Irreversible electroporation of pancreatic adenocarcinoma

CHRISTOPHER MÅNSSON
Abstract

Pancreatic cancer (PC) is a severe diagnosis with poor prognosis. Radical surgery is the only treatment that can possibly lead to a cure, and even with surgery, the 5-year survival is only 20%–25%. The majority of patients cannot be resected due to metastases or having a tumour that is too advanced locally (LAPC) with encasement of blood-vessels.

Short electrical pulses can change the cell membrane, creating reversible pores in it. With a higher current, the pores become permanent, resulting in irreversible electroporation (IRE). This leads to specific cell death, with the chance to save surrounding scaffold material, such as the walls of blood vessels and bile ducts. This led to the theory that IRE might be suitable for treating LAPC.

In Paper I, we found that IRE can be safely performed percutaneously with ultrasound guidance in humans with PC, with promising efficacy, since one of the five patients included was downstaged due to the IRE and could be surgically resected. In Paper II, which is an extension of Paper I, we treated 24 patients with LAPC (3 were also included in Paper I) who had received chemotherapy and, after IRE, stable disease was seen. Median overall survival was 17.9 months. Eleven patients had some form of complication, but we still concluded that IRE is reasonably safe in LAPC patients, with promising efficacy. In Paper III, we chose to treat LAPC with IRE followed by adjuvant chemotherapy. We compared the overall survival of our patients with those with LAPC in the National Quality Registry for Pancreatic and Periampullary Cancer. No significant survival gain could be seen in the group that received IRE compared to the registry group (13.3 months versus 9.9 months, p=0.511). In the IRE group, there were six major complications and we found no support for using IRE in this setting. Paper IV examines the response on the tumour marker CA19-9 in PC treated with IRE. We found 35 patients suitable for this analysis. The hypothesis that IRE would lower the CA19-9 value could not be proven. In fact, the CA19-9 was slightly higher one month after IRE (282 U/ml versus 315 U/ml). However, the 25th percentile of patients with the best CA19-9 response had a better survival (p=0.01) compared to the 25th percentile with the worst response, indicating that CA19-9 can be used as a prognostic marker after IRE in PC.

Keywords: Pancreatic Neoplasms, Electroporation, Interventional Ultrasonography, CA 19-9.
To Mirja and Vidar
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV C. Månsson, A. Nilsson, J. Urdzik and B-M. Karlson. The Value of CA 19-9 after Irreversible Electroporation for Pancreatic Cancer Manuscript

Additional publications during my PhD studies on irreversible electroporation in the pancreas, included in the thesis appendix:

C. Månsson, A. Nilsson, and B-M. Karlson. Severe complications to irreversible electroporation of the pancreas in the presence of a metallic stent: a warning of a procedure that never should be performed. Acta radiol. Short rep 2014 Dec3;3(11)

C. Månsson, A. Nilsson, D. Månsson, and B-M. Karlson. Response from the authors of the original article. Comment to: Månsson C, Nilsson A, Karlson B M. Severe complications to irreversible electroporation of the pancreas in the presence of a metallic stent: a warning of a procedure that never should be performed: Regarding Scheffer, Voge, van den Bos et al.’s comments. Acta Radiol Open. 2015 Sep;4(9)

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Abbreviations

IRE  Irreversible electroporation
LAPC  Locally advanced pancreatic cancer
CEUS  Contrast-enhanced ultrasound
US  Ultrasound
CT  Computed tomography
OS  Overall survival
N  Number
RF  Radiofrequency ablation
PanIN  Pancreatic intraepithelial neoplasia
IPMN  Intraductal papillary mucinous neoplasm
MCN  Mucinous cystic neoplasm
PPPD  Pylorus preserving pancreaticoduodenectomy
MRCP  Magnetic Resonance Cholangiopancreatography
CEA  Carcinoembryonic antigen
CA 19-9  Carbohydrate antigen 19-9
CA 242  Carbohydrate antigen 242
AJCC  American joint committee on cancer
NCCN  National Comprehensive Cancer Network
CA  Celiac axis
SMA  Superior mesenteric artery
CHA  Common hepatic artery
IVC  Inferior vena cava
SMV  Superior mesenteric vein
PV  Portal vein
ECOG  Eastern cooperative oncology group
ESPAC  European study group for pancreatic cancer
FOLFIRINOX  Folinic acid, fluorouracil, irinotecan, oxaliplatin
ERCP  Endoscopic retrograde cholangiopancreatography
PTC  Percutaneous transhepatic cholangiography
ASA  American Society of anesthesiologists
Pancreatic cancer

Epidemiology

Pancreatic cancer is the 4th leading cause of cancer death worldwide (1) with an estimated overall 5-year survival between less than 4% up to 7% (2, 3). The overall prognosis has been roughly the same for decades (4) and according to recent numbers from the Swedish National Quality Registry for Pancreatic and Periampullary Cancer, is currently 6%, see Figure 1 (5). The incidence of pancreatic cancer varies in different parts of the world. In Europe, it is reported to be around 10/100 000. The variation in the world is probably partly explained by how accurate the diagnosis is done since it is more prominent in more developed countries (6). Its incidence in Sweden appeared to decline during the eighties and nineties (7). However, the last ten years have seen an increased number of cases and today in Sweden, the incidence is estimated to be 13.3 new cases/100 000 (8).

![Figure 1. Total survival in years from the diagnosis. Data from the Swedish National Quality Registry for Pancreatic and Periampullary Cancer between 2010 and 2016. The red line represents pancreatic adenocarcinoma.](image)

Smoking is a known and preventable risk factor for pancreatic cancer. Reports have described a 75% increased risk compared to non-smokers (9). Other risk factors for developing pancreatic cancer include advancing age, male gender (10), family history (11), chronic pancreatitis (1), diabetes (12), being overweight, exposure to nickel, alcohol abuse and previous gastric ulcers (13).
Familial pancreatic cancer accounts for five to ten per cent of all pancreatic cancer cases, which means that at least two first-degree relatives have been diagnosed with pancreatic cancer. However, among this familial pancreatic cancer cases, only 20% have a known genetic disorder (14). Besides the familial pancreatic cancers there are other hereditary conditions associated with increased risk for pancreatic cancer including Peutz-Jehgers syndrome, familial adenomatous polyposis, hereditary pancreatitis, familial atypical multiple mole melanoma, breast and ovarian cancer syndrome, cystic fibrosis, von Hippel-Lindau disease and hereditary non-polyposis (13).

Pathophysiology

Most pancreatic tumours are exocrine tumours, a group which includes ductal adenocarcinoma, acinar cell carcinoma, cystadenocarcinoma, adenosquamous carcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma and undifferentiated carcinoma. Only 1%-2% of all pancreatic tumours are endocrine (15) and over 90% of pancreatic cancers are ductal adenocarcinoma (16). The term “pancreatic cancer” is commonly used synonymously with ductal adenocarcinoma (10). This thesis studies exocrine pancreatic tumours and will not include endocrine tumours, which have a better prognosis (17).

The ductal adenocarcinoma often evolves through the microscopic precursor lesion pancreatic intraepithelial neoplasia (PanIN), which is not visible on conventional imaging but can be seen in the microscope (10, 15). The stages of PanIN before cancer are graded from 1-3. It has been estimated that the risk of progressing from PanIN 1 to pancreatic cancer is 1.5% in males and takes 35.3 years to develop, while the corresponding numbers for women are 1.3% and 33.6 years. The mean time of development from PanIN 3 to cancer takes 11.3 years for men and 12.3 years for women. This long timespan may offer the opportunity for future early detection (18).

Although it is estimated that it takes many years for a precursor lesion to develop into a cancer and even longer into metastases (10), many patients first present when they already have metastases or locally advanced disease (19). The majority of these patients are older with the peak incidence between 80 and 90 years old (7). Therefore, two associated lesions are of interest: IPMN and MCN, which can be seen on imaging and can thus be included in surveillance.

**IPMN**

Intraductal papillary mucinous neoplasm (IPMN) comprises cystic lesions in the pancreas in the main or branched pancreatic ducts. It is more common among men than women. The risk of malignancy varies depending on size and where in the pancreas the lesion is located (20).
There is no general consensus for the optimal treatment of IPMN and the guidelines from Europe (21), North America (22) and Asia (23) differ. In Uppsala, we follow the recently revised European guidelines.

These guidelines state that there is an absolute indication for surgery if there is a positive cytology for malignancy/high grade dysplasia, solid mass, tumour-related jaundice, or contrast-enhancing mural nodule (≥5 mm), and if the main pancreatic duct is dilated to ≥10 mm. Relative surgical indications encompass, depending on comorbidities, a growth rate ≥5 mm/year, increased levels of serum CA 19-9 (>37 U/mL), main pancreatic duct between 5 and 9.9 mm, cyst diameter ≥40 mm, new onset of diabetes mellitus, acute pancreatitis (caused by IPMN) and enhancing mural nodule (<5 mm) (21).

**MCN**

Mucinous cystic neoplasms (MCN) represent cystic lesions other than IPMN with malignant potential. These occur more often in females and the risk of malignancy increases with the size of the lesion. They are often located in the tail of the pancreas. Resection is recommended for larger lesions > 40 mm. If the lesion is smaller, with no other worrisome features, surveillance is adequate, especially since these lesions cannot always be distinguished from side-branch IPMN (21). Figures 2 and 3 are examples as seen on magnetic resonance imaging (MRI) and perioperatively.

Figure 2. MRI of a 12 cm large mucinous cystic neoplasm in the tail of the pancreas.
Figure 3. The same lesion as in figure. 2. 1=splenic artery, 2=splenic vein can be seen. The pancreas=3 is dislocated by the cystic lesion.

Diagnosis

Symptoms
Even though there is a considerable time span from a precancerous lesion to a developed cancer, most patients are diagnosed at a late stage. The symptoms with which the patients present are usually weight loss and abdominal pain, with the addition of jaundice if the lesion is located in the pancreatic head (24).

Radiology
The diagnosis is often done by radiology. Computerized tomography (CT) will show a hypo-attenuating lesion in the pancreas and can also demonstrate metastatic disease, dilatation of the bile- and pancreatic-ducts and vascular involvement of the tumour. To get an adequate CT, intravenous contrast should be administered and imaging performed at arterial and portal vein phases with small intervals between imaged sections (see Figure 4, 5 and 6) (25).
Figure 4. Without contrast, the tumour in the head of the pancreas is hard to see.

Figure 5. Arterial phase with intravenous contrast on the same patient as in figure 4, the tumour can be seen in the head of the pancreas
Figure 6. Portal vein phase with intravenous contrast on the same patient as in figure 4 and 5.

An ultrasound is often performed as a first investigation for jaundiced patients and may visualise a hypoechoic mass, metastases and vascular involvement. Ultrasound contrast can be given to improve the visualisation.

Although CT is sensitive for detecting lesions, MRI and magnetic cholangiopancreatography (MRCP) are recommended for surveillance of cystic lesions. MRI with MRCP is better for finding communications between the cyst and the main pancreatic duct as well as contrast-enhancing mural nodes (21).

Laboratory markers

Since many patients present with obstructive jaundice, laboratory signs of this can often be seen with elevated bilirubin and alkaline phosphate.

Carbohydrate antigen 19-9 (CA 19-9) is the most commonly used tumour marker and also has a role in evaluating the treatment effect. CA 19-9 is synthesised by epithelial cells including those in the pancreatic and biliary ducts (26, 27). Limitations are that some tumours do not express CA 19-9, and that obstructive jaundice per se may display a false-positive elevation which thus lowers the specificity (28).

Other tumour markers that can be used in the diagnosis of pancreatic cancer are CEA (carcinoembryonic antigen) and CA 242, with lower sensitivities and specificities than CA 19-9 (28).
Staging

We have used the 7th edition AJCC staging system in this thesis - see Tables 1 and 2. The 8th edition exhibits some changes, such as emphasising the size of the tumour (29, 30). When investigating whether a pancreatic cancer is resectable, borderline or locally advanced, the National Comprehensive Cancer Network (NCCN) guidelines are often used (Table 3) (31), even if there are some controversies regarding venous involvement (see the chapter on Treatment).

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastases (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1</strong> Tumour limited to the pancreas &lt; 2 cm at greatest dimension</td>
<td>N0 No regional lymph node metastasis</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td><strong>T2</strong> Tumour limited to the pancreas &gt; 2 cm at greatest dimension</td>
<td>N1 Regional lymph node metastasis</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td><strong>T3</strong> Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T4</strong> Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1 and 2. The 7th Edition AJCC Staging System.

<table>
<thead>
<tr>
<th>Stage 1A</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1B</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>T1-T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 3</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Table 3. National Comprehensive Cancer Network (NCCN) guidelines for staging between resectable, borderline resectable and locally advanced pancreatic cancer.

<table>
<thead>
<tr>
<th>Resectability Status</th>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>No arterial tumour contact (celiac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA). No tumour contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.</td>
<td>No arterial tumour contact (celiac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA). No tumour contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.</td>
</tr>
<tr>
<td>Borderline Resectable</td>
<td>Pancreatic head /uncinate process: • Solid tumour contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumour contact with the SMA of ≤180°. • Presence of variant arterial anatomy (e.g. accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origin of replaced or accessory artery) and the presence and degree of tumour contact should be noted, if present, as it may affect surgical planning. Pancreatic body/tail: • Solid tumour contact with the CA of ≤180°. • Solid tumour contact with the CA of &gt;180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery. (Some physicians prefer this criteria to be in the unresectable category.)</td>
<td>• Solid tumour contact with the SMV or PV of &gt;180°. • Solid tumour contact with the SMV or PV of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumour contact with the inferior vena cava (IVC).</td>
</tr>
<tr>
<td>Unresectable</td>
<td>• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumour contact with SMA &gt;180°. • Solid tumour contact with the CA &gt;180°. • Solid tumour contact with the first jejunal SMA branch. Body and tail: • Solid tumour contact of &gt;180° with the SMA or CA • Solid tumour contact with the CA and aortic involvement.</td>
<td>Head/uncinate process • Unreconstructable SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus). • Contact with most proximal draining jejunal branch into SMV. Body and tail • Unreconstructable SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus).</td>
</tr>
</tbody>
</table>
Treatment

Surgery

Surgical resection is considered the cornerstone in the treatment of pancreatic cancer (32) and although the 5-year survival after curative resection differs between studies, it is estimated to be around 10%-20% (3, 33). Bad prognostic signs are size of the tumour, poor tumour differentiation, positive resection margin and lymph nodes (10). Previous reports show that the median survival in Sweden after surgery for pancreatic cancer is 12 months with a 5-year survival rate around 10% (7, 34). However, recent data from the National Quality Registry for Pancreatic and Periampullary Cancer show a median survival of 26 months after resection and 5-year survival of 25% after resection for adenocarcinoma in the pancreas. See Figure 7 (5).

![Figure 7](image)

Figure 7. Total survival in years from the diagnosis. Data from the Swedish National Quality Registry for Pancreatic and Periampullary Cancer between 2010 and 2016 after surgical resection with curative intent. The red line represents pancreatic adenocarcinoma.

The majority of pancreatic cancers are located in the head of the pancreas and treated with pancreaticoduodenectomy (35). This operation includes resection of the duodenum, head and uncinate process of the pancreas, distal common bile duct, gallbladder and reconstructive anastomosis of the duodenum/stomach, pancreatic remnant and bile duct (36). It is possible to either divide the distal stomach (Whipple) or perform a pylorus preserving pancreaticoduodenectomy, 2 cm below the pylorus (PPPD/Longmire), with equal results (37). Previously, invasion of the portal vein or superior mesenteric vein was considered a contraindication for resection. However, today, vascular resection and reconstruction is considered feasible with survival rates similar to standard pancreaticoduodenectomy (38). Figure 8 shows the operative field after a
PPPD with resection and reconstruction of the superior mesenteric vein. Note the proximity between the portal vein, superior mesenteric artery, hepatic artery and inferior vena cava. Pancreaticoduodenectomy is most often performed as an open procedure, but in recent years several studies regarding minimally invasive pancreaticoduodenectomy have been published showing increased 30-day mortality. This procedure is still not considered standard care (36).

Distal pancreatectomy with concomitant splenectomy is performed when the pancreatic cancer is located in the body or tail of the pancreas, and in a few cases vascular resection and reconstruction may be done (39).

Figure 8. The operative field after a PPPD with resection and reconstruction of the superior mesenteric vein. 1= Remnant pancreas, 2=Proper hepatic artery, 3=Vascular anastomosis, 4=SMV, 5=SMA, 6=PV, 7=IVC.

Chemotherapy
Chemotherapy has several roles in the treatment of pancreatic cancer. As with surgical treatment, it is important to determine the patient’s performance status prior to the treatment. One way of doing this is by using the ECOG/WHO performance scale. See Table 4 (40). The majority of patients with an ECOG/WHO performance of 3-4 will only receive best supportive care.
Table 4. The performance scale from the Eastern Cooperative Oncology Group.

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG/WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house-work, office work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>

**Adjuvant treatment**

Adjuvant chemotherapy is an accepted treatment after pancreatic resection with curative intent. In this setting, gemcitabine has been shown to delay recurrent disease compared to observation (41), although in that particular study overall survival was not significantly longer (p=0.06). The ESPAC-3 trial showed that it is possible to use fluorouracil (5-FU) with folinic acid (leucovorin) as adjuvant after resection with similar survival rates, but with higher toxicity than gemcitabine (42). The ESPAC-4 trial showed additionally increased survival with gemcitabine combined with capecitabine (43). Primary data from the PRODIGE 24/CCTG PA.6 trial were presented at the ASCO 2018 meeting, demonstrating an increased median survival with a modified FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) protocol, compared to gemcitabine alone (54.4 vs 35.0 months), but with increased and severe side effects (76% vs 53%) (44). At the Uppsala University Hospital, the general current practice is to use gemcitabine alone for frail patients and gemcitabine with capecitabine for less frail patients. The use of FOLFIRINOX in the adjuvant setting has not yet been delineated but might be considered in patients who may tolerate intensive therapy and, based on subgroup analysis, following R1-resection.

**Borderline resectable tumours**

Borderline tumours are tumours that are initially considered unresectable but which may become resectable after neoadjuvant chemotherapy, with or without the addition of radiotherapy, to induce a tumour downsising. In a study published in 2008, out of 160 patients who were found to be borderline resectable, 66 were resected after successful conversion treatment, following which...
the tumour was deemed resectable, with a median survival of 40 months compared to 13 months for the remaining 94 (45). There is currently no standard of care for chemotherapy for borderline tumours, and most oncologists offer the most intense treatment the patient can tolerate. In Uppsala, FOLFIRINOX if considered tolerable; otherwise gemcitabine with albumin-bound paclitaxel (nab-paclitaxel) is given. If there is a response, but it is still not fully effective, radiochemotherapy may also be given to initiate further reduction in size and downstaging.

**Metastatic disease**
The prognosis for metastatic pancreatic cancer is poor. Twenty years ago it was shown that gemcitabine could alleviate some of the disease-related symptoms, with a slight survival benefit compared to 5-FU (5.56 vs 4.41 months) (46). The combination of gemcitabine with added nab-paclitaxel has shown a better OS, although with increased side effects (47). It has also been shown by Conroy et al. that an improved survival of 11.1 vs 6.8 months can be seen with FOLFIRINOX compared to gemcitabine. However, this study only included patients below 76 years of age with a good performance status. Moreover, there was an increased toxicity in the FOLFIRINOX group (44). Our current practice today for frailer patients is gemcitabine alone, and for those with a better performance status we add nab-paclitaxel, and for those with the best performance status, FOLFIRINOX. As second-line treatment, we either offer 5-FU, capecitabine or irinotecan with or without 5-FU.

**Locally advanced pancreatic cancer**
Most authors agree on the definition of LAPC as an unresectable disease and use the NCCN guidelines based on CT findings: no metastases and greater than 180° encasement of the superior mesenteric artery or celiac axis or unreconstructable portal vein/superior mesenteric vein (31). However, after treatment with chemotherapy, some have argued that LAPC may become downstaged and resectable (48). Thus, an evaluation of the treatment is in order. Arterial involvement below 180° should be considered borderline resectable and conversion treatment is recommended despite the lack of randomized trials (48, 49). There is an ongoing debate concerning venous involvement. NCCN guidelines define borderline resectable as solid tumour contact with the superior mesenteric artery or portal vein >180°. However, the International Study Group of Pancreatic Surgery recommends exploration in all cases if the veins are reconstructable (31, 49, 50). Treatment of LAPC with chemotherapy is sometimes offered in conjunction with radiotherapy, as shown below.

The type of chemotherapy for LAPC depends on the comorbidities and performance status of the patient. The majority of studies on unresectable pancreatic cancer have been based on metastatic disease and many have extrapolated these results to evaluate LAPC (48).
In Uppsala, we use the same chemotherapy principles for LAPC as we do for metastatic pancreatic cancer.

**Neoadjuvant treatment**
There are several current and ongoing trials concerning neoadjuvant chemotherapy before surgery, such as the ESPAC-5F on borderline resectable tumours. However, to date, its recommendations are not considered standard of care (48).

**Radiotherapy**
In some cases, radiotherapy is used together with chemotherapy for the treatment of pancreatic cancer. This combination can be used in borderline pancreatic cancers to achieve further downstaging to allow surgical resection (51). It can also be used in LAPC after induction therapy with chemotherapy, to improve survival compared to treatment with chemotherapy alone (52). It has also been shown that radiochemotherapy for treating LAPC is more effective after a period of induction treatment with chemotherapy, perhaps by excluding the patients with rapid metastatic disease (53). However, these results have been questioned by the randomised LAP 97 trial, where no increase in survival was seen when radiochemotherapy was added after induction with chemotherapy (54). In that study, the median OS was 16.5 and 15.2 months, respectively. The chemotherapy was either gemcitabine or gemcitabine with erlotinib, also with no survival differences between the two groups of chemotherapy. Overall, radio(chemo)therapy currently plays a limited role in the treatment of pancreatic cancer in Europe.

**Best supportive care**
Since most patients with pancreatic cancer are not cured, the symptomatic treatment is important. The number of patients with unmet needs for treatment tends to increase after the diagnosis, especially in metastatic disease, with the dominant symptoms being pain and anxiety (55). Anxiety is believed to be more frequent in pancreatic cancer patients than with other malignancies (56).

Orally administered opioids are the gold standard for treating pain from pancreatic cancer, but several other treatments may also be given, such as antiepileptic drugs (57), corticosteroids (57), celiac plexus block/neurolysis (58), intrathecal therapy (59), ketamine (60) and high-intensity focused ultrasound (61).

It is not clear which treatment is optimal for the anxiety related to pancreatic cancers, although short-acting benzodiazepines are often used in the terminally ill patients by palliative care specialists (62).

**Jaundice**
Jaundice due to biliary obstruction is common when pancreatic cancer arises in the head of the pancreas. As many as 70% of patients have bile duct
obstruction upon diagnosis (63). There are several ways to treat the obstruc-
tion. If the patient’s tumour is deemed resectable, early surgery has shown
fewer complications compared with preoperative biliary drainage (at least
with a bilirubin count < 250 μmol/l) (64). If the tumour is not resectable, the
bile duct obstruction can be relieved endoscopically, percutaneously or by sur-
gical methods. Most authors advocate endoscopic decompression, which can
be done with either plastic stents or self-expanding metallic stents. Metallic
stents have shown better results (63, 65, 66) and the percutaneous decompres-
sion should be second-line treatment (67).

Surgical bypass with a hepaticojejunostomy is mostly used when the tu-
mour is found to be unresectable during surgery (68). Today, however, there
is a growing preference to use endoscopic treatment on demand rather than
perform a hepaticojejunostomy (69).
Irreversible electroporation

Background
Reversible electroporation on cells was demonstrated in two articles in 1982. The authors demonstrated that it is possible to transfer genes in mouse cells by applying an electric field. It was postulated that this was possible due to increased permeability in the cell membrane. Further, it was also demonstrated that with increased electric voltage, cell death occurred, i.e. irreversible electroporation (see figure 9) (70, 71). In these early works, cell death was not the aim of the studies, but in 2005 an article using a mathematical model speculated that it is possible to use IRE to ablate tissue with temperatures below those needed for thermal ablation (72). In the same year, a follow-up study showed that in vitro the application of 1500 V/cm in three sets of pulses during 300 microseconds could generate complete cancer cell death in human hepatocarcinoma cells without exceeding 50° C (73). Indeed, it has been shown that some heat is generated through joule heating (the phenomenon that an electric current passing through a conductor generates heat) (74). Two years later, the first in vivo study on IRE on tumours implanted on mice showed that tumour ablation is possible using IRE (75). In the same year another in vivo study with pig liver demonstrated complete ablation with intact larger vascular structures within the ablated area (76). The same authors also showed that when treating the prostate in dogs, the urethra, as well as surrounding vessels and nerves were undamaged (77). The findings that vessels and other structures are unaffected by IRE is thought to be explained by the mechanism of IRE since it affects the cell membrane for ablation, while the connective tissue which does not contain a cell membrane is spared (76).

Since IRE is not dependent on generating heat for complete ablation, there is no risk of the so-called heat-sink effect that can occur when using thermal ablation (radiofrequency or microwave), if larger vessels within or close by the intended area cool the nearby tissue, leading to a lesser amount of damaging heat and incomplete ablation (78).

The fact that blood vessels are unharmed with IRE ablation makes this method theoretically interesting for treating tumours in the pancreas, since LAPC includes larger vascular structures. IRE in the pancreas has been studied in several animal models. A pilot in vivo study on 4 female pigs was done by Charpentier et al. and showed that the pigs survived for 2 hours (n=1), 2
days (n=1) and 2 weeks (n=2) and that IRE ablations appeared safe for pancreatic ablation (79). Similar results on pigs were shown by Bower et al. with vascular structures remaining intact after IRE in the pancreas (80). In 2012, a study was published using mice with human pancreatic cancer cells xenografted into their pancreas followed by treatment with IRE. Compared to an untreated control group, the IRE-treated group showed extensive tumour necrosis and reduced tumour cell proliferation (81).

Figure 9. An illustration of IRE-ablation. The needles placed and an irreversible electroporation-zone (red) which covers all of the tumour (white) is formed by electricity. A zone of reversible electroporation (blue) and unaffected tissue (green) can also be seen.

Human treatment

IRE in other organs
IRE has been used in organs other than the pancreas, such as the liver, to treat both primary liver malignancies as well as metastases (82, 83). IRE has also been used in the prostate (84), the kidney (83, 85), cholangiocarcinoma (86), the pelvic cavity (87) and the lung (83).

IRE in the pancreas
Based on the in vitro and animal studies mentioned above, there has been an increasing interest in treating pancreatic cancers with IRE. The first papers published on humans came in 2012 with a case report by Bagla (88), followed by two case series with promising results in the same year (89, 90).
Thereafter, several case reports and case series have been published (see Tables 5 and 6) with somewhat promising results. However, none of these studies was randomised, thus leading to a low level of evidence.

**Technique**

The technique used today for delivering IRE to the pancreas is by means of needles, although it is possible to use paddles for IRE (81). The needles are normally placed after a laparotomy (91) or percutaneously. If a percutaneous technique is used, placing the needles can either be CT-guided (92) or guided by ultrasound (93). Even if a percutaneous technique is used, the patient must be under general anaesthesia with muscle relaxation to avoid seizures (92, 93). These days, a commercial device is available, the NanoKnife, (AngioDynamics Inc., Queensbury, NY, USA). The active length at the tip of the needles is 10-15 mm (92). The needles are placed parallel to each other (90, 93) outlining the tumour, and, if the tumour is larger than 2 cm, one needle is placed in the centre of the tumour (94). After positioning, 10 test pulses are delivered and the machine’s setting is adjusted according to the response. We used 1500 v/cm and a pulse length of 70 μs for the test pulses and then changed the setting, aiming for an end current of 30-50 amperes (93, 94). When the pulses are delivered they need to be synchronised with the patient’s electrocardiogram, to avoid cardiac arrhythmias (95). It is estimated that three needles placed 2 cm apart will give an ablation zone of 3x3 cm with a depth of 2 cm. A pullback technique must usually be used to cover the whole tumour (93). A pancreatic tumour with a diameter exceeding 5 cm is suggested as an upper size limit for IRE treatment (92).
Table 5. Studies of IRE for pancreatic tumours with > 19 cases.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Method of delivering IRE</th>
<th>Findings</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al. (96)</td>
<td>54</td>
<td>Open, 52, laparoscopic 2</td>
<td>Improved progression-free survival and overall survival compared to a control group with standard care</td>
<td>32 patients had 67 complications</td>
</tr>
<tr>
<td>Martin et al. (91)</td>
<td>200</td>
<td>Open, 50 patients with concomitant resection</td>
<td>OS 24.9 months</td>
<td>37% had complications, 2% 90-day mortality</td>
</tr>
<tr>
<td>Venkat et al. (92)</td>
<td>43</td>
<td>CT guided, included 13 patients with metastatic disease</td>
<td>Two patients had a R0-resection after IRE, OS 16.2 months after IRE for LAPC</td>
<td>Pancreatitis (n=7), abdominal pain (n=10), haematoma (n=7) sepsis (n=1) duodenal stent (n=1) pneumothorax n=1</td>
</tr>
<tr>
<td>Belfiore et al. (97)</td>
<td>20</td>
<td>CT guided</td>
<td>3 R0-resections</td>
<td>No major complications</td>
</tr>
<tr>
<td>Mansson et al. (94)</td>
<td>24</td>
<td>Percutaneous US-guided</td>
<td>OS 17.9 months. Patient overlap with (93)</td>
<td>3 serious complications, 8 minor complications</td>
</tr>
<tr>
<td>Lambert et al. (98)</td>
<td>21</td>
<td>19 open, 2 percutaneous</td>
<td>Median survival 10.2 months after IRE</td>
<td>Complications in 5 patients</td>
</tr>
<tr>
<td>Kluger et al. (99)</td>
<td>50 (53 IRE procedures)</td>
<td>Open</td>
<td>Several serious complications. IRE should not be considered a minimally invasive procedure.</td>
<td>6 deaths within 90 days</td>
</tr>
<tr>
<td>Yan et al. (100)</td>
<td>25</td>
<td>Open</td>
<td>All patients had a lower CA 19-9 at discharge</td>
<td>9 post-procedural</td>
</tr>
<tr>
<td>Zhang et al. (101)</td>
<td>21</td>
<td>Booth CT and US guided</td>
<td>73% showed a radiological response 1 month post-operatively</td>
<td>4, all mild</td>
</tr>
<tr>
<td>Scheffer (102)</td>
<td>25</td>
<td>Percutaneous CT Guided</td>
<td>OS from IRE was 11 months and 17 from diagnosis</td>
<td>10 patients had major complications</td>
</tr>
<tr>
<td>Leen et al. (103)</td>
<td>75</td>
<td>Percutaneous CT Guided</td>
<td>OS was 27 months, 3 downstaged and R0-resected</td>
<td>25% had complications</td>
</tr>
<tr>
<td>Huang et al. (104)</td>
<td>70</td>
<td>Open (N=65) or laparoscopic (N=5)</td>
<td>OS 19.1 months after gemcitabine and 28.7 months after TS-1 (tegafur, gimeracil and oteracil)</td>
<td>3 major and 27 minor complications</td>
</tr>
</tbody>
</table>

The group led by Martin has published several articles regarding IRE on LAPC (90, 91, 96). However, due to unclear overlap of patients, not all of Martin’s studies are included in the table.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Method of delivering IRE</th>
<th>Findings</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagla et al. (88)</td>
<td>1</td>
<td>Percutaneous US, CT confirmation, 2-stage</td>
<td>Mild pain 2 weeks after treatment. The patient was alive at 6 months.</td>
<td>None</td>
</tr>
<tr>
<td>Narayanan et al. (89)</td>
<td>14</td>
<td>Percutaneous CT-guided</td>
<td>2 patients were R0-resected post IRE</td>
<td>Pneumothorax (n=1), pancreatitis (n=1)</td>
</tr>
<tr>
<td>Mansson et al. (93)</td>
<td>5</td>
<td>Percutaneous US-guided</td>
<td>1 patient downsized and R0-resected</td>
<td>No serious complications</td>
</tr>
<tr>
<td>Mansson et al. (105)</td>
<td>1</td>
<td>Unknown, treated at another centre</td>
<td>Severe complications when a metallic stent was in place.</td>
<td>1/1 mortality</td>
</tr>
<tr>
<td>Paiella et al. (19)</td>
<td>10</td>
<td>Open</td>
<td>OS 7.5 months, from IRE and 16.8 from diagnosis</td>
<td>2 complications in one patient</td>
</tr>
<tr>
<td>Wichtowski et al. (106)</td>
<td>2</td>
<td>Open</td>
<td>No sign of progression after 7 months</td>
<td>3 complications</td>
</tr>
<tr>
<td>Trueba-Aranguinarena et al. (107)</td>
<td>1</td>
<td>CT-guided</td>
<td>Disease-free at 12 months’ follow-up</td>
<td>Pain and haematemesis post-procedure</td>
</tr>
<tr>
<td>Scheffer et al. (108)</td>
<td>1</td>
<td>CT-guided</td>
<td>Percutaneous using dorsal approach</td>
<td>No major complications</td>
</tr>
<tr>
<td>Tartaglia et al. (109)</td>
<td>1</td>
<td>Laparoscopic US-guided</td>
<td>First laparoscopically guided</td>
<td>None</td>
</tr>
<tr>
<td>Orcutt et al. (110)</td>
<td>1</td>
<td>Open</td>
<td>Liver metastases after 2 months</td>
<td>Delayed gastric emptying and wound infection</td>
</tr>
<tr>
<td>Marsanic et al. (111)</td>
<td>7</td>
<td>Open</td>
<td>2 patients had LAPC, both dead within 6 months. The remaining 5 were borderline resectable.</td>
<td>No major complications</td>
</tr>
<tr>
<td>Stillström et al. (112)</td>
<td>3</td>
<td>Laparoscopic with computer-assisted guiding</td>
<td>A new method for guiding the probes</td>
<td>Complications in 2 of the 3 patients</td>
</tr>
</tbody>
</table>
Other ablative treatments of LAPC

Several other experimental ablative treatments besides IRE have been tried in the pancreas. Besides animal trials on ethanol injections (113) and YAG laser (114), there have been several human studies.

**Electrochemotherapy**

Electrochemotherapy is a treatment modality that is closely related to IRE. This treatment uses *reversible* electroporation to transfer cytotoxic drugs into the cells. Electrochemotherapy has been used on colorectal liver metastases with some promising results (115).

A preclinical study has been performed in rabbits using bleomycin (116) followed by a recently published study on LAPC also using bleomycin and electrochemotherapy (117). This article focused on radiological findings after the treatment, and no reports on survival were provided.

In immunocompromised mice with orthotopic human pancreatic adenocarcinoma, electrochemotherapy led to higher gemcitabine concentrations in the tumours compared to systemic treatment (118).

**Radiofrequency ablation**

Radiofrequency ablation (RF) is a tumour treatment with needles that generates heat by means of RF waves. The temperature should be between 50°C and 100°C within the area to be treated (119).

In 2000 after treating 20 patients, Matsui et al. showed that RF may be possible in the pancreas, if the temperature was kept at 50°C. They used a laparotomy to place the needles and had 2 fatalities due to intestinal bleeding and sepsis (120). After this study, another paper reported 2 deaths after RF in the pancreas using a needle temperature of 90°C. These deaths were due to induced severe necrotizing pancreatitis and led to a decline of interest in using RF on pancreatic tumours (121).

Recently a study using percutaneous RF of LAPC in 24 patients was published, with a mean survival of 185 days and no post-procedure complications. In this study, the ablation zone was deliberately kept within the tumour to avoid the nearby vessels (122). Since some of the tumour is left untreated, this process is not likely to be curative but RF may be considered as a palliative procedure for LAPC. However, validating studies are needed.
Microwave ablation
Microwave ablation is another heat-based thermal ablation utilizing micro-waves to generate the heat. Very few articles have been published on microwave ablation in the pancreas. A case series on 15 patients was published in 2007 with minor complications in 6/15 patients (123). Carrafiello et al. reported a series of 10 patients with an overall 1-year survival of 80%. One of the patients in this series developed a pseudoaneurysm in the gastroduodenal artery one month after treatment. Interestingly, five of the patients were treated percutaneously without general anaesthesia (124).

Cryoablation
Cryoablation is also a temperature-based ablation but, instead of heat, it is based on cold. In one study, a series of 49 patients with unresectable pancreatic cancer was treated by cryoablation in conjunction with implantation of $^{125i}$iodine seed (as a combined radiotherapy). Out of the 49 patients, 12 had hepatic metastases; histopathology was missing for 11 patients, and mean 12-month survival was 63.1% (125).

High-intensity focused ultrasound
High-intensity focused ultrasound is a non-invasive ablative method where ultrasound waves are generated extracorporeally to create heat in the pancreas, inducing necrosis. Xiong et al. reported a series of 89 patients (46 with metastatic disease) who were treated with high-intensity focused ultrasound. No severe complications were seen and interestingly 80.6% of the patients with pain prior to the treatment reported pain relief (126). In the future, this may be a treatment option for the alleviation of pain related to pancreatic cancer.

Photodynamic therapy
Tumour necrosis can be achieved by injecting a photosensitizer called verteporfin intravenously and then illuminating the tumour through a needle which emits laser and is placed percutaneously. In a study of 15 patients with LAPC treated with photodynamic therapy, no major complications were seen and in one patient the tumour was reduced from the superior mesenteric artery and an R0 Whipple procedure could be performed (127).
Aims

Paper I
Based on previous animal studies (79-81) of IRE in the pancreas, a phase 1 study was conducted to evaluate the safety of IRE in humans with pancreatic cancer.

Paper II
The aim of Paper II was to further evaluate the safety and efficacy of IRE in LAPC, previously treated with chemotherapy.

Paper III
Paper III evaluated the survival and complication rates after IRE followed by chemotherapy in LAPC.

Paper IV
The aim of Paper IV was to investigate responses in CA 19-9 after IRE treatment and whether these correlated to OS.
Patients and Methods

Paper I

Five patients with pancreatic cancer who were not deemed suitable for resection, either due to comorbidities or locally advanced disease, were recruited for IRE treatment. Prior to being recruited all five were discussed at a multidisciplinary team conference. Prior to treatment, all of the patients had biopsy-proven pancreatic cancer and had undergone a CT of the thorax and chest, which showed no signs of metastatic disease. Also, a contrast-enhanced ultrasound (CEUS) was performed to plan for needle placement. Before IRE, all patients were treated for jaundice. One patient had had a previous laparotomy with curative intent but was deemed unresectable perioperatively. Three patients had LAPC and the remaining two were deemed unfit for pancreatic surgery or chemotherapy. The maximum American Society of Anesthesiologists’ score was 30, as shown in Table 7.

The IRE treatment was conducted under general anaesthesia with deep muscle relaxation (see Figure 10). All needles were placed by the same radiologist under US guidance. The active part of the needle was 1.5 cm and the maximum distance between the needles was 2 cm. Since an active length of 1.5 cm and a maximum distance of 2 cm yields an approximate ablation zone of 3x3 cm with a depth of 2 cm, we had to replace or pull back the needles several times to fully cover the tumours with the planned safety margin of 0.5 cm. A total of 90 pulses were given. The V/cm was adjusted after the first test pulses to give a resulting current of 30-50 amperes.
We used the NanoKnife equipment from AngioDynamics (see Figure 11). After IRE treatment, the patients underwent a CEUS and were observed for at least 3 days before discharge. We used the Dindo-Clavien scale to define complications, and those of grade 3 or higher were deemed severe (128). After discharge, the patients had a follow-up CEUS. Biochemical analyses were performed after 1 month, followed by CT of the thorax and abdomen, CEUS and new biochemistry every three months until death or clear signs of progressive disease.
Table 7. Patient characteristics before treatment with irreversible electroporation.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72</td>
<td>65</td>
<td>89</td>
<td>46</td>
<td>65</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Tumour size (mm)</td>
<td>20x20x20</td>
<td>35x30x40</td>
<td>10x15x20</td>
<td>25x30x35</td>
<td>35x35x35</td>
</tr>
<tr>
<td>Preoperative CA 19-9 (U/ml)</td>
<td>360</td>
<td>1.0</td>
<td>413</td>
<td>38.7</td>
<td>4 916</td>
</tr>
<tr>
<td>ASA score</td>
<td>30</td>
<td>30</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Previous ERCP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Previous PTC</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>
Paper II

We recruited 24 patients with biopsy-proven LAPC for this study, three of whom were also included in Paper I. Fourteen patients received only chemotherapy; three received up-front radiochemotherapy, and seven patients received induction chemotherapy followed by radiochemotherapy before study inclusion. After the chemotherapy/radiochemotherapy, all cases were discussed at a multidisciplinary team conference and still deemed unresectable. Five patients had previously had a laparotomy with curative intent, but were deemed too locally advanced perioperatively. See Table 8. We used the same machine, protocol and post treatment surveillance for the IRE treatment as described for paper I.
Table 8. Patient characteristics before treatment with irreversible electroporation in Paper II.

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Tumour-localisation</th>
<th>Tumour size at time of IRE (cm)</th>
<th>Chemo-therapy</th>
<th>Radio-chemo-therapy</th>
<th>Surgical exploration before IRE</th>
</tr>
</thead>
<tbody>
<tr>
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<td>3.0 x3.5 x2.5</td>
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</table>
Paper III

We planned to recruit 25 patients with biopsy-proven LAPC. The diagnosis of LAPC was determined either radiologically or perioperatively. We used the same protocol for the IRE treatment and post-IRE surveillance as described for Papers I and II. Follow-up was performed one month after the IRE treatment. If there were no signs of complications at this stage, chemotherapy was started. A severe complication noted within 30 days of treatment was defined as Dindo-Clavien grade 3 or higher (128).

As a comparison, we extracted survival data from the Swedish National Quality Registry for Pancreatic and Periampullary Cancer for LAPC. As in the study’s IRE group, the diagnosis in the registry could have been made either radiologically or perioperatively.

Paper IV

In this paper, we investigated whether CA 19-9 decreases after IRE treatment, and if there is any correlation to survival. We have treated 71 patients with pancreatic cancer with IRE. The indication was recurrence after attempted curative resection or LAPC either before or after chemotherapy. Of these 71 cases, we excluded patients with missing data, metastatic disease and normal pre-IRE CA 19-9 levels. This left 35 cases to analyze. The patients with normal CA 19-9 were excluded because it is fairly common that a pancreatic cancer does not express CA 19-9 and we wanted to study the effect on an elevated CA 19-9 level, since that if the tumour does not express CA 19-9 at the beginning of the treatment, it seldom does later on. See Table 9.
Table 9. Consortium chart showing the exclusions in Paper IV.

- 71 patients
  - 2 missing data pre-IRE

- 69 patients
  - 14 missing data post-IRE

- 55 patients
  - 10 metastases at 1 month

- 45 patients
  - 10 normal CA 19-9 pre-IRE

- 35 patients
Results

Paper I

No severe complications were found during the first 30 days. However, one patient died from pneumonia on day 32. This patient received chemotherapy 2 weeks after the IRE treatment and his death was presumably related to the chemotherapy rather than the IRE treatment.

The postoperative stay at the hospital was 14 days, mostly because of pain and inflammation. One patient had delayed gastric emptying both before and after the treatment and finally underwent a gastroenteroanastomosis. One case of mild pancreatitis was observed. After 6 months’ follow-up, three patients had died from progressive disease and two were alive with no signs of recurrence. (See Table 10.) One of these patients showed a good radiological response to the treatment and could undergo a PPPD with portal vein resection. (See Figures 12 and 13.) The subsequent histopathological examination showed that the margins were free.
Table 10. Patient characteristics after treatment with irreversible electroporation in Paper I.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated CRP (mg/l)</td>
<td>Yes (190)</td>
<td>No</td>
<td>Yes (225)</td>
<td>No</td>
<td>Yes (316)</td>
</tr>
<tr>
<td>Elevated leukocytes (X10⁶)</td>
<td>Yes (18.6)</td>
<td>No</td>
<td>Yes (23.4)</td>
<td>No</td>
<td>Yes (23.8)</td>
</tr>
<tr>
<td>Elevated amylase</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Postoperative pain</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ablation zone on CEUS (mm)</td>
<td>20x20x20</td>
<td>30x35x35</td>
<td>25x25x25</td>
<td>40x45x42</td>
<td>38x41x40</td>
</tr>
<tr>
<td>Signs of complications on post-operative US</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CA 19-9 (U/ml) One month</td>
<td>579</td>
<td>Not done</td>
<td>160</td>
<td>51.3</td>
<td>5425</td>
</tr>
<tr>
<td>CA 19-9 (U/ml) Three months</td>
<td>Not done</td>
<td>Deceased</td>
<td>348</td>
<td>147</td>
<td>-</td>
</tr>
<tr>
<td>CA 19-9 (U/ml) Six months</td>
<td>Deceased</td>
<td>Deceased</td>
<td>991</td>
<td>23.5</td>
<td>Deceased</td>
</tr>
<tr>
<td>Time to metastasis</td>
<td>1 month</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 months</td>
</tr>
<tr>
<td>Time to local recurrence</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Survival</td>
<td>108 days</td>
<td>32 days</td>
<td>Alive after six months</td>
<td>Alive after six months</td>
<td>138 days</td>
</tr>
</tbody>
</table>


Figure 12. Before IRE treatment with an advanced tumour in the pancreas.

Figure 13. The same patient as in figure 12 after IRE treatment with the tumour downsised.
Paper II

With regards to safety, there was no mortality within 30 days. As stated above, one patient died after 32 days (not 34 days as stated in the paper) from pneumonia.

Minor complications was seen in 8/24 patients with infection being the dominant one (n=5). Portal vein thrombosis (n=2) and pancreatitis (n=2) were also seen. Three patients had serious complications. One had a superior mesenteric vein thrombosis with bleeding into the bowel from the ablation, which was treated with portography and a stent. The second patient had an ulcer that was present before the IRE treatment, but started to bleed and was treated with both endoscopy and angiographic embolisation. The third patient was also in Paper I and needed a gastroenteroanastomosis.

Local progression was noted in 14 patients with a median time of 6.1 months and metastatic disease in 13 patients after 2.7 months.

The median overall survival was 17.9 months after diagnosis and 7.0 months after IRE treatment. (See Figures 14 and 15.) The individual results for Paper II are shown in Table 11. As in Paper I, an R0-resection was achieved in one patient, and in another abdominal exploration for a planned resection due to presumed effective downsising, peritoneal carcinoma was found at the time of surgery.
Figure 14. A Kaplan-Meier curve showing the overall survival for the patients in Paper II after the diagnosis of LAPC.

Figure 15. A Kaplan-Meier curve showing the overall survival for the patients in Paper II after IRE.
Table 11. Results after IRE for the patients in Paper II (at the time of submission).

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Days at hospital post IRE</th>
<th>Survival after diagnosis (days)</th>
<th>Survival after treatment (days)</th>
<th>Dindo-Clavien score</th>
<th>Time to local recurrence (days)</th>
<th>Time to metastases (days)</th>
<th>Chemo-therapy after IRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>Male</td>
<td>5</td>
<td>199</td>
<td>34</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>65</td>
<td>Male</td>
<td>65</td>
<td>239</td>
<td>139</td>
<td>3a</td>
<td>47</td>
<td>56</td>
<td>No</td>
</tr>
<tr>
<td>46</td>
<td>Female</td>
<td>4</td>
<td>695</td>
<td>426</td>
<td>1</td>
<td>-</td>
<td>361</td>
<td>No</td>
</tr>
<tr>
<td>71</td>
<td>Male</td>
<td>16</td>
<td>239</td>
<td>93</td>
<td>2</td>
<td>-</td>
<td>11</td>
<td>Yes</td>
</tr>
<tr>
<td>68</td>
<td>Female</td>
<td>5</td>
<td>557</td>
<td>164</td>
<td>1</td>
<td>148</td>
<td>148</td>
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<tr>
<td>65</td>
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<td>3</td>
<td>643</td>
<td>451</td>
<td>1</td>
<td>207</td>
<td>234</td>
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<tr>
<td>65</td>
<td>Male</td>
<td>4</td>
<td>879</td>
<td>570</td>
<td>1</td>
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<td>-</td>
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<tr>
<td>62</td>
<td>Male</td>
<td>8</td>
<td>491</td>
<td>193</td>
<td>1</td>
<td>101</td>
<td>-</td>
<td>No</td>
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<tr>
<td>61</td>
<td>Female</td>
<td>4</td>
<td>693</td>
<td>427</td>
<td>1</td>
<td>181</td>
<td>-</td>
<td>No</td>
</tr>
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<td>56</td>
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<td>664</td>
<td>531</td>
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<td>344</td>
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<td>54</td>
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<td>375</td>
<td>159</td>
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<td>-</td>
<td>70</td>
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<td>76</td>
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<td>532</td>
<td>286</td>
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<td>188</td>
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<td>77</td>
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<td>401</td>
<td>109</td>
<td>1</td>
<td>-</td>
<td>56</td>
<td>Yes</td>
</tr>
<tr>
<td>66</td>
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<td>6</td>
<td>233</td>
<td>119</td>
<td>1</td>
<td>-</td>
<td>82</td>
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<tr>
<td>66</td>
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<td>3</td>
<td>503</td>
<td>345</td>
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<td>-</td>
<td>97</td>
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</tr>
<tr>
<td>57</td>
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<td>4</td>
<td>589</td>
<td>233</td>
<td>3b</td>
<td>219</td>
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<td>42</td>
<td>Male</td>
<td>6</td>
<td>663</td>
<td>173</td>
<td>2</td>
<td>-</td>
<td>56</td>
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</tr>
<tr>
<td>61</td>
<td>Male</td>
<td>5</td>
<td>321</td>
<td>111</td>
<td>3a</td>
<td>-</td>
<td>29</td>
<td>No</td>
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<tr>
<td>54</td>
<td>Male</td>
<td>5</td>
<td>533</td>
<td>291</td>
<td>2</td>
<td>194</td>
<td>194</td>
<td>No</td>
</tr>
<tr>
<td>65</td>
<td>Female</td>
<td>7</td>
<td>736 (alive)</td>
<td>428 (alive)</td>
<td>2</td>
<td>246</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>76</td>
<td>Female</td>
<td>19</td>
<td>682</td>
<td>259</td>
<td>2</td>
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<td>-</td>
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</tr>
<tr>
<td>61</td>
<td>Male</td>
<td>26</td>
<td>523</td>
<td>109</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>67</td>
<td>Male</td>
<td>3</td>
<td>615 (alive)</td>
<td>219 (alive)</td>
<td>1</td>
<td>65</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>68</td>
<td>Female</td>
<td>5</td>
<td>859 (alive)</td>
<td>204 (alive)</td>
<td>1</td>
<td>92</td>
<td>-</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Paper III

Twenty-four patients with biopsy-proven LAPC were recruited (inclusion closed due to increased waiting time in the health organisation). The diagnosis of LAPC was determined radiologically in 16 and perioperatively in eight patients. All patients had been discussed preoperatively in a multidisciplinary team conference before inclusion and were given both oral and written information about the study, according to the ethics permit. For details regarding the patients, see Table 12.

In the comparison group from the Swedish National Quality Registry for Pancreatic and Periampullary Cancer, 299 cases of LAPC was found. Out of these 299, 260 were diagnosed radiologically and the remaining 39 perioperatively. The mean age in our study group and comparison group was 67.6 and 69.3, respectively (p=0.04).

There was no statistical survival advantage in the IRE group (p=0.511). The median survival after the diagnosis was 13.3 in the IRE group and 9.9 in the comparison group, as shown in Figure 16.

Table 12 A summary of the patients in paper III.

<table>
<thead>
<tr>
<th></th>
<th>N or median</th>
<th>% or Q1-Q3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>63</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>68.0</td>
<td>(60.5-74.5)</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Surgical exploration before IRE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>67</td>
</tr>
<tr>
<td>Time from diagnosis to treatment (days)</td>
<td>89</td>
<td>(62-118)</td>
</tr>
<tr>
<td>Location of tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caput</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>Corpus</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Tumor maximal diameter (mm)</td>
<td>35</td>
<td>(30-40)</td>
</tr>
<tr>
<td>Dindo-Clavien score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none or ≤ 2</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>3a</td>
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<td>8</td>
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<td>3b</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hospital Stay (days)</td>
<td>6.0</td>
<td>(4.0-12.5)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>88</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Survival after diagnosis (months)</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Survival after treatment (months)</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
Unfortunately, there were several severe complications in the IRE group. Six patients had a severe complication with one mortality caused by a duodenal perforation and three patients needed a laparotomy; one perforation of the common bile duct and two suspected perforations which could not be found during surgery.

**Paper IV**

We could not detect any decrease in CA 19-9 after the IRE treatment. In fact, the median CA 19-9 was higher after the treatment, 282 U/ml versus 315 U/ml. (See Figure 17.) We also examined the 25% percentile with the best response on CA 19-9 versus the 25% percentile with the worst response regarding OS. The 25% percentiles meant roughly an increase or decrease of 50% from the initial CA 19-9 value. We found an improved OS for the 25% percentile with the highest decrease of CA 19-9 compared to those with the highest increase (13.1 versus 8.1 months respectively, p=0.01). See Figure 18.
Figure 17. Boxplot of the CA 19-9 levels before and after IRE.

Figure 18. Kaplan-Meier curve showing survival for the 25th percentile with best and worst responses in CA 19-9.
Discussion

During the time this thesis was done, the field of IRE in the pancreas has developed. When we started recruiting and treating patients, there had been no IRE studies reported in humans. Therefore, Paper I was a pilot study investigating ultrasound-guided IRE in the human pancreas. After this case series of five patients, we came to the conclusion that IRE in the human pancreas is safe, since we noted no severe complications related to the ablation. This conclusion was supported by some other studies which were published at the same time (89, 90). Obviously, the safety of IRE had to be validated in further studies after these initial steps. Regarding efficacy, we noted that at the 6 month follow-up only two out of five patients were alive and three had died. Further, in one patient the tumour had reduced in size and an R0 resection was possible. In conclusion, we stated that IRE in pancreatic cancer showed promising results regarding efficacy and could possibly be a way to downsize LAPC to offer the opportunity for radical resections, and in a few cases might even lead to curing LAPC. Encouraged by this, we continued to investigate IRE in the human pancreas in Paper II, as an extension of Paper I. Here, we included three out of the five patients in Paper I with LAPC, and an additional 21 LAPC patients. As previously described in Paper I, one patient was R0 resected after the treatment. No further patients in Paper II had an R0 resection, although in one patient the apparent downsizing led to hope for an R0, but unfortunately peritoneal carcinosis was found perioperatively. Nevertheless, for certain LAPC patients, it may be fruitful to use IRE to achieve the chance for RO-resections (89) (97).

In Paper II, local progression was noted after a median of 6.1 months, and metastatic disease appeared after a median of 2.7 months. Unfortunately in the paper it is wrongly stated that the patient that died after 32 days were excluded. Since the patients were not closely followed after recurrence appeared, we are unable to clearly present data on metastases and recurrence in all patients. In these pilot studies, it is difficult to define a local recurrence, since we do not know how the ablation zone in the pancreas after IRE should look. When CT was performed early after the treatment, we saw signs of bubbles in the ablation zone, followed by a hypoechoic appearance. We classified the findings as a local recurrence if the ablation zone began to grow or new contrast-enhancing areas were seen.

In Paper II, survival after the diagnosis and IRE treatment was 17.9 months and 7.0 months, respectively. This seems promising compared to previous
studies which had presented a mean overall survival of 6-10 months after the diagnosis of LAPC. Indeed, our results can be explained by the fact that all patients in Paper II were without metastases at the time of IRE treatment, and the prolonged survival may be explained by a selection bias. However, when compared with the survival in the study on LAPC by Krishan et al. (53) with induction treatment by chemotherapy followed by radiochemotherapy (11.9 months) versus radiochemotherapy alone (8.5 months), patients’ survival in Paper II still seems favourable. The LAPC study by Huguet et al. (52) shows similar results. In this study, induction therapy was compared with radiochemotherapy versus additional chemotherapy, with overall survival of 15.0 and 11.7 months, respectively. When we compare our results with those two studies, improved survival may be due to the IRE treatment, and possibly not only to selection bias.

The other aim of Paper II was to further assess the safety of IRE treatment for LAPC. Eleven of the 24 patients had some form of IRE-related complication within 30 days, but of these only three patients had a serious complication and no mortality was observed. Moreover, of those three patients, it can be argued that two already had signs of the complication before IRE and that the complications were not IRE-related. One of them had an ulcer before the treatment that started to bleed and the other had gastric retention, in fact the last one were part of paper I and not deemed a complication in this paper. In some patients, local infection and thrombosis recurred, which led us to include antibiotic and antithrombotic prophylaxis before IRE. As in all invasive treatment, the risk of complications should be closely considered. We consider a rate of 12.5% for serious complications a reasonable number when treating a disease as severe as LAPC.

The rationale for Paper III was that when pancreatic cancer is considered resectable, upfront surgery with adjuvant chemotherapy is recommended (although neoadjuvant protocols are under investigation). We therefore performed a study where IRE followed by adjuvant chemotherapy in LAPC with the aim of increasing OS, compared to only offering palliative chemotherapy for LAPC. However, we could not prove this hypothesis. The obvious problem with this study is that it is not randomised and not matched. We know that there were exclusion criteria in the IRE group that are not present in the registry group (tumour diameter> 5.0 cm, pacemaker) and that the patients in the registry group were significantly older. Thus, had we been able to demonstrate increased survival in the IRE group, the exclusion criteria could have been the explanation. Further, we noted six severe complications in the IRE group, one of which was fatal. We are unaware of the number of complications in the control group. Indeed, the complications in the IRE group seemed to be related to the treatment, and it is therefore unlikely that they should appear in the control group. There were three patients in the IRE group who did not receive
chemotherapy, even though it was planned, and in two of these, this was related to IRE complications that required intervention.

There were more complications in Paper III than in Paper II, although the treatments were done in the same way by the same interventional radiologist. However, we have not come to the conclusion that the difference between them, i.e. the timing of chemotherapy, is the explanation.

Unlike Papers I and II, there were no cases in Paper III where the CT after ablation indicated that radical surgery was possible, and no attempts for resection were made.

Another weakness of Paper III is that, although the registry group contained 299 patients, we only know in 77 cases whether or not they actually received the planned chemotherapy.

Since we saw several complications and no survival gain, we found no reason to use IRE in this setting. A study similar to Paper III was done by Belfiore et al. and, although the survival was slightly shorter than in Paper III, they concluded that IRE is effective for producing local control.

A way of measuring the effect of treatment on pancreatic cancer is by determining the CA 19-9 levels in serum. In Paper IV we hypothesised that IRE could decrease CA 19-9 levels, but we could not support this hypothesis. The reason for this is unknown, but there are several possible explanations: IRE may not affect the tumour in a way which reduces the CA 19-9 levels or it could be due to micro-metastatic disease not seen on imaging but which is the reason for the pre-IRE elevated CA 19-9 levels. It could also be that in some cases the CA 19-9 levels are elevated by the IRE treatment.

No chemotherapy was given between the pre- and post-ablative CA 19-9 determinations, suggesting that any CA 19-9 changes are not due to chemotherapy.

The fact that some patients had a response in their CA 19-9 implies that CA 19-9 can be used as a prognostic marker after IRE ablation of pancreatic cancer, similar to the effect of surgery and chemotherapy. This implication may have future clinical impact when selecting which patients are suitable for surgical exploration after IRE and chemotherapy.

Where do we stand today? There seems to be little support for upfront IRE on LAPC cases without systemic control, and IRE should only be used on patients who do not show disease progression while on chemotherapy. Results from randomised clinical trials are currently lacking. There is also an ongoing interest in attempting resection of LAPC, including arterial resections (129). An interesting study was performed by Vogel et al., where patients with LAPC (according to the somewhat conservative Dutch definition) received FOLFIRINOX, and those with stable disease underwent a laparotomy with resection if this was found possible. If not, they underwent IRE ablation instead. Improved OS was noted if resection was performed compared to IRE, but an obvious criticism is that those who underwent IRE ablations had more advanced disease. Another noteworthy finding in this study is that those patients
with stable disease who underwent neither surgical resection nor IRE had a similar survival as the group which underwent IRE (130).
Conclusion

Paper I
Ultrasound-guided IRE treatment in humans for pancreatic cancer seems reasonably safe with some promising results regarding efficacy.

Paper II
Ultrasound-guided IRE of LAPC is reasonably safe with further promising results regarding efficacy. A randomized clinical trial is justified.

Paper III
Since we saw no gain in OS and there were several complications, we do not recommend ultrasound-guided percutaneous IRE treatment before chemotherapy.

Paper IV
CA 19-9 did not decrease after IRE treatment. However, those patients who did have a decrease had a better prognosis.
Ongoing studies

1. Irreversible electroporation against local recurrence after pancreatic resections for pancreatic cancer

In this safety study, we are including patients with a local recurrence after pancreatic resection for pancreatic cancer and treating them with IRE. We will investigate the complications according to the Dindo-Clavien scale (128). To our knowledge, this has not been studied before, other than in 1 patient treated in the series by Narayanan et al. (89) We planned to include 10 patients and all are today included. One patient needed a laparotomy after the IRE and pancreatitis was found. Another patient had an occlusion of the hepatic artery followed by another in the superior mesenteric artery and was treated with three angiographic procedures, and unfortunately lived for only 110 days after the IRE procedure. The survival data have not yet been analysed.

2. Simulation of the heat generated around a metallic stent when applying irreversible electroporation

We have previously published a paper describing a case with severe complications after IRE in the presence of a metallic stent in the biliary tract (105). In this patient and in the following correspondence, there was discussion about whether the stent was the reason for the complications or not (131). The manufacturers of the IRE device consider metal close to the ablation zone a contraindication for IRE (132). The planned study is a preclinical numerical simulation (using a so-called finite element method, “FEM”) of the heat generated in and around a metallic stent, using the commercial software Comsol. This parameter study investigates the heat generated in different parts of the tumour, the stent and the bile duct for different tumour and stent parameters and different applied voltage pulses forms. The project will be performed in collaboration with the School of Electrical Engineering at the Royal Institute of Technology (KTH) in Stockholm.
Future perspectives

There is an obvious need for a randomized study on IRE for pancreatic cancer. The CROSSFIRE trial is a Dutch ongoing study comparing the efficacy of chemotherapy and IRE (experimental arm) to that of chemotherapy and radiation (control arm) on LAPC. This study is currently recruiting patients and the estimated primary completion date is May 2019. In both arms, the chemotherapy will be with FOLFIRINOX, a combination of drugs which has shown promising results but with increased side-effects. Moreover, the role of IRE as a marginal enhancement together with resection has not been fully investigated.

A problem with the IRE technique is the placement of the needles, not to get too great a distance between the needles. A solution for this problem would be to use a single needle in the middle of the tumour. Theoretically this is possible and there is an abstract published on the use of this single needle technique on pig liver (133).

Another future perspective that might emerge is treatment with electrochemotherapy, which might make it possible to be more locally aggressive against LAPC and thereby enable radical surgery.
Bakgrund
Pankreascancer är en allvarlig sjukdom med dålig prognos. Det är den fjärde vanligaste orsaken till död i cancer i världen med en 5-årsöverlevnad på 4-7 %. Enda möjligheten till bot är en komplett kirurgisk resektion av tumören. Bland de som genomgår en sådan operation kommer majoriteten att få återfall av sin cancer. Vidare kan de flesta inte bli föremål för operation, antingen på grund av att tumören redan har spridit sig med metastaser eller att den växer för avancerat kring viktiga blodkärl. I dessa fall så är det i huvudsak bromsande cellgifter som står tillbuds.

Så kallad reversibel elektroporation innebär att man sänder elektriska pulsar och får då mikroskopiska hål (porer) i cellmembranet där man sett att passage av bland annat gener kan ske. Dessa porer försvinner efteråt. Om man däremot ökar strömmen så kommer inte porerna att försvinna, detta kallas för irreversibel elektroporation (IRE).

IRE används som en ny lokalbehandling av tumörer och man har sett att den kan skapa celldöd. Effekten av IRE är inte beroende av värmeutveckling för att fungera, vilket en del andra lokalbehandlingar av tumörer är. Likaså så kommer inte effekten att minskas av att det går stora blodkärl i närheten, vilka kan fungera som en kylare.

Då IRE fungerar trots att det finns stora blodkärl i närheten och överväxt på blodkärl är en vanlig orsak till att det inte går att operera pankreascancer så ter sig IRE lämplig som behandling av lokalt avancerad pankreas cancer och det är den behandlingen som denna avhandling handlar om.

Delarbete I
I det första delarbetet som är en pilotstudie så har vi fokuserat på säkerheten av behandlingen. Då vi började delarbete I fanns det några få djurstudier (gris och mus) på IRE av pankreas men inga studier på behandling med IRE i pankreas på människa. Därför valde vi att börja med att behandla fem patienter med pankreascancer som inte var aktuella för operation och inte hade spridd sjukdom. Av dessa fem var tre lokalt avancerade och de andra två var inte operabla av andra orsaker. Alla behandlingar gjordes i narkos och likstömspulsarna levererades mellan nålar. Dessa nålar stoppades in via huden med hjälp av ultraljud för att se att de hamnade rätt. Nålarna kopplades till en maskin som är gjord för att ge IRE-behandlingar.
Vi fann då vi gick igenom våra resultat att ingen av patienterna hade dött av behandlingen och att ingen hade allvarliga biverkningar. Vidare så hade en av de fem svarat så bra på behandlingen att det var möjligt att gå vidare till operation och plocka bort tumören.

**Delarbete II**
I nästa delarbete så inkluderade vi tre av de ursprungliga fem och behandlade ytterligare 21 patienter med lokalt avancerad pankreascancer. De behandlades på samma sätt som i det första delarbetet med ultraljudsledd IRE i narkos. Alla dessa 24 patienter hade innan behandlingen fått cellgifter och ingen av dem hade tecken till spridd sjukdom med metastaser. Efter behandlingen hade åtta patienter hade mindre komplikationer och tre hade större komplikationer men inga dödsfall. Förutom den patienten i delarbete I som vi kunde operera var det en patient till som gick till kirurgi, men då vi öppnade buken hittades metastaser på bukhinnan och vi fick avbryta. Efter behandlingen fick de flesta återfall av sin sjukdom och de levde i median i 17.9 månader efter sin pankreascancerdiagnos, vilket då vi jämförde med andra studier med liknande patienter antydde en överlevnadsvinst även om den inte är säkerställd.

**Delarbete III**

**Delarbete IV**

Sammanfattning

IRE kan ges till människa med pankreascancer.

IRE för de med stabil sjukdom kan möjligt förlänga livet.

IRE kan i något enstaka fall leda till att tumören krymper så att den går att operera bort.

IRE innan cellgifter har getts gav ingen överlevnadsvinst men däremot en del komplikationer.

CA 19-9 kan användas efter IRE-behandling för att bedöma prognosen.
I want to express my sincere gratitude to the following people, whose help has been invaluable.

Main supervisor, residency supervisor and mentor in pancreatic surgery, Britt-Marie Karlson. “Get into the vascular sheath!”.

Co-supervisor and Head of the Department of Surgical Sciences, Uppsala University, Per Hellman.

Co-supervisor, Anders Nilsson.

Co-author and unofficial Co-supervisor, Peter Nygren.

Co-author and brother, Daniel Månsson.

Friend, co-author and brother-in-arms in the RUQ, Jozef Urdzik.

Co-authors, Richard Brahmstaedt and Magnus Bergenfeldt.

My past and current colleagues at the HPB unit, Abhishek Roshan, Agneta Norén, Ann Langerth, Arne Eklund, Bengt Isaksson, Boris Bajic, Christophe Ansorge, Frans Duraj, Maria Johansson, Peter Moberger, Petter Frühling, Stefan Gilg, Stefan Linder and Ulf Haglund.

Former and current Heads of the Department of Surgery, Uppsala University Hospital, Staffan Wollert, Claes Juhlin and Kristiina Kask, and Olle Nilsson, former Head of the Department of Surgical Sciences, Uppsala University, for giving me the opportunity to do the this thesis.

My colleagues with whom I share an office, Olov Norlén, Lana Ghanipour, Linda Adwall and Åsa Collin for all the discussions regarding research, surgery, parenthood and life.

David Edholm, Malin Enblad, Willhelm Graf, Jakob Hedberg, Gustav Linder, Eduardo Sima, Martin Skogar, Magnus Sundbom, for all discussions at the seminars, and Joakim Folkesson for making them possible.
Anders Magnusson for helping me with the figure on the front page.

All who have worked with the National Quality Registry for Pancreatic and Periampullary Cancer.

My parents Laroy and Ingrid Månsson for all support through the years

My good friend Erik Nilsson for being larger than life.

My son Vidar Månsson Cedercrantz and my wife Mirja Cedercrantz for everything.
References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)