse prognosis after surgery (1). The greatest utility of CA 19.9 is patient's follow-up once they are diagnosed, and the evaluation of the treatment response (12).

- **Anatomopathological diagnosis:**

  There is a consensus statement about the mandatory sampling of pancreatic tissue before starting the treatment according to the stage of the tumor.

  - The presence of pancreatic tissue, in the context of a pancreatic neoplasm, is essential and obligatory in any patient who is being considered for neoadjuvant therapy, or if the patient is not a surgical candidate (14).
  - If the patient is a good surgical candidate and the imaging is typical for resectable pancreatic adenocarcinoma, the excision of the tumor can be performed without a tissue diagnosis, thought is controversial for some cases. (14)

The sample, can be obtained percutaneously, guided by echography, CT, or by endoscopic ultrasound. EUS-guided fine needle aspiration (FNA) is currently the elective method used in making the cytological diagnosis of pancreatic adenocarcinoma. It is the most cost-effective approach to tissue acquisition in suspected pancreatic cancer (13) with very low false-positive rate and accuracy > 90%.

Two recently published meta-analyses totaling more than 8400 patients and 67 studies reported a pooled sensitivity for the diagnosis of malignancy based on cytology of 85% and 89% and a pooled specificity of 98% and 99%, respectively (15,16). Despite excellent sensitivity, the negative predictive value (NPV) of EUS FNA for pancreatic tumors remains somewhat

limited at 55%. Therefore, a negative or non-diagnostic biopsy does not completely exclude the possibility of malignancy.

A recent systematic review by Wang and colleagues included 8246 patients with pancreatic lesions, 7337 of those being solid masses, and reported complications occurring in 60 patients (0.82%). The overall rate of pain, bleeding, fever, and infection were 0.38%, 0.10%, 0.08%, and 0.02%, respectively (17).

Peritoneal seeding of tumor cells following EUS FNA has been reported in up to 2.2% of patients but appears to be less than CT-guided FNA (16.3%) (18).

The main limitation is that EUS is highly operator dependent and demands significant experience before reaching user proficiency. The presence of chronic pancreatitis may also hinder cytologic interpretation of pancreatic biopsy, thus decreasing sensitivity of EUS FNA of pancreatic masses (19,20)

EUS-guided FNA also permits the sampling of local lymph nodes and incidental accessible hepatic metastases.

- **Current imaging modalities**: the imaging work-up is done to diagnose pancreatic neoplasm, to give information about the tumor size precise burden, and also, arterial and venous local involvement. All this information allows the physician to sort out the pancreatic cancer by the TNM classification, and to identify candidates for surgery.

    - **Abdominal ultrasound**: is the first prove done once there is a suspected pancreatic cancer. It is the most accessible imaging technique, especially for its safety, but unfortunately is not the best for diagnosing a pancreatic cancer; so then, more imaging proves must be done(12). It is also useful when sampling metastatic hepatic lesions.
      The use of Doppler adds information about the involvement of vascular structures.

    - **Multidetector computed tomography:** with three dimensional reconstruction is the best method to diagnose and stage pancreatic cancer, and select patients who could benefit for surgical treatment (14). CT has been shown to have a high predictive value of unresectability (90% to 100%) with a lower predictive value of resectability (76% to 90%) (13).
      Overall sensitivity of CT for pancreatic cancer is 86% to 97%, but sensitivity for lesions less than 2 cm is probably near 77% (21).
      The pancreatic CT protocol consists of dual-phase scanning (arterial and portal) using intravenous and oral contrast agents.

In most cases, pancreatic cancer appears in the arterial phase, 30 seconds after the start of the injection. An hypoattenuating homogeneous mass with indistinct margins can be appreciate (1); in this phase, it can be seen an opacification of the celiac axis, superior mesenteric artery (SMA) and peripancreatic arteries. The normal pancreas enhances better than tumoral tissue, for that reason pancreatic adenocarcinoma has lower density compared with the normal pancreatic tissue that surrounds the neoplasm.

It can be completed with a third phase called equilibrium phase, useful to see possible hepatic lesions (12).

- *What it must be evaluated?*

1. The size of the tumor (longitudinal diameter).
2. Where the lesion is located
3. Infiltration of surrounding organs
4. Vascular involvement. It determines the resectability of the tumor.
5. Tumor extension, it is important to evaluate the interruption (with or without dilatation) of the biliary duct, because most pancreatic cancers will result in obstruction of it. Sometimes, if the tumor is in the pancreas head, the obstruction can be found either in the pancreatic duct, in the common duct or both.
6. Extra-pancreatic extension must be studied: enlarged lymph nodes, hepatic, or peritoneal nodules, which are the main metastatic sites.

- **Magnetic resonance imaging:** is useful to detect pancreatic cancer and metastatic disease, especially hepatic lesions that cannot be seen by CT. MRI has showed equal benefit to CT scanning in vascular assessment (1). Unlike CT, MRI does not involve radiation and uses an iodine-free contrast agent that cannot be used in the setting of renal insufficiency but has rare renal toxicity.

- **Endoscopic retrograde cholangiopancreatography (ERCP):** may be considered as a therapeutic technique when obstructive jaundice, in patients who are waiting for surgery or as a palliative treatment. Tissue sampling can also be obtained during ERCP with endoscopic forceps or via brush biopsy for routine cytology but the sensitivity is low (20%).

- **Magnetic resonance cholangiopancreatography (MRCP):** can also be obtained at the time of MRI. Images obtained are highly comparable with those obtained with ERCP and can demonstrate pancreatic ductal obstruction, ectasia, and calculi. In contrast to ERCP, MRCP is non-invasive and does not require injection of contrast into the pancreaticobiliary tree, avoiding potential complications.

- **Endoscopic ultrasound** is particularly useful for identifying small tumors that have been undetected by other imaging modalities. For tumors ≤ 20 mm in diameter EUS was found to have a sensitivity of 90 % compared to 40% to 67% fot CT and 33% for MRI.

  EUS is also used to give additional information about lymph nodes and vascular involvement mainly being used to give additional information about the tumor, especially about lymph nodes and vascular involvement (22), and it has also an important role in detecting tumors smaller than 2 centimetres (12).

  The confirmation of pancreatic adenocarcinoma must be done before starting neoadjuvant chemotherapy treatment, in locally advanced pancreatic cancer or in metastasis stage (12).

- **Staging laparoscopy:** The role of laparoscopy in the staging of pancreatic cancer patients remains controversial. Potential predictors of unresectability to select patients for SL include CA 19.9 levels > 150 UI/ml and tumour size > 3 cm (23).

3.1.6. Staging

Pancreatic adenocarcinoma can be classified by the TNM: ***(see Table 1)***, and by anatomical staging ***(see annex 1).***

STAGE	DEFINITION
Primary Tumor	
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to pancreas, ≤ 2cm
T2	Tumor limited to pancreas, > 2 cm
T3	Extension into peripancreatic tissues
T4	Tumor involves celiac axis or superior mesenteric artery
REGIONAL LYMPH NODES (N)	
Nx	Regional lymph nodes not assessed
N0	No metastatic regional lymph nodes
N1	Metastatic regional lymph nodes
DISTANT METASTASIS (M)	
M0	No distant metastasic disease
M1	Distant metastatic disease

Table 1. AJJC, American Joint Committee on Cancer

We refer to regional lymph nodes those which are peripancreatic nodes ***(see Annex 2)***

The consensus report of the American Hepato-Pancreato-Biliary-Association, classifies pancreatic ductal adenocarcinoma (when metastases are absent) as*:* ***(see Table 2)***

- Resectable
- Borderline resectable
- Unresectable: locally advanced pancreatic cancer and metastatic disease

Only 15%-20% of patients have resectable pancreatic ductal adenocarcinoma at the time of diagnosis.

Resectability status	Arterial	Venous
Resectable	No arterial tumor contact - Coeliac axis (CA) - Superior mesenteric artery (SMA) or - Common hepatic artery (CHA)	No tumor contact with: - Superior mesenteric vein (SMV), or - Portal vein (PV) or - ≤ 180º contact without vein contour irregularity
Borderline resectable	Pancreatic head/uncinate process - Solid tumour with CHA without extension to coeliac axis or heaptic artery bifurcation allowing for safe and complete resection and reconstruction - Solid tumor contact with SMA ≤ 180º - Presence of variant arterial anatomy and the presence and degree of tumour contact should be noted if present as it may affect surgical planning Pancreatic body/tail • Solid tumor contact with de CA of ≤ 180º • Solid tumor contact with the CA of > 180 without involvement of the aorta a with intact and uninvolved gastroduodenal artery	• Solid tumor contact with the SMV or PV of >180º, • Contact of ≤ 180º with contour irregularity of the vein or thrombosis of the vein but with suitable vessels proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction • Solid tumor contact with the inferior vena cava (IVC)
Unresectable	• Distant metastases Pancreatic head/uncinate process • Solid tumor contact with SMA >180º • Solid tumor contact with the CA >180º • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact with the SMA and CA • Solid tumor contact with the CA and aorta	Pancreatic head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion

***Table 2**. Definition of resectability according to NCCN guidelines.*

So, in artery vessels it exists: ***(see figure 1):***

- Vessel tumour contact ≤ 180 º without deformation
- More than 180º without deformation
- With deformation

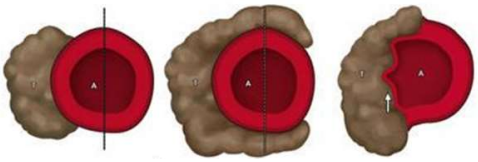


Figure 1*. Artery vessels involvement* (12)

For venous vessels, it is added a tear drop deformation at the tumour contact (1). ***(see Figure 2)***

Is in this moment when de multimodal CT and the MRI are important just to determine the potential resection of the tumour, once a suspected or confirmed pancreatic cancer is diagnosed.

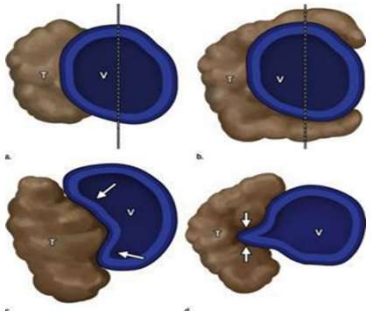


Figure 2*. Venous vessel involvement*

3.1.7. Treatment

Before starting treatment, the patient should have been staged according to the findings in imaging proves, and also general and nutritional status would have been taken into account.

3.1.7.1. TREATMENT OF LOCALIZED PANCREATIC CANCER

Patients with a resectable tumor will benefit from surgical treatment, which is the only curative treatment. The size and the localization of the tumor will determine the type of surgery:

- Head tumor or periampullary location: cephalic pancreatoduodenectomy (Whipple procedure). Although performing this surgery, the 5-year rate after it is 20 % to 25% with a median survival of 15-19 months.
- Body and tail tumor localisation: distal pancreatectomy +/- splenectomy.

The main objective of this treatment is to achieve negative resection margins (R0) to improve the prognosis of this disease.

According to the adjuvant treatment performed in the HDJT in resectable pancreatic cancers, two situations are described:

- N0 tumors and R0 surgeries: chemotherapy with Gemcitabine 1000 mg/m^2 for 6 months.
- R1 surgery and/or N1 tumour: Gemcitabine before and after radiotherapy plus 5- fluorouracil (5-FU) in continuous perfusion.

3.1.7.2. TREATMENT OF BORDERLINE PANCREATIC CANCER

Patients with borderline resectable tumours do not have the same probability to achieve R0 resection, so surgery excision should not be considered a first line treatment. These patients must be evaluated in interdisciplinary tumor board in order to decide the best treatment for each case. **(See annex 3)**

- **Neoadjuvant treatment**: chemotherapy induction. The performance status of the patient orientates the type of chemotherapy that it can be used. It is described as:

- PS 0-1: Gemcitabine plus Oxaliplatine (GEMOX) or FOLFIRINOX for three months followed by a full-dose radiotherapy treatment plus 5-FU.
- PS 2 and comorbidities: Gemcitabine for three months

  After finishing the treatment, it must be evaluated the tumoral response. So, surgery can be raised if exists a response or a stable disease.

  Surgery technique will be the same as in resectable tumors, but also a resection of the portal vein with its reconstruction will be done. This type of surgery facilitates a complete R0 resection.

3.1.7.3. TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER

The treatment of this type of neoplasm is similar to those patients who have borderline resectable pancreatic cancer. **(See annex 4)**

Neoadjuvant treatment is also focused and divided in patients with PS 0-1 vs. PS 2.

On one hand, the first group can be treated with either GEMOX or FOLFIRINOX, on the other hand, patients with PS 2 are treated with Gemcitabine alone.

In both groups, chemotherapy treatment will last three months; a response evaluation with CT and tumoral markers must be done.

A clinical trial, performed by the Eastern Cooperative Oncology Group (24), randomized 74 patients with locally advanced pancreatic adenocarcnioma in two different treatment groups: Gembcitabine alone vs. Gemcitabine plus radiotherapy (50.4 Gy). They reported an increased survival

in patients with combined treatment (11.1 months vs. 9.2 months p 0.017), with similar toxicity. So, taking into account those results, the current situation in our hospitals of reference is the support of adjuvant chemoradiotherapy in patients with locally advanced pancreatic cancer. But nevertheless, the use of induction chemotherapy followed by chemoradiotherapy will be finally decided by the tumoral committee.

According to the results obtained from the imaging proves, two situations are described **(adjuvant treatment):**

- If there is a **stable disease** or a **tumoral response** (RECIST 1.0 criteria) is found, radiotherapy should be started with simultaneously 5FU continuous infusion.

  Four weeks after the RT is completed the tumoral response should be evaluated performing a CT and CA 19.9 levels.

  And so, taking into account that 20 % of patients who at the beginning of the disease they are not resectable candidates, after the treatment with chemotherapy and radiotherapy they become clearly resectable.

- If patient's **disease progresses**, first line chemotherapy treatment of metastatic disease can be done if PS is low. Also, Basic Supportive Care will be the first option if patient's status does not accept chemotherapeutical treatment.

3.1.7.4. METASTATIC OR RECURRENT DISEASE TREATMENT

First line treatment of metastatic disease is divided in three groups, according to the performance status and Karnofsky performance scale.

It has been reported that Gemcitabine reduces pancreatic pain and the need of analgesia, increasing survival. Later this chemotherapy drug was compared with FOLFIRINOX and other combinations, such as Gemcitabine plus Nab-Paclitaxel, resulting with better rates of response, quality of life and progression-free survival rate (12)

- Patients with PS 0-1: treatment with → **FOLFIRINOX** (Oxaliplatin, Leucovorin, Irinotecan, 5FU).
- Patients with PS 0-1 but with contraindications to be treated with FOLFIRINOX, PS 2 and Karnofsky Scale 70% → **Gemcitabine plus Nab-Paclitaxel**
- Patients with PS 2 and/or contraindications of other treatments → **monotherapy with Gemcitabine**

3.2. ENDOSCOPIC ULTRASOUND-GUIDED RADIOFREQUENCY ABLATION

EUS was introduced in the 1980s. First it was a diagnostic tool, later fine-needle aspiration became possible thanks to the introduction of curvilinear-array endoscope (25), and so, using fine needle aspiration accessories, interventional EUS has based many therapeutic approaches on FNI therapy (26).

Different ablative methods have been performed in locally advanced pancreatic cancer, but only few of it can be guided by endoscopic ultrasonography.

According to the type of the ablative technique, we can find:

- **Thermal methods**:

  -Radiofrequency ablation
  - Microwave ablation
  - Cryoablation

- **Laser based ablative therapy**
  -Photodynamic ablation
  - YAG laser

3.2.1. Radiofrequency ablation

Radiofrequency is the most well-studied ablation source, and also is one of the safest ablative techniques (25). RFA is widely used for the treatment of solid tumors, such as liver neoplasm, lung kidney and prostate tumors. Also, those located in the adrenal gland can be treated with RFA (27).

Radiofrequency ablation, causes tumoral tissue destruction through the use of electromagnetic energy that induces thermal injury (25,28). The result of it, is a coagulative necrosis of the area where the thermal energy has been applied. The tissue ablation ranges from 1 to 3 cm from the needle catheter (26).

There are two main systems:

The monopolar RFA is composed by:

- a radiofrequency generator ***(Figure 3)***
- an electrode needle, that delivers the energy to the tumor, heating it ***(Figure 4)***

- a dispersive electrode (ground pad), to disperse the energy and avoid thermal injury to the skin.

***Figure 3**. VIVA ComboTM Generator* (51)

- The bipolar RFA: a ground pad is not necessary in this case because the current oscillates between 2 interstitial electrodes (25). It combines radiofrequency ablation with cryotechnology. The advantage of this system is that it ablates producing less collateral thermal damage, but it has been seen that the ablation is less efficient than a monopolar system.

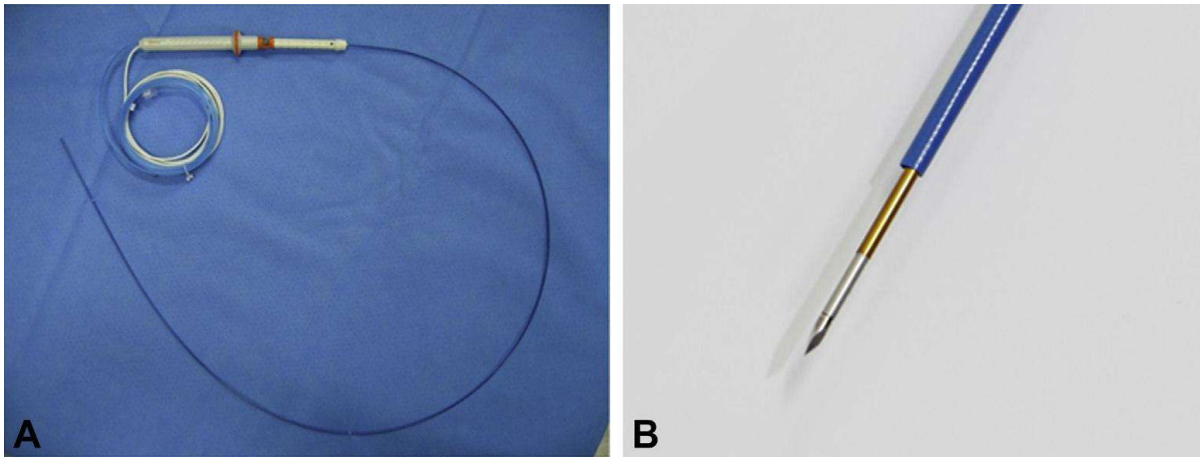


***Figure 4**. **A**, A radiofrequency ablation (RFA) electrode. An 18-gauge RFA electrode is composed of an electrode covered with protective tubing, a handle, and catheters for the cooling system**. B**, The exposed, distal end of the electrode. (19)*

Apart from the thermal destructive effect of the RFA, this ablative technique also generates amounts of cellular debris. This debris work like tumor antigens that can be targeted by the host's immune system and so, combined with proinflammatory molecules, an antitumor immunity mediated by tumor-specific T lymphocytes is generated (29).

Increasing evidence reflects that RFA stimulates anti-tumor immunity, thanks to the induction heat shock protein 70 (30).

3.2.1.1. TECHNICAL APROCHES

The main approach to perform RFA in many studies has been by open laparotomy (31). This access should be considered an additional aggressive and stressful situation to the patient because of the possible surgical complications.

Some laparoscopic pancreatic cancer access cases have also been described. One of the most practiced in our environment is the percutaneous approach. But, the most promising one is ecoendoscopically-guided via transgrastic or transduodenal access.

3.2.2. The beginnings of RFA

The first application of the RFA was in 1999 by Goldberg at al. (32). RFA was applied in normal porcine pancreas, and their main objective was to assess the safety and feasibility of the procedure in animals.

All the RFA were performed by EUS-guided *(figure 5)*; although, future RFA started to be performed intraoperatively or percutaneously.

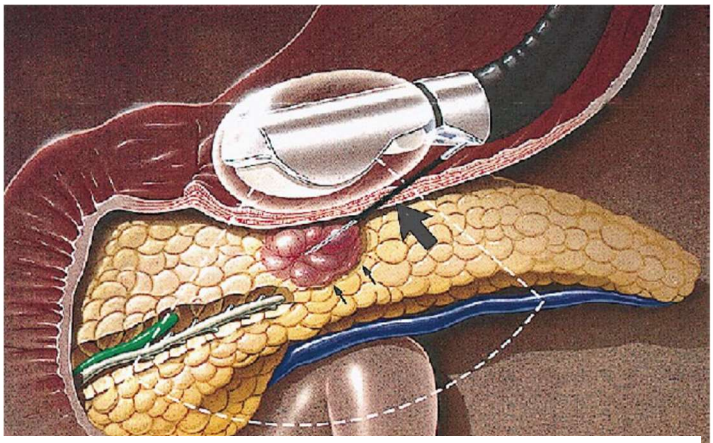


***Figure 5**. EUS-guided RFA (23)*

The main problems of early clinical applications of RFA in pancreatic tumors were related with unacceptably high rates of morbidity and mortality (28,33–36).

Wu et al (31) reported a total of 3 pancreatic fistula, all treated with abdominal drainage and healed in 7-10 days; and 3 massive gastrointestinal haemorrhage of the 16 treated patients. The tumor in these patients was located close to portal vein. All of them died due to the massive haemorrhage. Only one acute renal failure was registered. The mortality rate was 25%. In this four death cases, tumors were located in the pancreatic head.

Girelli et al. (35) reported 40% total morbidity in their first 25 patients. This was related with the probe temperature. Later, they reported results from a cohort constituted by a total of 107 patients. 47 patients were treated with intraoperatively RFA ± primary pancreatic cancer treatment. And 60 patients treated with conventional QT and later RFA (intraoperatively). The overall morbidity was 28% with a rate of abdominal complications 26.2 %. A total of 20% of patients were considered

RFA-related morbidity in accordance to mechanical and thermal injuries (6 pancreatic fistula, 3 acute pancreatitis, 5 portal vein thrombosis, 3 duodenal injuries).

In all these studies, RFA was performed intraoperatively and as a device, a Cool-Tip ™ RFA ablation system was used. The ablation technique was followed by a palliative bypass. The proximity of major vascular structures and close relation to the duodenum and stomach were the main obstacles, so this was also related with a major risk of complications. (37).

In conclusion, high rates of complications ranged from 10-43% and morbidity reported from 10-37% and also high rates of mortality (0-19%) (31) were related with non-optimal settings of RFA, so more studies were needed to solve this (28).

3.2.3. The present of RFA

When Goldberg et al. published their results of EUS-RFA performed in normal porcine pancreas, remarked that further studies were needed to determine the optimal duration of ablation, and also the applied temperature (32). One of the main intrinsic factors affecting the effectiveness of ablation are tissue impedance and the proximity of large calibre vessels (38).

Many efforts have been made to reach a consensus on the optimal RFA parameters (37).

On one hand, a Manchester group defined and validated some thermokinetic principles, studied in an *ex-vivo*, non-tumor bearing, porcine model (38):

- Target temperature and effect of ablation: 90°C is the recommended
- Optimum duration: a minimal duration of 5 minutes is required to produce a 2 cm ablation.

On the other hand, Fegrachi et al. (39) in a porcine model study, recommended to respect a distance of at least 10 mm from duodenum and portomesenteric vessels during the RFA ablation. Also, an active duodenal cooling with saline 5°C should be performed at the same time; those two actions reduce the morbi-mortality.

Wu et al. (33) reported a minimum distance of 5 mm between RFA and major vessels, so, for that reason, this thermal ablation performed so near from vascular structures resulted in a higher complication rate (from a total of 16 treated patients, 18.8% developed a pancreatic fistula, 18.8% had a massive gastrointestinal haemorrhage and the rate of mortality was 25%) (31).

The outcomes related with median survival after RFA performed in patients with unresectable locally advanced pancreatic cancer were ranged from 20 months to 33 months (31). But there is a heterogeneous consensus with the inclusion criteria that can modify final results.

Firstly, Spiliots et al.(40) studied the results of a retrospective cohort of 25 patients including either stage III or stage IV; they concluded an overall survival rate of 13 months in patients who did not received the RFA, but the other 12 patients in which the RFA was performed intraoperatively, the final results indicated a significant survival benefit. The survival rate in this groups of patients was estimated at 33 months, with a patient alive at present. They concluded that the benefit survival by RFA treatment was better in stage III patients.

Then, Girelli et al. (35) published one of the largest studies of a prospective cohort, cited a median survival of 20 months (31). A half of patients with locally advanced pancreatic cancer received primary treatment before RFA performance; so, final results reflected an inherent selection bias in patients who received second-line RFA, who should have benefited from an earlier treatment, in order to receive RFA later.

We can conclude that the most relevant studies which have performed RFA therapy in patients with locally advanced pancreatic cancer or metastatic disease have some limitations, especially those related with the inclusion criteria, and the additional treatments done pre- or post- RFA. The most important think of current situation of EUS-RFA and locally advanced pancreatic cancer is that there are no randomized controlled trial of RFA in locally advanced pancreatic cancer (31).

3.2.4. Current situation of EUS-guided RFA

It is known that the RFA is a safe and feasible ablative technique in locally advanced pancreatic cancer, but new approaches are being implemented.
Ecoendoscopy-guided radiofrequency ablation has many advantages compared to other technical approaches:

- Real-time imaging guidance; this may result in safe tissue ablation
- There is the option to ablate the tumor in non-surgical candidates
- It has a reduce morbidity compared with surgery treatments
- It can be performed on an outpatient basis.

Other advantages are: the evolution of image quality, manageability of the instrument and the increased diameter of the endoscope channel which has made possible the use of more accessories. Also, thanks to Doppler effect, vascular structures and small lesions can be detected (26).

There are some studies describing EUS-RFA in solid pancreatic lesions (31). Those actual studies did not include the same type of pancreatic lesion, so EUS-RFA was not focused only in locally

advance pancreatic cancer, but also in mucinous cysts, insulinomas and pancreatic adenomas.

Song et al. (27), one of the studies included in the latest review of EUS-RFA (41), aimed to assess the feasibility and safety of EUS-guided RFA in six patients with locally advanced pancreatic cancer. They could not evaluate long-term survival, but they concluded that this approach is technically feasible and safe for that patients. EUS-RFA should be used as an adjunct alternative treatment method for unresectable pancreatic cancer (27).

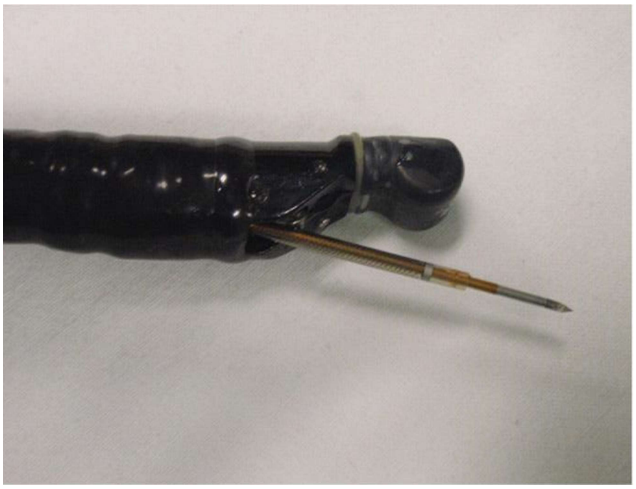


Figure 6*. The tip of the RFA electrode* (42)

Before Song et al. performed EUS-RFA in humans, they studied in 2012 this technique in porcine pancreas (42). They decided to use EUS-RFA because of real-time imaging and the possibility to perform a selective ablation. The RFA system was composed by an 18-gauge electrode ***(figure 6)*** and a VIVA RF generator (STARmed, Korea). During *ex-vivo* test, they used bovine liver to achieve the optimal ablation power. They concluded that the ablation power of 50 W, was the most effective in depth and size. So, in *in-vivo* method (porcine pancreas), the RFA was performed with a 1 cm electrode tip at 50 W for 5 minutes, producing a coagulative zone of 2,5 cm.

Goldberg et al. (32) in 1998, with their first experience of RFA in porcine pancreas, reported an ablative focus limited to < 10 mm. Finally, when Song et al. applied this technique in humans, they worked with frequencies between 20W and 50 W, and they made repeated needle punctures according to the tumural size and the necrosis that appeared once the thermal ablation was applied.

Wang et al. (43) concluded the same as Song et al. , but they also reported a considerable reduction in tumor size and CA 19.9 levels.

The aim of their study was to evaluate the feasibility and safety os EUS-RFA. The population of interest was patients with non-resectable pancreatic cancer. The technical success was complete and none complications were described. But, one more time, there is the limitation of the sample; only three patients were included in this study, so may be, the final results could not be extrapolated to the general population.

The RFA equipment used by Wang et al. was composed by a 22-gauge FNA needle and a radiofrequency catheter (Habib EUS-RFA catheter, Emcision Ltd, London). The Habib ™ EUS-RFA ***(figure 7)*** is a monopolar device and is used together with a patient grounding pad was placed through

the FNA needle. RFA was applied at 10 W and 15 W for two minutes, and the needle was passed several times in concordance to the tumor size (43).

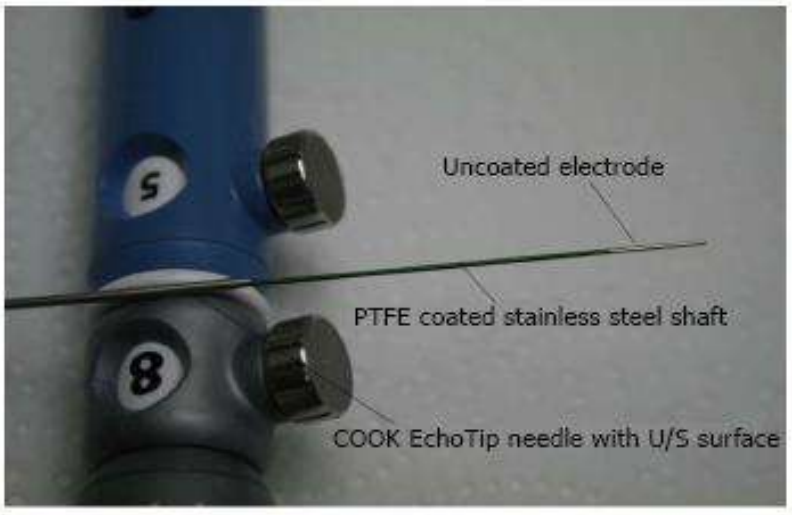


***Figure 7**. Close up of the Habib ™ endoscopic ultrasound-radiofrequency ablation catheter showing uncoated electrode at the tip and the PTFE Coated stainless steel shaft* (41).

One of the most important thinks that it has been studied, is the feasibility and the safety of this new method. All studies had positive conclusions, but larger studies should be done to know how this new technique can impact on the survival of patients with non-resectable advanced pancreatic cancer.

4. JUSTIFICATION

Pancreatic adenocarcinoma is an important health problem in our environment. It is the fourth most lethal cancer worldwide. Also, its incidence has been increasing for lasts years.

It has a bad prognosis, with a 1-year survival rate of 20% and a 5-years survival rate of 6%.

Only 15%-20% of patients with pancreatic cancer can be treated with surgical excision, but this treatment is not absent from complications.

Other treatment options for pancreatic cancer are limited. There is a stagnation in surgical total excision and there is evidence of poor responses with oncological chemotherapy. This is because ductal adenocarcinoma usually elicit an intense stromal reaction which can act like a barrier to chemotherapy (8); so new therapeutic measures should be advocated.

Radiofrequency ablation uses high-frequency alternating current to destroy solid tumors. When attached to a generator, radiofrequency current is emitted from the exposed portion of the electrode. Then this current translates into ion agitation within the surrounding tissue, which is converted by friction into heat inducing cellular death and so, producing a necrosis coagulation. Its minimally invasive approach and good tolerability are the advantages of using RFA.

Thermal based ablative techniques are widely used in solid tumoral lesion, reporting similar results compared to surgical treatments. Initial studies of RF implemented in pancreatic tissues were associated with significant morbidity and mortality. Thanks to various modifications, in particular those related with the technique and the combining real time imaging (EUS), important improvements in safety and feasibility have been achieved.

Studies of cases-series in which RFA was performed ecoendoscopically-guided, reported no significant adverse events (mild abdominal pain and mild pancreatitis). Nevertheless, this technique is not absent from major complications (acute gastrointestinal haemorrhages, mesenteric thrombosis, peripancreatic fluid collection and sepsis), as other interventional treatments.

The importance of conducting a clinical trial such this is to evaluate if it exists a positive impact on overall survival in patients with non-resectable locally advanced pancreatic adenocarcinoma. Also, it will be registered carefully how was the EUS-RFA performed, to report more information about the exact technique setting and possible complications.

We have focused this project selecting patients with some strict inclusion criteria. Taking into account last studies, RFA was performed in heterogeneous population (with pancreatic cancer). So, confusing variables like previous chemotherapeutic treatment or metastatic disease will be avoided in ours, minimizing the impact of selection biases.

5. HYPOTHESIS

The treatment of unresectable locally advanced pancreatic adenocarcinoma with EUS-guided radiofrequency ablation plus conventional treatment (QT± RT) versus protocolised treatment (QT ± RT), achieves an increase on overall survival in those patients.

6. OBJECTIVES

6.1. MAIN OBJETIVE

To assess 2 and 5-years overall survival rate in patients with locally advanced pancreatic cancer treated by endoscopic ultrasound-guided radiofrequency ablation plus QT ± RT, compared to conventional treatment.

6.2. SECONDARY OBJECTIVES

- To evaluate the progression-free survival rate in patients with pancreatic adenocarcinoma treated with EUS-guided RFA plus chemotherapy.
- To assess the safety and feasibility of radiofrequency ablation technique, evaluating complication rates related with this procedure.
- To assess surgical conversion rate once the treatment has been implemented.
- To evaluate pain control with the Visual Analogue Scale (VAS) ***(see annexe 5)***
- Length of stay

7. SUBJECTS AND METHODS

7.1. SETTING

Universitary Hospital of Girona, Dr. Josep Trueta will be the reference centre. Other universitary hospitals of Barcelona area included in the study will be: Vall d'Hebron and Bellvitge Hospitals. Also, the Hospital Clinic of Barcelona will take part in the study. All of them will have an assigned principal investigator. One of the most important point that those three centres must cover, is an expert ecoendoscopist. Those physicians are going to perform, in each center in which they work

at, the ablative technique. They will be the main investigators of the study, sometimes accompanied by the oncologist.

We have decided to plan this clinical trial as a multicenter study specially because of the low incidence of locally advanced pancreatic cancer in the area of Girona. So, being a total of 4 referent centers, the length of the study could be affordable.

7.2. STUDY DESIGN

A multicenter open-labelled randomized interventional clinical trial will be carried out. This clinical trial will be controlled and randomized to assess the effect of EUS-guided RFA plus conventional treatment in patients with pancreatic adenocarcinoma. Those patients with pancreatic cancer, confirmed anatomopathologically (by cytology or histology) thanks to the acquisition of tumoral tissue, will be introduced into the study performed in centres of reference such as: Doctor Josep Trueta Hospital, Vall d'Hebron Hospital, Bellvitge Hospital and Hospital Clinic of Barcelona.

7.2.1. Randomization methods

Once the patients are diagnosed and all meet the inclusion criteria, they could be included into the study after they have signed the informed consent.

Randomization, ensures that each patient has an equal chance of receiving any of the treatments under study (44). A simple randomization will be done, in order to avoid the selection bias.

Patients, will be assigned randomly in a 1:1 ratio. Two treatment groups are going to be done (group A and group B), so they could receive either QT±RT or EUS-RFA plus conventional treatment, respectively.

An external researcher will be the person who randomly assigned each patient into a group. The SPSS software will be used to make the simply randomization.

7.2.2. Masking techniques

This is an open-labelled randomized trial. On one hand, the patient (in group B) cannot be blind by treatment received. It is impossible to avoid the ignorance of performed EUS-RFA.

On the other hand, blinding physicians is not either possible. The ecoendoscopist will be the person who will perform the ablation technique.

Any masking technique can be done when talking about patient's follow-up. The physician must know in which of the two groups of treatments the patients was included. Especially, because they have to be aware of possible EUS-RFA complications. Also, communication between patient and clinical would reveal the treatment received. So, no masking techniques will be implemented in the follow-up part of the study.

The only person that would be external from the study is the statistic. He or she would not know the intention of the simple randomization.

7.3. POPULATION OF INTEREST

Our population will be composed by those patients with unresectable locally advanced pancreatic cancer, confirmed by histological or cytological proves.

7.3.1. Inclusion criteria

- Histologically or cytologically proven ductal adenocarcinoma before start of EUS-RFA
- Unresectable locally advanced pancreatic cancer with no metastatic disease
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 (45). **(See annex 6)**
- Measurable or evaluable disease as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) (46)
- Fully informed written consent given **(see annex 10,11)**

7.3.2. Exclusion criteria

- Unidimensional measurable disease as assessed by computed tomography
- Concomitant disease, like clinically significant history of cardiac disease
- Prior chemotherapy/radiotherapy or other investigation drug treatment for either (neo)adjuvant or advanced disease settings
- Contraindications of receiving protocolised treatment
- History of another cancer (diagnosed less than 15 years ago)
- Active infection
- Pregnancy or breast feeding
- Patients younger than 18 years
- Pancreatic cystic lesion

7.3.3. Withdrawal criteria

All patients have the right to withdraw from the trial at any time. Some causes of the withdraw can be: chemotherapy side effects, complications of EUS-RFA procedure or medical reasons such as an adverse event, that will be under investigator criteria.

We also assume that some patients can be lost to follow-up. We define this lost when after calling the patient three times, he/she does not assist to the visit, or he does not come for two successive visits. Therefore, we will declare the subject lost to follow-up.

Another situation described as a withdrawal is when the patient in group B (EUS-RFA + QT±RT) does not sign the informed consent of the ablative technique accepting a revocation of it **(annex 11)**.

Subjects withdrawn from the clinical trial will not be replaced and will be included in the statistical analysis (analysis by intention to treat).

7.4. SAMPLING

To calculate sample size for our principal variable (overall survival), power calculator GRANMO was used.

We assumed an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast.

The proportion of overall survival in group A was 4%, the actual 5-year survival rate in patients with locally advanced pancreatic adenocarcinoma.

Our objective is to achieve 15% 5-year overall survival in group B.

The ratio of the study will be 1:1.

The proportion of suspected patients lose is 10%

So, we will need to recruit 274 patients. A total of 137 patients for group A and 137 for group B.

In Girona, there were diagnosed a total of 44 locally advanced pancreatic cancer between 2012 and 2015. In order to achieve the estimated sample size and not prolonging the study to much, we will need to recruit additional patients that will be treated in the other centers of reference. So, taking into account that:

- Current population of Girona province → 753 576 inhabitants.

- Current population of Barcelona province → 5 523 922 inhabitants (47)

We had to extrapolate current data of Girona, to the Province of Barcelona because of a lack of information about the actual number of diagnosed cases of locally advanced pancreatic cancer in Barcelona's province.

We conclude that in a period of time of three years, 322 patients with locally advanced pancreatic cancer will be diagnosed in Barcelona province.

So finally, patient's recruitment in both Girona and Barcelona will take 2.5 years.

7.5. VARIABLES

7.5.1. Independent variable

- Use of endoscopic ultrasound-guided radiofrequency ablation therapy in patients with non-resectable pancreatic adenocarcinoma.

  It is a dichotomous qualitative variable (yes/no). We will consider if the technique has been performed, or not, once evaluating the final outcome, the overall survival.

7.5.2. Dependent variable

- Overall survival rate.

  It is defined as the percentage of patients in the study who are alive 2 and 5 years after the diagnosis (specifying as *diagnosis*: the moment when the pancreatic cancer is confirmed anathomopathologically, and not only by imaging techniques). The study of the overall survival rate will be done in two different periods of time is because of its bad prognosis.

7.5.3. Secondary variables

- **Progression-free survival rate**. PFS, is defined as the period of time that passes from the diagnosis of pancreatic cancer until the progression of the disease or death from any cause. RECIST 1.0 criteria will be used to define this situation:
  - **Progressive disease**: at least a 20% increase in the sum of the longest diameter (LD) of the target lesion, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

- In that period of time with no progression, patients will have a **stable disease**, known as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify progressive disease, take as reference the smallest sum longest diameter since the treatment started.

  So, PFS rates will estimate the proportion of patients with no progression disease and patients who are also alive during follow-up period.

- We will evaluate the **safety** (time frame: 30 days after the RFA procedure).

  This variable will be specified as the percentage of patients with complications directly related to EUS-RFA technique (acute pancreatitis, acute gastrointestinal haemorrhage, pancreatic pseudocyst, abscess, mesenteric or portal thrombosis). All in-hospital complications or complications developed within 30 days after RFA procedure will be evaluated according to the Clavien-Dindo classification **(see annex 7)**.

  This evaluation is explained as discrete quantitative variable (grades of Clavien-Dindo), but we will transform this variable in a dichotomous one:

  - **0** → those patients with grade 1 or 2
  - **1**→ those with any complication classified in grade 3, 4 or 5

- **Surgical conversion rate:** some patients could benefit from surgical treatment if they respond to the previous treatment. So, we define this concept, as the percentage of patients who can be treated with a surgical excision at any moment of the follow-up of the disease. Resectability criteria must be fulfilled.

  We will also transform it in a dichotomous variable: surgical conversion yes or not, along the follow-up.

- **Pain Evaluation**: with the Visual Analogue Scale (VAS). The pain VAS pain score is a continuous scale comprised of a horizontal 10 cm line. The patient is asked to place a line perpendicular to the VAS line at the point that reflects their pain. The patient will self-complete the line. “No pain”, represents level 0, and “pain as bad as it could be” or “worst imaginable pain”, level 10 (48). This is defined as continue quantitative variable **(see annex 5).**

- **Length of stay (LOS)**: Each patient's LOS will be based on the number of days between their admission and discharge from the Centre of reference. It will be analysed as a discrete quantitative variable.

7.5.4. Covariables

Covariables are summarized in the following table:

Covariables	Characteristics of the variable	Measurement unit	Measure instrument
Age	Discrete quantitative	Years	Clinical history, anamnesis
Gender	Dichotomous nominal qualitative	Female/Male	Clinical history, anamnesis
PS	Discrete quantitative	0-1-2	ECOG Performance Status Scale
Size of the tumor	Quantitative continuous	Millimetres (AxBxC)	EUS and CT
Localization of the tumor	Discrete qualitative	Head/Body/Tail	EUS and CT
Type of chemotherapeutic agent	Discrete qualitative	GEMOX-FOLFIRINOX-Gemcitabine	Neoadjuvant Treatment
Radiotherapy	Dichotomous qualitative	Yes/No	Adjuvant radiotherapy treatment
Number of RFA punctures	Discrete quantitative	1-2-3…	EUS-RFA punctures

***Table 3**. Clinical trial Covariables*

7.6. INTERVENTION

Firstly, people who can participate in this clinical trial because they meet all the inclusion criteria, they must be informed about the possibility to enter in the study. All the information about the study will be in the Information Sheet **(see annex 8)**. Then, the informed consent must be signed.

Once the randomization is done, the patient enters randomly in one of the two interventions of the study.

7.6.1. Treatment A: conventional treatment for unresectable locally advanced pancreatic adenocarcinoma

Patients randomized in group A will received conventional treatment for locally advanced pancreatic adenocarcinoma. It does not exist a consensus on the best chemotherapeutic agent and the option of performing adjuvant radiotherapy, so a multidisciplinary team will be needed in all cases.

Once they are diagnosed they must be treated immediately and the beginning of the treatment cannot be delayed more than one week (patients in group A).

Two main neoadjuvant chemotherapeutic schedules can be used, but the final decision about the type of the chemotherapeutic agent will be took by the oncologist team.

Neoadjuvant treatment:

Patients with **PS 0-1**: initial treatment is going to be done with **GEMOX or FOLFIRINOX** (oncologist decision).

GEMOX consists in intravenous infusion of **gemcitabine** 1g/m^2 for 100 minutes plus intravenous infusion of **oxaliplatin** 100 mg/m^2 for 2 hours the first day of each cycle. This cycle it will be repeated every two weeks, completing a total of 6 cycles (3 months):

GEMOX → 1 cycle, every two weeks→ a total of 6 cycles (3 months)

FOLFIRINOX: this chemotherapeutic agent is composed by:

- FOL: folinic acid (leucovorin) → 400 mg/m^2 (2 hours)
- F: fluorouracil (5-FU) → bolus 2400 mg/m^2 + 2400 mg/m^2 continuous infusion for 46 hours
- IRIN: irotecan → 180 mg/m^2 in continuous infusion for 90 minutes
- OX: Oxaliplatin → 85 mg/m^2 continuous infusion for 2 hours.

Then, a CT will be performed to evaluate the tumoral response:

- Stable disease o tumoral response seen in CT: start treatment with radiotherapy (a total of 45 Gy, fractionated in 1.8 Gy per session) plus 5 FU in continuous infusion (250mg/m2/day), 5 days per week. It will be finished, when arriving to the maximum dose of radiation.
    - Four weeks after finishing radiotherapy treatment, it will be performed a CT and CA 19.9 to evaluate again the tumoral response.
        - If stable disease or tumoral response: evaluate the possibility of surgery
- If progression disease: evaluate first line chemotherapy treatment of advanced disease if good PS; if not, Best Supportive Care should be the best option.

Patients with **PS 2** or with relevant comorbidities: simulation for radiotherapeutic treatment and initial monotherapy treatment with **Gemcitabine** (1000 mg/m^2) days 1, 8, 15 every 28 days, 3 cycles (3 months). Then evaluate tumoral response with CT and CA 19.9.

- If stable disease or tumoral response: start treatment with 5-FU in continuous infusion (250 mg/m^2/day) and concomitant radiotherapy 5,5 weeks and then evaluate tumoral response.
    - If tumoral response or better PS: evaluate the possibility of surgery
- If progression disease: treatment of advanced disease or BSC.

7.6.2. Treatment B: EUS-RFA plus conventional chemotherapy ± radiotherapy

The main procedure in this group of patients consists in performing endoscopic ultrasound-guided radiofrequency ablation before starting the conventional treatment of unresectable locally advanced pancreatic cancer.

This endoscopic intervention will be performed in the endoscopic room of each hospital that participates in the study.

An important requirement is that the person who is going to perform the ablative technique, must be an expert in echoendoscopies (a person who performs at least 300 ecoendoscopies, and more than 100 are EUS-FNA). This experience will be required in all centers.

This procedure (EUS-RFA) can be regretted, by the patient, at any moment before the performance. If he/she accepts, they must sign the Informed Consent of it.

Before starting the intervention, each patient will be classified with the ASA system. Then a broad spectrum prophylactic antibiotic will be administered, and to perform a non-harmful procedure, each center will follow the sedation protocol used for EUS.

Cardiac and respiratory parameters will be monitored throughout the intervention.

The device that is going to be used is the HABIB^{TM} EUS-RFA. It is a 1 Fr wire and it has a working length of 190 centimeters. The catheter can be inserted through the biopsy channel of an ecoendoscope and then radiofrequency power is applied to the electrode at the end of the wire to coagulate tumoral tissue.

This device works like a monopolar system, so a ground pad will be needed. This grounding pad will be applied as close to the ablation zone as possible.

The procedure will start by connecting the HABIB ^{TM} catheter to the adaptor cable and then, this will be connected to the generator. In the next step, the ecoendoscope will be introduced through the mouth to obtain a proper sonographic visualization of the target lesion.

To avoid major vessel injury before puncture and during the procedure, real time Doppler imaging will be performed. Then, under EUS control, a 19-gauge biopsy needle will be inserted through the working channel of the endoscope. This needle will be used to puncture transgastrically or transduodenally, depending on the location, the target lesion.

Once the needle is into the lesion, the stylet will be removed, then the pilot RFA probe (HABIB catheter) connected to the generator (RITA Electrosurgical RF Generator, or other) will be advanced through the needle into the pancreas. The radiofrequency generator will be activated to deliver between 20 to 50 W ablation power, with a maximum of 5 minutes to achieve 2,5 centimetres of necrosis area.

It might be needed more punctures and less durable to achieve a homogenous and respectable necrosis so, the RFA can be repeated until a hyperechoic zone around the electrode tip sufficiently covers the tumor.

During the procedure, duodenal cooling, with 100 mL/min saline at 5°C, will be performed. Also, a probe distance of 10 mm from duodenum and portomesenteric vessels must be respected.

After procedure, patients will be observed for 24 hours to detect any related complication.

The beginning of conventional treatment will be initiated in the next 14 days after the procedure.

7.7. SAFETY

It has been reported in many cases studies, that EUS-RFA has no major complications and adverse outcomes. So, it has been described as a feasible and safety technique. It is also a well-recognized effective modality of treatment for pancreatic cancer.

Thanks to the minimally invasive characteristic of this technique, it has a good tolerability in comparison with surgical procedures that are associated with major morbidity and complications.

The main disadvantage of the radiofrequency ablation applied in pancreatic tissue is that it is very thermosensitive. A failure related with the technique, can produce an extensive inflammatory response causing edema and later fibrosis. Sometimes, it can be transformed in a pancreatic cyst. Generally, complications are more related with duration of ablation, for this, it is essential to perform the technique as is has been described (although it has not been standardized yet).

Those are the possible complications that can appear after the procedure:

- Mild abdominal pain. It will be evaluated by the VAS pain score.
- Mild pancreatitis
- Portomesenteric thrombosis. It can be avoided if 10 mm of distance from this structures is respected when performing the EUS-RFA.
- Acute gastrointestinal haemorrhage.
- Infection of necrotic pancreatic tissue.
- Related sedation complications

7.8. DATA COLLECTION

Baseline

Any patient, from the province of Girona or Barcelona, with a high suspicion or diagnosed of pancreatic adenocarcinoma, will be derived to any of the reference centres.

The first visit will include a complete clinical history and physical examination. It will be important to know general demographic patient's data such as: personal and family history, risk factors related to pancreatic cancer, regular medication intake, medicament allergies. Detailed signs and symptoms history will be written down. It will be also asked general symptomatology, as fatigue and weight loss. A complete analysis will be done: blood count, renal and liver function. Also, tumoral markers will be analysed.

In the following visits, imaging proves have to be done. The most important ones are CT and EUS. CT prove is important for the diagnose and the staging of the disease. The EUS-FNA and a posterior study, by a pathologist, of the sample obtained will give us the final result of ductal adenocarcinoma. If necessary, other imaging proves could be done such as MRI.

Pre-treatment work-up

It includes previous information about patient's clinical history and laboratory tests. Also, imaging proves must be done.

- A 12-lead electrocardiogram
- Abdominal ultrasound
- Contrast enhanced spiral computed tomography or contrast enhanced magnetic resonance imaging
- EUS-FNA to obtain tissue that will be analysed by the pathologist.

Once the patients' tumor is confirmed, they would be able to enter in the study. They must meet all the inclusion criteria and any of the exclusion ones. So, it will be proposed the possibility to participate in our study by giving them an Information Sheet **(annex 8)**. If the patient agrees, the Informed Consent **(annex 9)** must be signed. Then, a numeric code will be allocated to the patient to implement the simple randomization.

Preintervention assessment

The ASA classification will be used to evaluate patients' comorbidities before starting EUS-RFA procedure. A nurse will record the overall health status of those patients. Before the intervention, patients must sign the Informed consent related to the procedure **(annex 11)**.

Study treatments

An experienced ecoendoscopist will perform EUS-RFA. Patients' cardiorespiratory parameters will be registered during EUS-RFA procedure **(annex 10)**.

An expert oncologist in pancreatic cancer will treat each patient after the resolution of the type of chemotherapeutic treatment accorded by the oncologic team.

Postintervention assessment

After performing EUS-RFA, the patient will be under observation for 24 hours. Analgesic will be administered and possible complications will be registered.

The patient will be discharge once achieving a stable hemodynamic situation and no major observed risks. It will be prescribed, for a week, a broad-spectrum antibiotic.

Follow-up

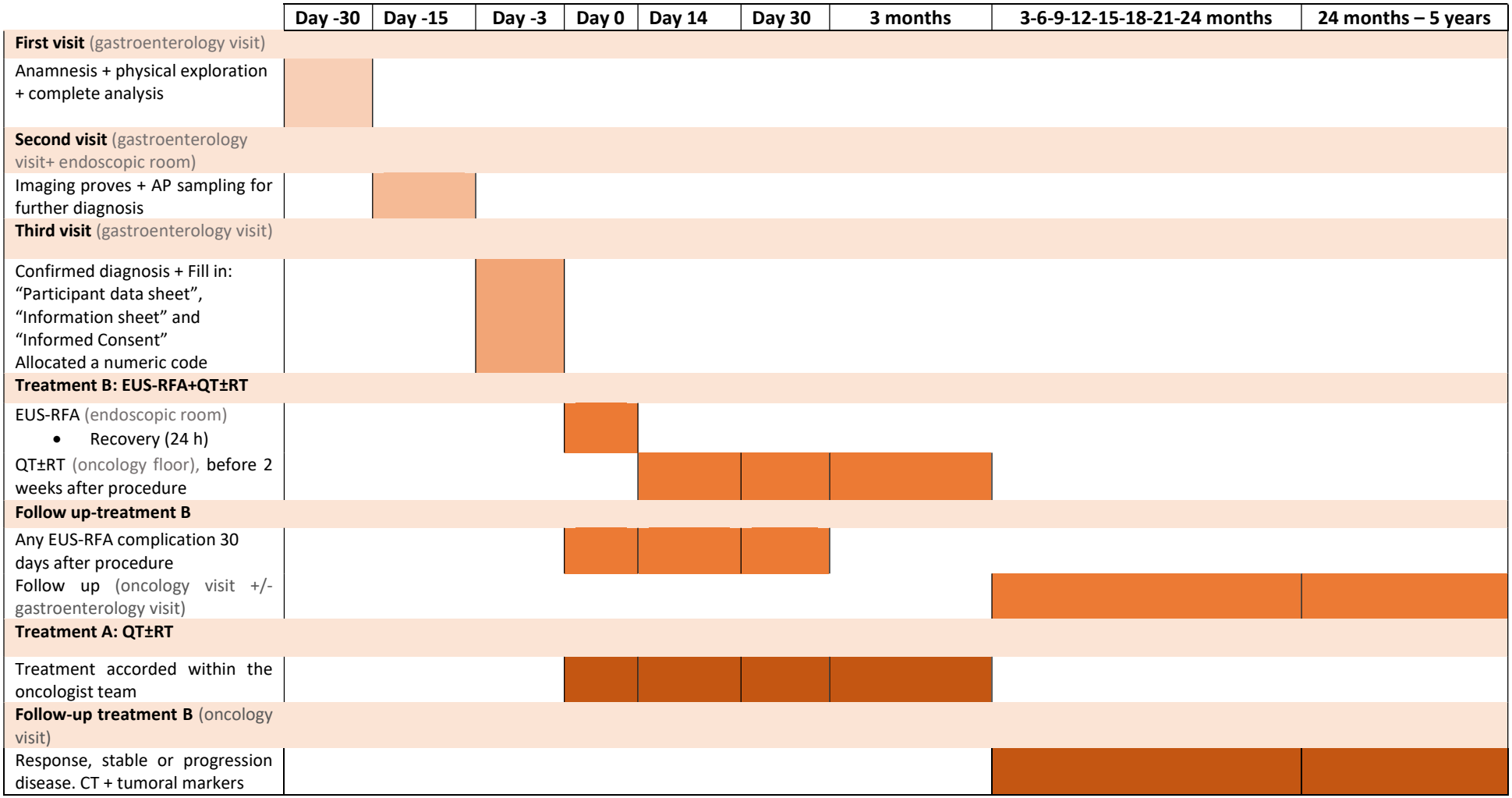
Those patients who received EUS-RFA, will be followed-up by the endoscopist, and also by the oncologist. Both, will collect information about patients' evolution.

The oncologist will control the chemotherapy treatment and future response, stability or progression disease.

When QT ± RT have finished, the follow-up will consist in:

- Clinical control, physical exploration + CA 19.9 levels every 3 months and CT every 6 months, for the first 2 years
- Clinical control, physical exploration + CA 19.9 levels every 6 months, and CT annually, until completing 5 years.

7.9. SCHEDULE OF ASSESSMENT



8. STATISTICAL ANALYSIS

Statistical analysis will be held with Statistical Package for Social Sciences (SPSS) software for Windows®.

Univariate analysis

Results for categorical variables will be represented as percentages or proportions, and as mean ± SD or median (quartiles) for continuous variables, depending on whether they are normally distributed or not.

Bivariate analysis

A survival analysis will be done to study our survival rates (OS, PFS). They will be analysed by the Kaplan Meier method. It will permit us to compare results of both treatment groups.

A t-student test will be used to analyse pain control (VAS) and LOS. Both, are discrete quantitative variables.

For analysing complications related with EUS-RFA and surgical conversion rate (variables transformed to dichotomous one), a Chi Square test is going to be used.

Multivariate analysis

To adjust confounding factors a multivariate analysis should be done. For survival variables, a Cox Model is going to be used. All confounding variables will be studied with this model. It is essential to analyse those variables that could influence in our results, and therefore can give information about prognosis factors (especially age, PS and type o chemotherapy received).

A general linear model (GLM) will be done to study quantitative continue variables and the relation with the performance or not of EUS-RFA.

For dichotomous variables, it will be used the logistic regression model.

A confidence interval of 95% will be assumed and P-value < 0.05 to consider there is a significance difference.

9. WORK PLAN

Personnel involved:

- Investigators: ecoendoscopists from gastroenterology department and onocologists
- Collaborators: laboratory team, nursing team, radiological team and pathologists

- Statistical consultant
- Responsible data manager: ecoendoscopist who will be chosen by each center.

The approximated length of this project will be 7.5 years, with a period of recruitment of 2.5 years. It has been designed in 5 stages:

Stage 0: Preparation (1 month)
Conducted by: Researchers **Date:** January 2017 **Objective:** Protocol elaboration, bibliographic research. Presentation to the Clinical Research Ethic Committees. Contact with other participant centers.

Stage 1: Coordination (1 month)
Conducted by: Investigators and collaborators **Data:** February 2017 **Objective:** Meeting all the team members and discuss the main objective and variables of study, methods, schedule and data collection. To maintain professionality of members participating in the study, qualifications and experience will be asked, especially in ecoendoscopists.

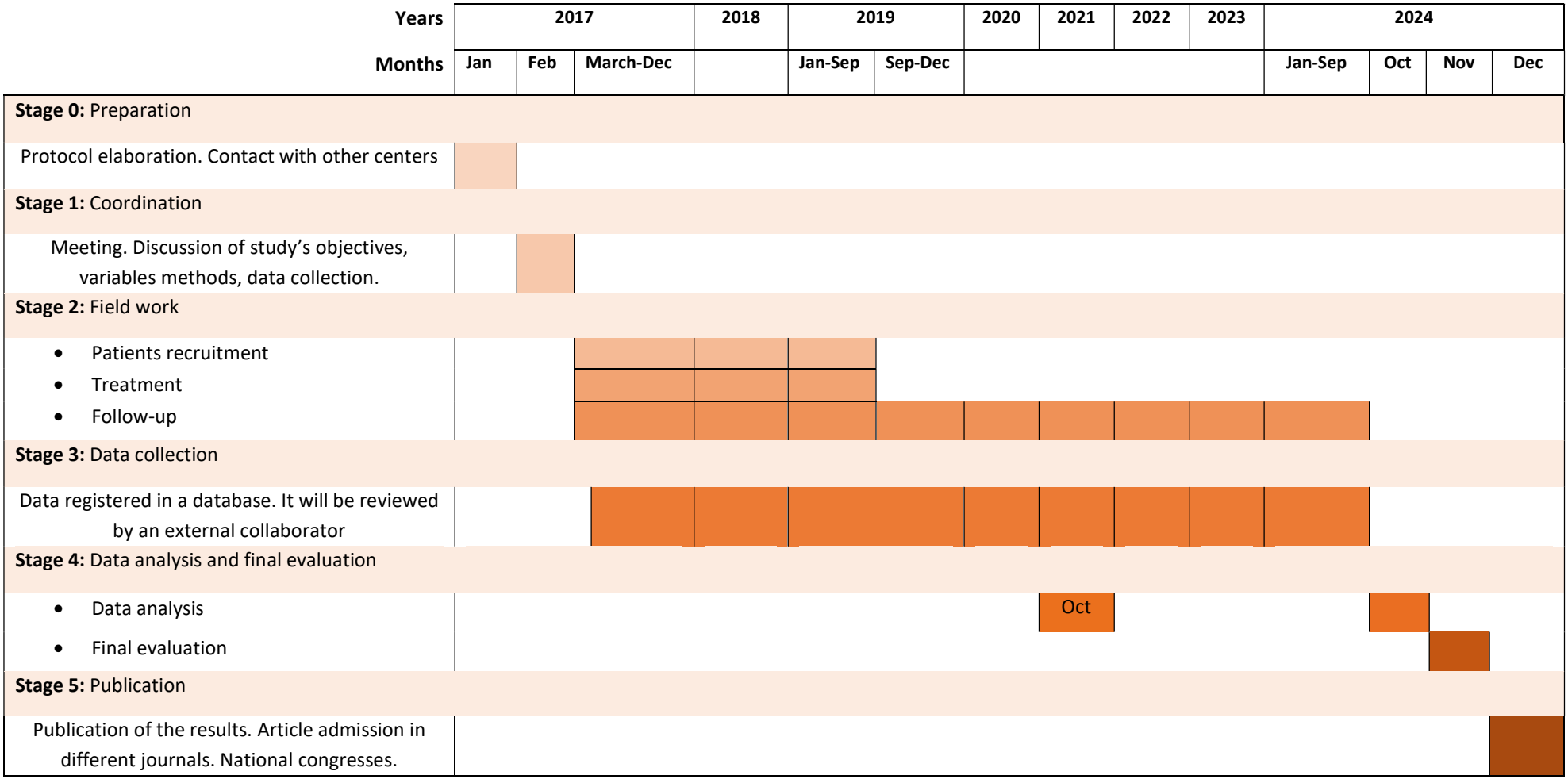
Stage 2: Field work (30 months + 5 years)
Patients recruitment: (March 2017 – September 2019). Patients will participate in the study if they meet all the inclusion criteria and none of exclusion criteria. All documents must be signed. Then, they will be randomly assigned to one of the treatment groups. **Treatment A or B:** EUS-RFA, 24 h + control of complications within 30 first days. QT±RT, at least 3 months. **Follow-up:** until September 2024. Firsts visits, every 3 months for 2 years. Then, visits will be every 6 months until completing 5 years.

Stage 3: Data collection (30 months + 5 years)
Conducted by: all study team members **Date:** (March 2017 – September 2024) **Objective:** While the trial has started, data will be registered in the database. It will be regularly review by an external collaborator

Stage 4: Data analysis and final evaluation (2 months)
Data analysis: (October 2021 and Oct 2024). It will be done by the statistical, using appropriated tests after 2 and 5 years of follow-up. **Final evaluation:** (November 2024). Interpret results, write conclusions and the corresponding articles.

Stage 5: Publication (1 month)
Conducted by: coordinators **Date:** December 2024 **Objective:** Publication in different journals and present results in National Congresses.

10. CHRONOGRAM



11. ETHICAL AND LEGAL ASPECTS

The goal of clinical research is to develop generalizable knowledge that improves human health or increases understanding of human biology. This clinical trial will be carried out, reviewed and undertaken to guarantee respect, frankness and quality, in accordance with the medical ethics requirements defined in the World Medical Association Declaration of Helsinki of Ethical Principles for medical Research Involving Humans Subjects. It was created in 1964 and reviewed in 2013 for the last time.

We will also take into consideration "Real Decreto Legislativo 1/2015, del 24 de Julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitario" that regulates the use of medication and sanitary products; and "Ley 14/2007, 3 de Julio, de Investigación Biomédica" that regulates biomedical investigation involving humans and the invasive procedures.

This trial will be submitted and evaluated by the Ethics Review of the Clinical Research Ethics Committee (CEIC) of each participating center. A future approval must be done by the "Agencia Española de Medicamentos y Productos Sanitarios" (AEMPS).

All patients who will participate in the study will be informed entirely about the details of this clinical trial, such as purpose, methods and treatments of the clinical trial. It will be given an Information Sheet **(annex 8)**, an Informed Consent **(annex 9)** and a specific Informed Consent for the ablative therapy **(annex 11)**. Those documents will be distributed and written with comprehensive language to ensure a proper informed decision. If they agree, all documents must be signed.

Also, autonomy principle will be respected. It is regulated by ""Ley 41/2002 Básica reguladora de la automomía del paciente y de derechos y obligaciones en materia de información y documentación clínica".

Confidentiality of information given by participants will be respected as well as anonymity along all the study. Data collected regarding each patient will be analysed and kept confidential. So, this will be respected according to the "Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal" of Spain and approved by the "Real Decreto 1720/2007, de 21 de diciembre".

12. STRENGTHS AND LIMITATIONS

The strengths of this clinical trial have been described, but also, making a revision of our protocol, there are some limitations that should be considered because it can interfere in our research. All this information is explained bellow:

- Blinding measures.

The ideal for a clinical trial is a triple blinding. In our case, this cannot be possible. On one hand, it is found that the patient will know in what treatment group is he/she. This can be explained thanks to EUS-RFA procedure; it is not possible to blind the performance of it.

On the other hand, we are not able to blind the ecoendoscopist, because is the person who will perform the technique.

Referring to the follow-up, the ideal situation in clinical trials will be successive visits done by different physicians of the same team. In our study, future communication between patient and clinical cannot be avoid. So, the oncologist/endoscopist will have information about the performance of the ablative technique, unmasking them. In conclusion, the best option for the follow-up, is that each referent physician will be responsible of future visits.

A positive thing that benefits this trial is that in our case, masking physicians in the follow-up period is not necessary. It is important to know exactly if the patients have received the ablative technique, just to be aware of possible complications related with this procedure.

- Sample size and time of recruitment/length of the study.

As it was explained before, our sample has been based on the total of locally advanced pancreatic cancer diagnosed in Girona province (44 cases), for three consecutive years.

Because of the lack of information in the total number of locally advanced pancreatic cancer diagnosed in Barcelona's province, we had to extrapolate this results to the total population of that province.

The final result of length recruitment might not be as exact as it will be in the future study. Also, our inclusion and exclusion criteria will decrease the number of patients who can take part in the trial, prolonging the time of recruitment.

Another fact that goes against the duration of the clinical trial is the main objective of the study. We want to evaluate the overall survival rate in both treatment groups and compare results. This variable has been defined in a 2 and 5 years follow-up. So, adding the time of recruitment (2.5 years) to this five years, the result of the study length might be extended.

Due to the duration of the trial, we could consider that along this period of time, potential modifications of treatments could be implemented in pancreatic cancer guidelines.

But, patients who take part in our study will be treated with the last chemotherapeutic agents that have reported the best benefit in locally advanced pancreatic cancer. And so, reviewing current studies not finished yet, we determine that along this seven and a half years, they will not substitute the actual and safety treatment for locally advanced pancreatic cancer.

- Being a multicenter clinical trial

  On one side, being this type of trial facilitates the sampling recruitment. We needed more hospitals than the HDJT, to take part in this study, because of the low incidence of the disease in Cataluña region. But, on the other side some variability could be found when performing EUS-RFA and also deciding the correct chemotherapeutic treatment. We have thought about that, and we have solved these limitations by:

  - Requiring ecoendoscopists with the same experience (at least 300 EUS and 100 EUS-FNA performed per year).
  - Meetings with the coordinators of each reference center, will be done before and during the study.

- Potential confounding factors.

  Some of it and most important, will be: type of chemotherapeutic agent received, radiotherapy (yes/no), performance status and age. Also, all those variables related to EUS-RFA. So, we will analyse data from these different subgroups and then it will be interpreted for possible prognostic factors. Maybe, some of it could influence in our final survival results.

  We have taken into account that different therapeutic schedules are implemented in our clinical trial. We consider that it would not be ethical that patients with pancreatic cancer would not benefit from the best chemotherapeutic agent ± radiotherapy, always according to their performance status.

- One of the main strengths of this clinical trial is the safety, feasibility and accuracy of EUS-RFA. It is a well-established antitumor treatment and is recognized as one of the least invasive therapeutic modalities for pancreatic neoplasm.

  This fact allows us to start a clinical trial with no relevant ethical problems of technique performance (only few possible complications, as all interventional techniques).

13. FEASIBILITY

Medical team

In this clinical trial, a multidisciplinary team will be needed. The main investigators will be an expert ecoendoscopist, and the oncologist expert in pancreatic cancer. They will work hand to hand.

Also, more professionals such as nurses, radiologists, pathologists, and the rest of gastroenterology and oncology team, will form part in this clinical trial. That, would be fundamental for our study.

Thanks to the experience of radiologist in RFA for hepatic and lung tumors, endoscopists could have good feedback with them.

To avoid a great heterogeneity in clinical practice, continuous meetings, in different scales (investigators, collaborators and external meetings), will be needed before and during the study.

An external statistic will be the person who will analysed all collected data. So, he/she will be contracted per hours. All workers will be hired by the National Health System.

All participant centers can cover those requirements.

Available resources

An endoscopic room will be needed to perform EUS-RFA. In HDJT, there are three available rooms, so that it would not be an impairment. Also, the other centers have similar conditions.

An important fact related to EUS-RFA performance is the duration of the prove. This procedure it is closely duration related (30 minutes) with EUS-FNA, or EUS alone; so, it would not be an additional work load for the endoscopic department. Other proves performed in the same endoscopic room, would not be affected by the implementation of the EUS-RFA.

A linear endoscope, a 19-gauge, the Habib™ EUS-RFA catheter and a generator (RITA Electrosurgical radiofrequency generator or other) is the most important material for the ablative procedure. It will also be necessary material and drugs related with the previous and posterior intervention.

Patients receiving EUS-RFA, will be observed for 24 hours so, a room in the gastroenterology floor is necessary for this situation.

Chemotherapy and radiotherapeutic treatments are available in all centers.

Patients

All patients from the province of Girona and Barcelona will be derived to the reference centers. They must meet all the inclusion criteria and none of the exclusion ones.

As it was explained before, our calculations are based on the number of pancreatic cancer diagnosed in Girona for three years. Extrapolating this to the population of Barcelona, the length of recruitment will be 2.5 years, with a total of 274 participants.

14. IMPACT

As it was explained in the introduction and justification part, pancreatic cancer is the fourth leading cause of cancer-related death. It carries a poor prognosis, with a 5-year overall survival rate of <5% and a median survival of <6 months. The outcomes of chemotherapy treatment with or without chemoradiation therapy are not satisfactory at all, with most patients experiencing only a small benefit. Therefore, new advances for the treatment of pancreatic cancer are needed.

On one hand, EUS has been increasingly used for therapeutic purposes. It allows precise measurement of the location and size of the pancreatic masses and can be used to follow the area of ablation and help avoid surrounding structures.

On the other, radiofrequency ablation is the ablative technique that begins to be implemented as an added treatment to advanced pancreatic cancer. And so, combining those two techniques, it is obtained a safe and feasible technique, the EUS-RFA.

The main objective of this study (overall survival) has been proposed because, although pancreatic tissue is more susceptible to thermal energy, RFA is reporting comparable results (with surgery treatments) in lung and hepatocellular carcinomas. Also, the feasibility and safety of EUS-RFA for the treatment of locally advanced pancreatic cancer has already been described. This allows us to carry out this trial.

It is essential to know the epidemiology of this neoplasm, especially in our case of locally advance pancreatic cancer, to understand the importance of achieving and increase on survival.

Taking into account that a total of 40% diagnosed pancreatic cancer are classified as locally advanced pancreatic cancer and no surgical treatment can be performed, an increase from 4% to 15% 5 years overall survival rate by performing EUS-RFA, will have an important impact.

Along the clinical trial, variables related with EUS-RFA procedure will be registered. This will allow us to analyse which specific parameters had been used in relation with the best results, also those related with potential complications.

It is essential to register as much as available information we have about it, because although it has been described the safety of this technique, the setting of the EUS-RFA has not been standardized yet.

So, this clinical trial will be a study with a considerable number of patients who will receive RFA (a total of 137). Compared to other cohorts' studies or cases series (the biggest one with a sample size of 100 participants), our trial may provide important and relevant information that could be used in future performances and other studies of EUS-RFA.

15. BUDGET

		Quantity	Costs	TOTAL
Personnel costs	Statistical expert for analysis data	Randomization + 2 analysis (90h)	35€/h	3 150
Material expenses	HABIB ^{TM} catheter	137	1 100	150 700€
	RITA Electrosurgical RF Generator	4	700	2 800 €
Insurance policy		1	10 000 €	10 000 €
Meeting costs	Transport (AVE)	6 Investigators from Barcelona. 2 meetings per year (7.5 years) = 192 round trip tickets	12.95 €	2 486 €
	Food and miscellanea	16 meetings for 8 investigators	30€/pp	3 840
Publication and presentation costs	AEMPS authorization	1	1 500	1 500
	Publication		1 500	1 500
	Presentation to National Congresses	1	2 500	2 500
TOTAL				**175 676 €**

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17. ANNEXES

17.1. ANNEX 1. ANATOMIC STAGING

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

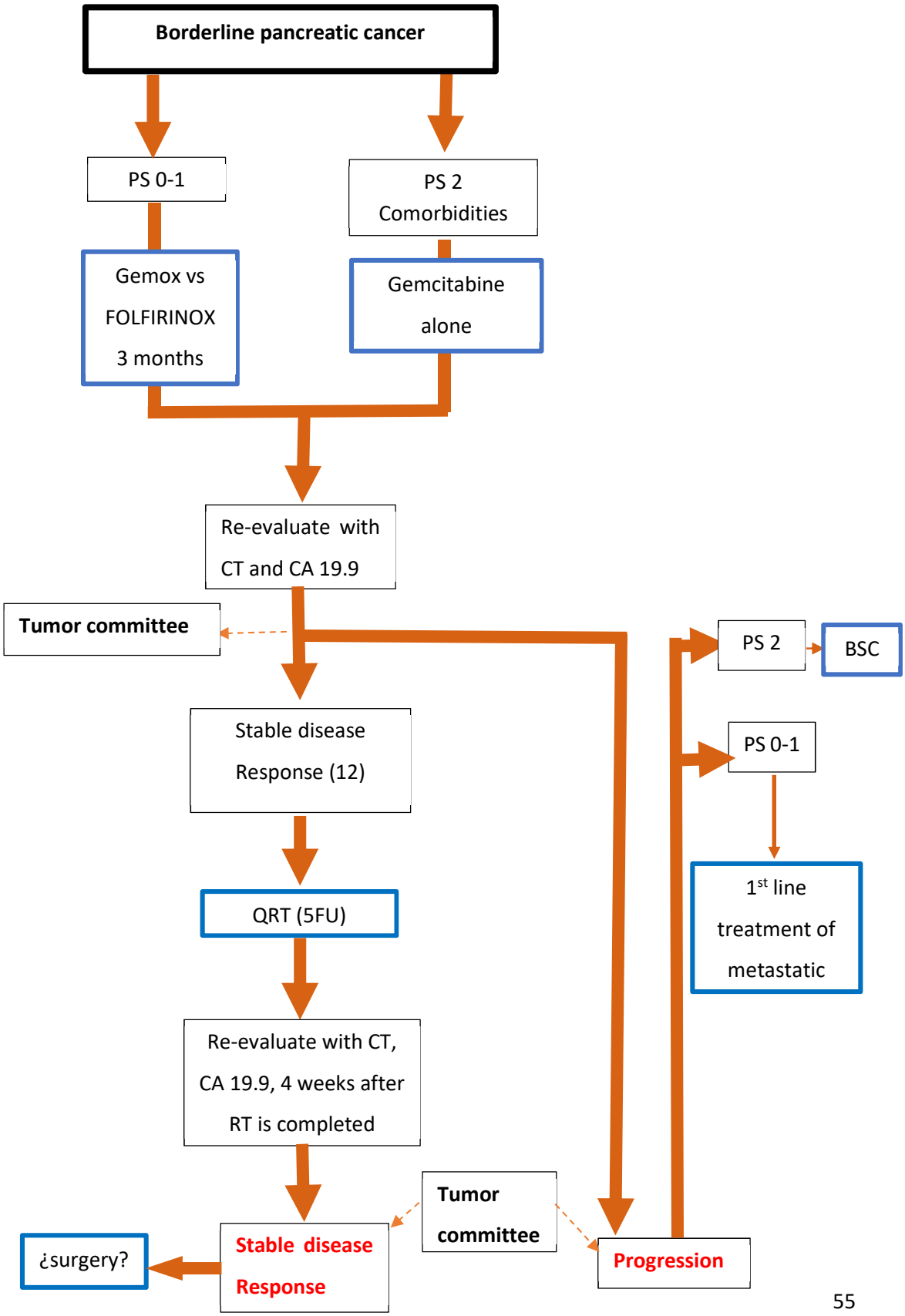
American joint committee on cancer. AJCC (1)

17.2. ANNEX 2. PERIPANCREATIC NODES

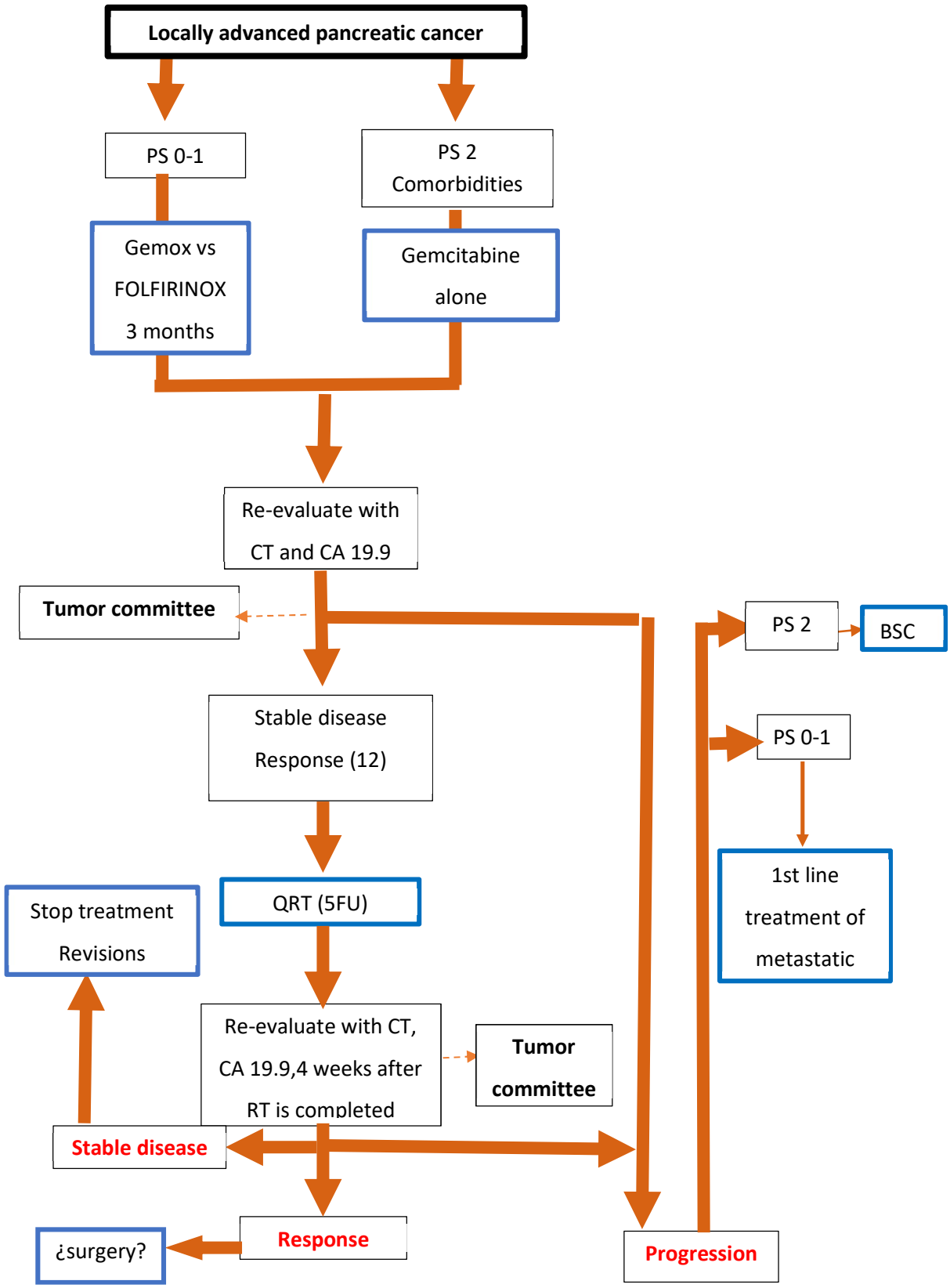
NODES	LOCALISATION
Superior	superior to head and body
Inferior	inferior to head and body
Anterior	anterior pancreaticoduodenal, pyloric (for tumors of head only), and proximal mesenteric
Posterior	posterior pancreaticoduodenal, common bile duct, and proximal mesenteric
Splenic	hilum of spleen and tail of pancreas (for tumors of body and tail only)
Coealiac	for tumors of head only.

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (1)

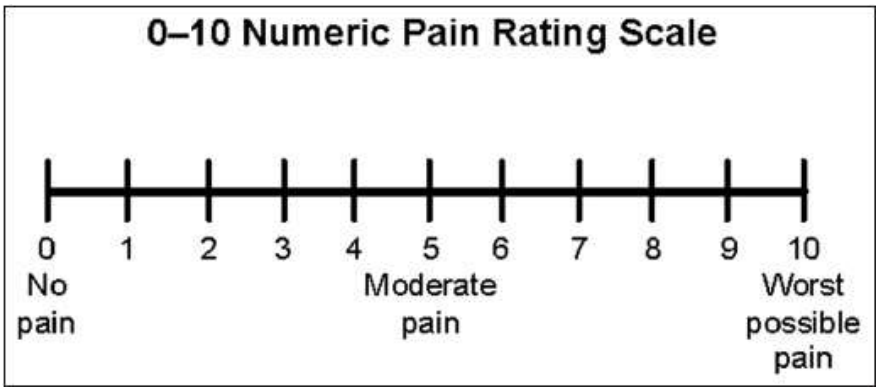
17.3. ANNEX 3. TREATMENT STRATEGY OF BORDERLINE PANCREATIC CANCER



17.4. ANNEX 4. TREATMENT STRATEGY OF NON-RESECTABLE LOCALLY ADVANCED PANCREATIC CANCER



17.5. ANNEX 5. VAS PAIN SCORE



VAS Pain Score (48)

17.6. ANNEX 6. ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.
2	Ambulatory capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Death

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17.7. ANNEX 7. CLAVIEN-DINDO CLASSIFICATION

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications: Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
• **III a**	Intervention not under general anestesia
• **III b**	Intervention under general anestesia
Grade IV	Life-threatening complication (including central nervous system complications) requiring IC/ICU management
• **IV a**	Single organ dysfunction (including dyalisis)
• **IV b**	Multiorgan dysfunction
Grade V	Death
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up evaluate the complication

IC: intermediate care. ICU: intensive care unit (50)

17.8. ANNEX 8. INFORMATION SHEET

Effect of endoscopic ultrasound-guided radiofrequency ablation plus chemotherapy VS. chemotherapy alone, on overall survival, in patients with locally advance pancreatic adenocarcinoma.

- Investigator/coordinators:
- Center:

This information sheet concerns women and men who attended Dr. Josep Trueta Hospital, Vall d'Hebron, Bellvitge hospitals and Hospital Clinic of Barcelona. Also, all affiliated centers.

General information

We inform you that this clinical trial is being conducted to evaluate the effect of the endoscopic ultrasound-guided radiofrequency ablation plus primary treatment, on overall survival in patients with locally advanced pancreatic adenocarcinoma. In comparison with the effect of conventional treatment, composed by chemotherapy ± radiotherapy.

This clinical trial, in which you are invited to participate, is being carried out in four different centers of Girona and Barcelona provinces.

We would like you to consider this research study, and then decide whether or not you wish to take part in it. It is very important for you to read and understand all this document. Also, why the research is being done and what it will involve. Please read the following information carefully. We will clarify any doubts you may have.

Volunteer participation

Your participation is totally voluntary. You are free to decide if you want to take part of this clinical trial or to withdraw at any time of the study. No reasons are needed to justify this. An informed consent must be signed if you decide to participate in the study. Your final decision will not affect to further treatments and follow-ups.

According to the inclusion and exclusion criteria of this clinical trial, you have been chosen to participate in it because you fulfil all what we are looking for in relation with locally advanced pancreatic adenocarcinoma.

Description of the study

This study randomizes patients in two groups: **group A**, will receive conventional treatment for pancreatic cancer (chemotherapy ± radiotherapy); **group B**, will be treated before the conventional chemotherapy, with an ablative technique named radiofrequency ablation. It will be performed ecoendoscopically. The main objective of this trial is to evaluate the effect of this technique on overall survival, measured in 2 and 5 years after finishing the procedure and chemotherapy treatment.

If you enter in group B, an informed consent about the technique must be signed. This procedure requires a previous preparation, and a 24-hour observation. Then, no further than 14 days after the radiofrequency ablation, the conventional treatment for pancreatic cancer will be stared.

A protocolised follow-up will be done. It will be exactly the same for both groups. The only difference is that, people treated with previous radiofrequency, will be closely follow-up for 30 days after the procedure. It is essential for detecting possible complications related to the technique.

Follow-ups, will be done by the oncologist and the endoscopist. In future visits, the oncologist will be the person who will follow you. It will last 5 years. The first 2 years, visits will be done every three months. Then, until completing 5 years, they will be every 6 months. Imaging proves and tumoral markers, have to be done to evaluate the situation of the disease.

Benefits and risks of participating in the study

Locally advanced pancreatic cancer has to be treated. If you participate in this study and you are randomly assigned to group A, you will receive the same treatment as the one as is given to all patients with this stage of pancreatic cancer. No additional benefits are added to this group, but it will be avoided those possible complications related to endoscopic ultrasound-guided radiofrequency ablation. Some risks will be related to chemotherapy toxicity and adverse effects of radiotherapy.

If you are randomly assigned to group B, you will benefit from the effect of the ablation technique. It burns tumoral tissue, and activates the immune system. This may prolong overall survival.

EUS-RFA is not absent from complications. Mild pain, pancreatitis, gastrointestinal haemorrhages are some and infrequent possible complications. More information will be given before the procedure. After the performance of EUS-RFA, no changes of conventional treatment will be between group A and B.

Responsibility and insurance

The responsible investigator has contracted and insurance to any damage you may suffer as a result of your participation in this trial, in accordance with the law.

Confidentiality

All patient data is stored on a password protected computer database. The information will be kept confidential according to current data protection law "Ley Orgánica 15/1999 de "Proteccion de Datos de Carácter Personal"). Records collected during the study will be identified by a numeric code and only the researchers and collaborators will have access to this information. Your identification will never be disclosed.

Economic compensation

Your participation in the study will not involve any additional cost. You would not pay for the medication prescribed during this study.

The investigator would not obtain any economic benefit from this clinical trial.

Contact

If there is any doubt or problem during the trial period, you can get in touch by calling:

- Telf: 972940200
- Hospital Dr. Josep Trueta. Plastic Surgery Department
- Av/ de Franca, s/n. 17007 – Girona

Thank you for reading this document.

Try to keep this information sheet for your records until you finish your participation in the study.

Any queries, questions or doubts, do not hesitate to ask us.

If you decide to participate in the study, sign the consent form below.

17.9. ANNEX 9. INFORMED CONSENT

Effect of endoscopic ultrasound-guided radiofrequency ablation plus chemotherapy VS. chemotherapy alone, on overall survival, in patients with locally advance pancreatic adenocarcinoma.

- Investigator/coordinators:
- Center:

Mr. / Mrs. _____
(Patient's name and surname in CAPITAL LETTERS)

- I have read the foregoing information, or it has been read to me.
- I have had the opportunity to ask questions to Dr. _____ about it and any questions that I have asked have been answered to my satisfaction.
- I consent voluntarily to participate as a participant in this research
- I have understood that I have the right to withdraw from the research at any time without in any way affecting my medical care.

So, I agree to participate in this clinical trial

Patient's signature Investigator's signature

Date: _____
(Written in their own handwriting)

REVOCATION OF INFORMED CONSENT

I, _____ withdraw the consent that it was given to me on ____/_____/20___, for the participation in the cited study.

Patient's signature: _____

Data: _____

17.10. ANNEX 10. PARTICIPANT DATA SHEET

Demographic data

○ Patient's code:
○ Name and surname:
○ Date of birth:
○ Sex:
○ Address:
○ Phone number:
○ Email:
○ First visit date:
○ Date of intervention (EUS-RFA):

Clinical history

○ Medical and surgical history:
○ Medical and surgical history of pancreatic cancer (date and type of initial symptomatology):
○ Family history of pancreatic cancer:
○ Allergies:

○ Regular medication:
○ Immunosuppression (yes/no, and why):

Preoperative information:

ASA CLASSIFICATION (American Society of Anesthesiologists)

I	II	III	IV

Data of EUS-RFA procedure:

○ Total procedure time:
○ Number of needle punctures:
○ Gauge size:
○ Time of ablation (specify for each puncture):
○ Ablation temperature:
○ Cardiac frequency and respiratory frequency:
○ Blood pressure:
○ Oxygen saturation:
○ Propofol dose:
○ Incidents:

17.11. ANNEX 11. INFORMED CONSENT FOR EUS-RFA

Nombre del procedimiento: Radiofrecuencia guiada por ecoendoscopia biliopancreatica.

Descripción del procedimiento: El procedimiento que le han solicitado es una técnica mixta que combina la endoscopia (tubo flexible con un sistema de iluminación y una cámara) y la ecografía junto con la radiofrecuencia. La prueba permite el examen ecográfico, la toma de biopsias por punción o la realización de la técnica ablativa. La ecoendoscopia por si sola también permite la realización de algunos tratamientos, tanto de lesiones en la pared del esófago, estómago y duodeno (primera parte del intestino delgado) así como de algunos órganos vecinos, como páncreas, vías biliares o ganglios linfáticos, directamente desde el interior del tubo digestivo. De esta manera se pueden estudiar detalles que de otro modo serían difícilmente valorables o accesibles.

La ecoendoscopia intervencionista permite realizar tratamientos endoscópicos sobre distintas lesiones situadas alrededor del tubo digestivo, como la punción y aspiración de quistes o cúmulos de líquido que estén en contacto con la pared digestiva, o la descompresión de la vía biliar obstruida. En algunos de estos casos puede ser necesario emplear contrastes yodados o Rayos X.

La aplicación de la radiofrecuencia permitirá ablacionar aquella zona de tejido tumoral.

Se realiza introduciendo a través de la boca un endoscopio que lleva acoplado en su punta un sistema de ecografía (ecoendoscopio). La exploración se realiza con el paciente recostado sobre su lado izquierdo (decúbito lateral izquierdo) bajo sedación moderada endovenosa, con monitorización constante durante la prueba de su frecuencia cardíaca, ritmo respiratorio y presión arterial. Con este fin se le colocará una vía venosa, unos electrodos adhesivos en la espalda, un manguito de presión arterial y unas gafas nasales con oxígeno suplementario. Se realiza en régimen ambulatorio de hospital de día (unidad de corta estancia) con controles médicos posteriores durante un tiempo variable (30-90 min) para controlar su seguridad tras la exploración. Una vez finalizada la prueba podría notar un ligero malestar en el abdomen y dolor de garganta, generalmente transitorios.

Riesgos generales:

Cualquier exploración, tratamiento o intervención quirúrgica presenta unos riesgos generales. El más grave es la posibilidad de un paro cardíaco. Otras complicaciones son las hemorragias y las infecciones. En caso de urgencia vital, se deberá actuar sobre estas complicaciones con los medios oportunos para el bien del paciente, de los cuales se informará (siempre que las circunstancias lo permitan) al paciente o la persona que sea responsable.

Riesgos específicos:

Cualquier actuación médica tiene riesgos. La mayor parte de las veces la intervención no produce daños o efectos secundarios indeseables. Pero a veces no es así. Por eso es importante que usted conozca los riesgos que pueden aparecer en este proceso o intervención**.**

LOS MÁS FRECUENTES: dolor de garganta o afonía. Otras complicaciones menores son roturas dentales, mordedura de lengua o luxaciones mandibulares. Dolor abdominal.

LOS MÁS GRAVES: son muy infrecuentes. Puede ocurrir sangrado, perforación de algún punto del tubo digestivo, la infección de alguna cavidad o la inflamación del páncreas (pancreatitis). Como consecuencia de alguna de estas complicaciones, excepcionalmente podría ser necesario un tratamiento urgente o una operación. A causa de la radiofrecuencia, también podría ocurrir trombosis portmesentérica.

Pueden producirse adicionalmente reacciones adversas a la medicación administrada (analgésicos, sedantes, antibióticos) tales como cuadros alérgicos, o bien relacionadas con la administración de sedantes (< 1%): insuficiencia respiratoria o cardíaca, arritmias, muy excepcionalmente convulsiones (0,035%) o trastornos neurológicos (0,002%).

Mortalidad: aunque es una eventualidad muy excepcional, algunas complicaciones podrían seguir una evolución fatal.

Sedación:

Hiposaturación de oxigeno - 046% (<80%)

Bradicardia - 0,21%

Broncoaspiraciones - 0,03%

Laringoespasmo - 0,03%

Convulsiones - 0,035 %

Transtornos neurológicos - 0,0002%

Complicaciones totales - 0,8%

LOS DERIVADOS DE SUS PROBLEMAS DE SALUD:

De cualquier forma, si ocurriera una complicación, usted debe saber que todos los medios técnicos de este centro están disponibles para intentar solucionarlo.

Riesgos personalizados:

Alergias a medicamentos: debe informar previamente si tiene alergia confirmada o sospechada a fármacos antibióticos, anestésicos, analgésicos o sedantes a fin de evitar su empleo. Aunque la alergia a contrastes yodados no supone contraindicación, debe conocerse este hecho.

Pacientes con tratamiento antiagregante o anticoagulante: tienen mayor riesgo de hemorragia por lo que se deberán tomar precauciones al respecto. Notifique con antelación (al menos una semana antes) si toma algún medicamento anticoagulante (Sintrom...) o antiagregante (aspirina, AAS, Tromalyt, clopidogrel, Disgren, Iscover...) ya que podría ser necesario suspenderlos temporalmente.

Embarazo: en algunas exploraciones se pueden precisar Rayos X que pueden dañar al feto. En caso de embarazo se debe recurrir a otras alternativas o planificar correctamente la técnica. Debe conocerse esta posibilidad.

La insuficiencia cardíaca, la insuficiencia respiratoria y el infarto agudo de miocardio reciente incrementan el riesgo de complicaciones.

Sugerencias del paciente:

Autorización:

He recibido la suficiente información verbal y/o escrita sobre la intervención quirúrgica que me realizarán. He podido hacer preguntas sobre este procedimiento. He comprendido la información que me ha sido dada. Por todo ello conscientemente autorizo que se lleve a cabo el procedimiento. También doy mi consentimiento para que, si en el momento del acto quirúrgico surge alguna complicación, el equipo médico modifique el procedimiento previsto y se pueda resolver el problema. Asimismo, autorizo una transfusión sanguínea si fuera necesaria durante la intervención. Puedo cambiar de opinión en cualquier momento y revocar el consentimiento antes de la realización del procedimiento, si así lo creo conveniente.

Este consentimiento se formula de acuerdo con lo establecido en la Ley 21/2000 de 29 de diciembre publicada en el DOGC núm. 3303 del 11 de enero de 2001

Servicio:

Profesional que informa:

Número de identificación:

Firma del paciente: **Fecha:** **Firma del profesional:**

Acepta:

No acepta:

Revocación del consentimiento informado

Yo, _____ revoco el consentimiento prestado en fecha ____/____/_____ y declaro por lo tanto que, después de la información recibida, no autorizo a someterme al procedimiento de Radiofrecuencia guiada por ecoendoscopia.