Surgical methods in treating pancreatic tumours

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“Improvise, adapt and overcome”

- Clint Eastwood

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ABSTRACT

Background: In patients with pancreatic cancer 15-20% are resectable at the time of diagnosis. Still another 8-20% are found to be unresectable at laparotomy. The optimal intraoperative strategy for this group is not known. Some patients experience early recurrence of the cancer indicating undetected advanced disease at the time of surgery. We need tools to detect these patients, who do not benefit from surgery. Pancreatic surgery is still associated with a high burden of complications, postoperative pancreatic fistula (POPF) being the potentially most harmful. The overall aim of this thesis project was to investigate whether modification of existing surgical techniques and preoperative routines can improve postoperative outcome in patients with pancreatic tumours.
Methods: Paper I was a retrospective study comparing postoperative outcome for patients diagnosed with unresectable periampullary cancer at laparotomy and treated either with endoscopically placed stents on demand or prophylactic double bypass surgery. Paper II was a prospective study where patients treated with PD for suspected periampullary cancer had lymph node (Ln) 8a separately analysed. Tumour status of the lymph node was compared regarding overall survival (OS). Paper III was an RCT randomizing patients planned for DP to stapler division of the pancreas with or without stapler reinforcement, looking at POPF frequency postoperatively. Paper IV is a registry-based study that retrieved data from the Swedish National Pancreatic and Periampullary Cancer Registry to compare two pancreatic reconstructions after PD, pancreatogastrostomy (PG) and pancreatojejunostomy (PJ), regarding POPF development.
Results: Paper I – There were more complications and longer hospital stay in the surgery group compared to the group treated with stent on demand. In addition a prophylactic gastroenteric anastomosis did not prevent future gastric outlet obstruction. Paper II - Tumour growth in Ln8a is associated with a substantial reduction of OS. Paper III – No differences in POPF between the study groups were observed. Paper IV - The PJ group had significantly more clinically relevant POPF and more severe complications than the PG group.
Conclusions: Patients with unresectable periampullary malignancies can safely be managed with endoscopic drainage on demand and with lower morbidity and shorter hospital stay than with surgical prophylactic bypass. Tumour involvement of Ln8a is associated with short OS. Reinforcement of the stapler line in DP does not reduce POPF frequency. PG might to be a safer pancreatic reconstruction than PJ due to less risk of developing clinically relevant POPF.

Keywords: pancreatoduodenectomy, distal pancreatectomy, pancreatogastrostomy, pancreatojejunostomy, postoperative pancreatic fistula, lymph node 8a, palliative surgery

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Sammanfattning på svenska

Bakgrund

Patienter med cancer i bukspottkörteln, eller pankreas, söker vård sent i sjukdomsförloppet eftersom sjukdomen ger få och diffusa symptom från början. Vid diagnostillfället har de flesta av tumörerna hunnit sprida sig och endast 15-20% har möjlighet till bot, vilket sker genom operation. Vid operation finner man i ytterligare 8-20% att tumören spridit sig varvid operation inte ger någon förlängd överlevnad. Vilken handläggning som är bäst för denna patientgrupp är ännu oklart. En grupp opererade patienter återfår sin cancer redan under första året vilket talar för att tumören hade oupptäckt spridning redan vid operationen. Denna patientgrupp har sannolikt inte nytta av operationen och vi saknar idag verktyg för att hitta dem under utredningsfasen. Operationer på bukspottkörteln är, trots uttalade förbättringar de senaste 20 åren, förenade med hög komplikationsrisk vilket kan försena återhämtningen efter operation.

Målsättning

Det övergripande syftet med detta avhandlingsprojekt var att undersöka huruvida modifiering av befintliga kirurgiska tekniker och utredningsrutiner kan förbättra utfallet efter operation för patienter med tumörer i bukspottkörteln.

Metod och Resultat

I delarbete I jämfördes två behandlingsstrategier vid fynd av spridd cancer i samband med operation. På Sahlgrenska Universitetssjukhuset görs förebyggande förbikoppling av tumören, vid samma operationstillfälle, och på Skånes Universitetssjukhus avslutas operationen och förbikoppling görs när symptom uppstår, med hjälp av gastroskopi och s.k. stent från insidan.

Studiegruppen utgjordes av ca 70 patienter från respektive sjukhus. I den opererade gruppen drabbades 67% av komplikationer och 31% i den konservativt behandlade gruppen. Vårdtiden i samband med operationen var också längre i den opererade gruppen, 14 respektive 8 dagar, men behovet av sjukhusvård under resterande livstid skiljde sig inte åt mellan grupperna. Operation gav alltså inte någon fördel framför konservativ behandling men den ger fler komplikationer.

I delarbete II undersöktes tumörförekomst i en av lymfkörtlarna (körtel 8a) vid bukspottkörteln, hos patienter som opererades för misstänkt cancer i bukspottkörteln. Gruppen med tumör i körtel 8a, 16 patienter, jämfördes med gruppen utan tumör i körtel 8a, 71 patienter, avseende överlevnad. Det visade sig att tumörförekomst i körtel 8a var associerat med avsevärt förkortad överlevnadstid.

I delarbete III jämfördes två grupper som opererade bort vänster sida av bukspottkörteln avseende utveckling av bukspottkörtelfistlar efter operationen. Grupperna randomiserades till antingen delning av bukspottkörteln på sedvanligt vis eller med tillägg av ett förstärkningsmaterial vid delningsstället. Förekomst av bukspottkörtelfistlar efter operationen jämfördes och det visade sig inte vara någon skillnad mellan de båda behandlingsgrupperna.

Delarbete IV är en registerstudie med data från det nationella registret för bukspottkörtelcancer. Vid borttagande av högra sidan av bukspottkörteln måste den kvarvarande bukspottkörteln sys till magtarmkanalen. Detta görs oftast till tunntarm (PJ) eller magsäck (PG). Vi jämförde patienter opererade mellan 2010 och 2016 på ovanstående sätt, 1118 patienter med PJ och 567 patienter med PG, avseende förekomst av bukspottkörtelfistlar och andra

komplikationer efter operation. PJ-gruppen hade fler fistlar och andra komplikationer än PG-gruppen.

Slutsatser

- Patienter med upptäckt av cancer som inte kan botas, under operation, kan på ett säkert sätt handläggas med s.k. stentning vid symptom, med färre komplikationer och kortare vårdtid som resultat jämfört med operation.
- Tumörförekomst i Ln8a är associerat med kort förväntad överlevnad.
- Användning av ett förstärkningsmaterial på bukspottkörtelns delningsställe vid vänstersidig bukspottkörteloperation leder inte till färre bukspottkörtelfistlar.
- PG skulle kunna vara en säkrare bukspottkörtelrekonstruktion, efter högersidig bukspottkörteloperation, än PJ på grund av lägre risk att utveckla bukspottkörtelfistlar efter operation.

List of papers

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

I. Williamsson, C., Wennerblom, J., Tingstedt, B., Jönsson, C. A wait-and-see strategy with subsequent self-expanding metal stent on demand is superior to prophylactic bypass surgery for unresectable periampullary cancer. HPB: the official journal of the International Hepato Pancreato Biliary Association 2015; 18: 107-112.

II. Wennerblom, J., Saksena, P., Jönsson, C., Thune, A. Lymph node 8a as a prognostic marker for poorer prognosis in pancreatic and periampullary carcinoma. Scandinavian Journal of Gastroenterology 2017; 2: 225-230.

III. Wennerblom, J., Zeeshan, A., Björnsson, B., Tingstedt, B., Jönsson, C., Ansorge, C., Blomberg, J., Del Chiaro, M. Closure of the pancreatic remnant with staple reinforcement fails to reduce postoperative pancreatic fistula (POPF) compared with standard staple technique after distal pancreatectomy: Result from a multicentre prospective randomized trial. Submitted 2018

IV. Wennerblom, J., Williamsson, C., Gasslander, T., Thune, A., Tingstedt, B., Jönsson, C. Pancreatogastrostomy results in less anastomotic leakage than pancreatojejunostomy – a Swedish register-based study. In manuscript 2018

Content

Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BRCA2	Breast Cancer 2 Gene
CR-POPF	Clinically relevant postoperative pancreatic fistula
CT	Computed tomography
DGE	Delayed gastric emptying
DoB	Double Bypass
DP	Distal Pancreatectomy
EUS	Endoscopic Ultrasound
GE	Gastroenteric anastomosis
GOO	Gastric Outlet Obstruction
IPMN	Intraductal papillary mucinous neoplasia
ISGPF	International study group of pancreatic fistulas
ISGPS	International study group of pancreatic surgery
ITT	Intention to treat
JPS	Japan Pancreas Society

Ln	Lymph node
LOS	Length of stay
MCN	Magnetic resonance Imaging
MRI	Magnetic resonance Imaging
OS	Overall Survival
PALB2	Partner And Localizer of BRCA2
PD	Pancreatoduodenectomy
PDAC	Pancreatic ductal adenocarcinoma
PG	Pancreatogastrostomy
PJ	Pancreatojejunostomy
POD	Postoperative Day
POPF	Postoperative pancreatic fistula
PPH	Postoperative pancreatic hemorrhage
PPPD	Pylorus Preserving pancreatoduodenectomy
RCT	Randomized Controlled Study
SEMS	Self Expanding Metal Stent
SNPPCR	the Swedish National Pancreatic and Periampullary Cancer Registry

TNM	Tumour Node Metastasis
UICC	the Union for International Cancer Control
WaS	Wait and See

1 Introduction

The pancreas is a gland, situated in the upper abdomen that consists of both endocrine cells, forming the islets of Langerhans, and exocrine cells, forming acini. The endocrine cells secrete the hormone insulin, necessary in carbohydrate (sugar) metabolism, into the blood circulation. The exocrine cells discharge digestive enzymes and bicarbonate into the gut.

Some of the most common diseases in the pancreas are acute or chronic inflammation (pancreatitis), diabetes and tumours[2]. The most common malignant tumour is pancreatic cancer (cancer in the exocrine cells) which is one of the most deadly cancers known. It constitutes 2% of the yearly incidence of cancer but is the fourth most common cause of cancer-related death in economically developed countries [3 4].

Symptoms of pancreatic cancer are initially vague and unspecific, and this contributes to a delayed diagnosis. Cardinal signs are unexplained weight loss, abdominal pain, sometimes radiating to the back, and jaundice[5, 6]. A first episode of pancreatitis or recent onset of diabetes can also signal development of a pancreatic cancer[7].

Surgery is the only potentially curative treatment for pancreatic cancer but unfortunately, only ≈20% of patients are considered resectable after work-up. Even when the patient is treated with surgery, and adjuvant chemotherapy, the five-year survival is poor (14-26%)[8, 9 10, 11] with a median survival time of only 14-22 months[12-14].

My thesis project was undertaken to elucidate various aspects of surgical approaches to tumours of the pancreas in order to improve work-up and

selection of patients taken to surgery, to reduce postoperative complications and thereby improve recovery.

The description of surgical methods in this thesis, curative resections and palliative operations, refers to patients with suspected pancreatic or periampullary cancer or other lesions in need of resection.

1.1 Historical perspective of pancreatic cancer surgery

In 1898 Codivilla, an Italian surgeon, performed the first pancreatoduodenectomy (PD), although the patient died after 18 days. The Swedish surgeon Dahl later performed the first Roux-en-Y choledocojejunostomy in 1908. The first successful regional resection of the head of the pancreas was performed by Kausch, a German surgeon, in 1909 and was reported in 1912. The operative procedure of pancreatoduodenectomy was further developed in the 1930s by the American surgeon Whipple. It was initially a two-stage operation, where the first operation was performed to relieve jaundice and thereby restore coagulation and fat digestion, with a cholecystogastrostomy. The pancreatoduodenectomy was done some weeks later with duodenoduodenostomy and pancreatic exclusion[15]. The procedure was developed into a one-stage operation in 1941, now with a choledocojejunostomy[16]. This development was facilitated by the discovery of and preoperative treatment with vitamin K and bile salts. It was not until the 1950s that the pancreatoenteric anastomosis became routine[10]. Whipple performed 37 procedures during his career[17]. During the 1950s and 1960s, extending into the 1970s, pancreatoduodenectomy did not become popular as a treatment modality because of the high mortality of about 25%[18-20]. The development of high volume centres came in the 1980s and 1990s, and mortality has gradually dropped to the present 3-5%[21].

1.2 Pancreatic and periampullary carcinoma

Pancreatic ductal adenocarcinoma (PDAC), often just called pancreatic cancer, comprises approximately 80% of cancers in the pancreas (Table 1). The periampullary region is situated in the head of the pancreas, where the intrapancreatic bileduct, the distal pancreatic main duct, the ampulla (of Vater) and the second portion of the duodenum join together anatomically. Tumours arising in this area, within 2 cm of the major papilla, are called periampullary cancers[22]. Although these tumours have different origins, it is difficult to tell them apart preoperatively and their proximity within that confined region generally dictates a common operative approach. The most common of the four is PDAC (Table 1).

1.2.1 Other malignant and premalignant lesions of the pancreas

The second most common solid tumour in the pancreas after PDAC (incidence in Sweden ≈2%, see Table 1) is the neuroendocrine tumour (PanNET) which is malignant but less aggressive than pancreatic adenocarcinoma, with a ten-year survival rate of 45%[7]. Localized disease is often treated with surgery whereas systemic treatment is the choice when metastases are present[23, 24].

The cystic neoplasms of the pancreas are intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), solid pseudo papillary neoplasm (SPN) and serous cystic neoplasm (SCN). In main-duct IPMN 45% harbour an invasive component, whereas in side-branch IPMN 25% progress to at least high-grade dysplasia and 17% have at least some invasive

component[25]. MCN has an estimated risk of malignancy of 10-50%[26]. SPN is a low-grade malignant neoplasm, curatively treated with surgery[27] and SCN is almost always benign[28].

1.2.2 Epidemiology

In Sweden approximately 1500 patients/year are diagnosed with pancreatic or periampullary cancer, with pancreatic cancer of the head being the most common (Table 1). Of these 20-25% are considered to have curable disease, meaning no distant metastases and no locally advanced tumour growth, whereas 50% have distant metastases[29, 30].

Table 1. Pancreatic and periampullary tumours reported in 2016 to the Swedish Cancer Registry [31]. n (%).

	2016
Malignant tumours Pancreas	1413 (78.2)
Caput (head)	716 (39.6)
Corpus (body)	213 (12.8)
Cauda (tail)	174 (9.6)
Other location	292 (16.2)
Extrahepatic bileduct	157 (8.7)
Duodenum	104 (5.8)
Ampulla of Vater (papilla)	91 (5.0)
Pancreatic Neuroendocrine tumours	42 (2.3)
Total	1807 (100)

1.2.3 Aetiology

Risk factors for pancreatic cancer can be divided into hereditary and non-hereditary ones. Among the latter increasing age is the strongest risk factor followed by smoking, with a more than two-fold increased risk for current smokers[32]. Long-standing type 2 diabetes has a 1.5-fold increased risk of

pancreatic cancer whereas recent-onset diabetes may be a sign of pancreatic cancer[33, 34]. Other known risk factors are obesity[35], heavy alcohol consumption[36] and chronic pancreatitis[37]. Recent pancreatitis may instead be a sign of undetected pancreatic neoplasm[7].

Hereditary pancreatic cancer consists of cancer susceptibility syndromes, where mutations are known and often associated with several kinds of cancer (e.g. BRCA2, PALB2, and others), and in families with two or more pancreatic cancers in first-degree relatives, without known mutations[38]. The latter make up at least 3% of the pancreatic cancers[39, 40].

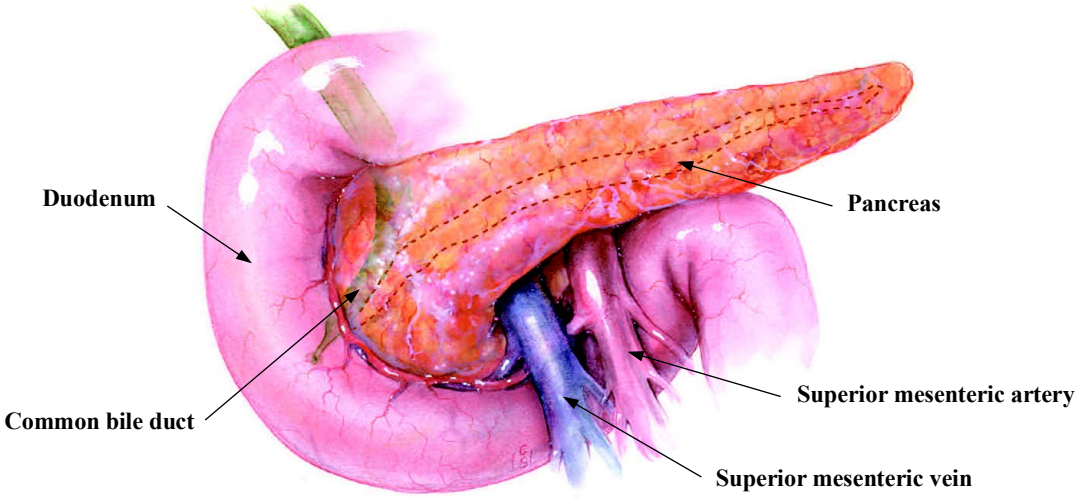

Figure 1. Pancreas and the periampullary region. Reprinted with permission, © Corinne Sandone, Johns Hopkins University.

1.2.4 Diagnosis and staging

In patients with an acute onset of symptoms, such as discovery of jaundice, radiological diagnostics often starts with an abdominal ultrasound, with a sensitivity of 50-90%[41, 42]. However, once there is a strong suspicion of

pancreatic cancer the preferred work-up is abdominal computed tomography (CT) with pancreas protocol, meaning intravenous and oral contrast and series taken before contrast and during arterial and venous phase separately. This will give information about the tumour, venous and arterial engagement, and signs of distant tumour engagement[42]. Pancreatic cancer primarily metastasizes to the liver, abdomen and the lungs[43]. To detect possible pulmonary metastases the work-up is completed with a thoracic CT. In spite of high quality imaging, metastatic disease is found during laparotomy in at least 16% of patients deemed resectable[31, 44].

In selected cases, further information can be retrieved from magnetic resonance imaging (MRI) e.g. evaluation of unclear tumours, cystic lesions or the pancreatic duct, suspected small metastases in the liver or peritoneal carcinomatosis[42, 45, 46]. In addition, endoscopic ultrasound (EUS) can add to differential diagnostics of unclear tumours and fine needle aspiration or biopsy for histopathology. Positron Emission Tomography (PET) has been extensively evaluated as a diagnostic tool but so far not exceeded CT in accurately separating benign or advanced malignant pancreatic disease from resectable pancreatic cancer[47]. There are no reliable tumour markers for pancreatic cancer to be used as screening tools, but the carbohydrate antigen 19-9 (CA19-9) can be used to monitor treatment response[48].

The tumour can now be staged according to the TNM classification [49] and evaluated regarding resectability[50]. The performance status of the patient determines operability. All this together will result in a treatment recommendation preferably decided in a multidisciplinary treatment board, as recommended by many authors[51, 52].

Unfortunately, the current radiologic work-up has a low sensitivity in diagnosing metastatic lymph node engagement[53]. Furthermore, this is hard to

diagnose even macroscopically, during surgery[54]. Pathologic engagement of Ln's is possibly better addressed with a biopsy or frozen section.

1.2.5 Treatment

Surgery

Pancreatoduodenectomy

Patients with a resectable tumour (no metastases, no or <180° venous engagement of the portal/superior mesenteric veins, no arterial engagement) of the head and uncinate process of the pancreas are treated with a pancreatoduodenectomy (PD) including resection of the extra hepatic bile ducts and gallbladder, duodenum, distal stomach and the pancreatic head. This procedure is also called a Kausch-Whipple operation[55].

An alternative resection is to spare the stomach and perform a pylorus preserving PD (PPPD) with division of the duodenum distal to the pylorus.

Figure 2. Pancreatoduodenectomy, here pylorus preserving. Reprinted with permission, © Corinne Sandone, Johns Hopkins University

The outcome for these two operations is equivalent[56] (Figure 2).

Regional lymph nodes (Lns) are resected en bloc, as defined by the International Study Group on Pancreatic Surgery (ISGPS)[11].

On reconstruction, the continuity is re-established with three anastomoses: hepaticojejunostomy (end-to-side), gastro or duodenojejunostomy (depending on resection with PD or PPPD), and pancreatic anastomosis to either the jejunum (pancreatojejunostomy, PJ) or the stomach (pancreatogastrostomy, The prevailing anastomosis worldwide is PJ, 89%, as compared to PG, 10%

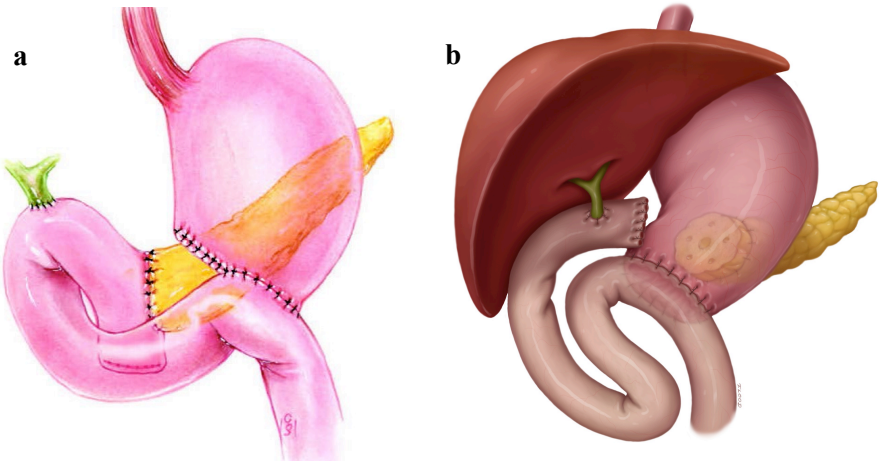

Figure 3. Pancreatic reconstructions, a. pancreatojejunostomy (PJ), b. pancreatogastrostomy (PG). Reprinted with permission, © Corinne Sandone, Johns Hopkins University and © Anders Flood.

(no or other anastomosis 1%)[57]. The many different reconstruction techniques probably reflect the efforts to minimize anastomotic leakage of amylase, a dreaded complication (see below), and the formation of a postoperative pancreatic fistula (POPF)[1]. There are also several modifications within PJ and PG, with the same intention. These are end-to-side/end-to-end, duct-to-mucosa/invagination, one or two-layer anastomosis as well as more advanced versions. The current literature regarding differences in leakage is

contradictory where non-randomized studies[58, 59], randomized controlled trials (RCT's)[60-63] and meta-analyses come up with conflicting results[64, 65]. Even if the ISGPS recently summarized that no major difference exists between the two reconstructions[66] some studies are old, many suffer from small study groups and the heterogeneity between even the randomized trials is substantial[64]. A more robust basis for clinical decision-making is needed and data from well-structured patient registries, with a larger number of patients, could be one way to achieve such knowledge.

Distal Pancreatectomy

Tumours in the body and tail are less common than in other locations in the pancreas (22-32%)[31, 67] and are also to a greater extent unresectable at diagnosis, partly due to late onset of symptoms[68]. If the tumour is found to be resectable (no metastases or major engagement of adjacent organs, no engagement of the celiac trunk) a distal pancreatectomy (DP) is performed, often including a splenectomy en-bloc (Figure 4).

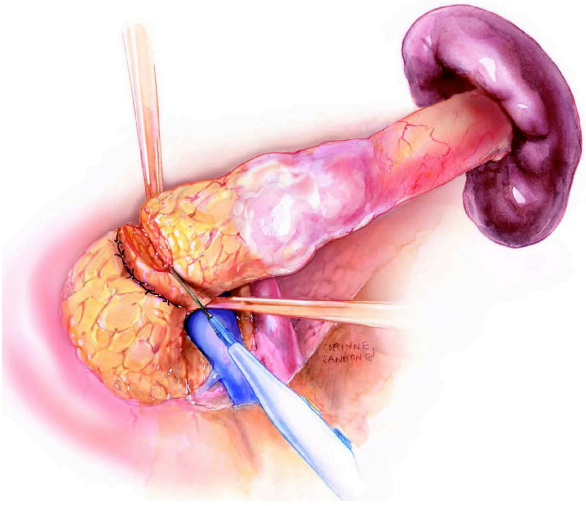

Figure 4. Distal pancreatectomy and splenectomy with division over the portal vein. Reprinted with permission, © Corinne Sandone, Johns Hopkins University

This procedure leaves no anastomoses. Closing the pancreatic remnant with a minimum of POPF development remains a challenge. Since POPF is the most common complication after DP and has the potential to severely delay the recovery after surgery, several methods to minimize leakage have been explored. Examples are absorbable sealant[69, 70] or anatomic flap covering the stump[71], hand-sewn vs. stapled closure of the remnant[72], internal stenting of the pancreatic duct[73], secretion inhibition[74] and anastomosis to the stomach or the jejunum vs. stump closure[75, 76] without significant difference. None of these techniques have so far been proven superior regarding the prevention of POPF[69, 73, 76]. However, mesh reinforcement on the stapler line has also been tried and has shown a significant reduction in POPF[77]. This is an interesting finding that deserves confirmation, and the design of such a trial became, therefore, one aim of the present thesis project (see below).

Lymphadenectomy

Because lymphatic metastases are thought to be a tumour-spreading pattern that is curable by resection, Lns in the proximity of a cancer are resected en-bloc at the time of surgery, to improve survival and furthermore to provide staging of the disease[78, 79]. The presence of Ln metastases, postoperatively examined, is one of the most important prognostic factors in pancreatic cancer[67, 80-82]. Studies of the lymphatic drainage of the head of the pancreas have pointed out primary order nodes; Lns 13 (a and b) and 17 (a and b), that drain to second order nodes, Lns 6, 8 (a and p), 12 (a, b and c) and 14 (a, b, c and d)[79, 83, 84]. This has an impact on the pattern of lymphatic metastases and prognosis. The Ln-stations that should be resected in a PD or DP have varied over time and geographically, where Japan often includes a wider range of Ln-stations compared to Europe and Northern America[85]. The recommendation regarding the extent of Ln dissection by ISGPS includes Ln numbers 5, 6, 8a, 12b1, b2 and c, 13a and b, 14a and b and 17a and b for PD

and numbers 9 (for tumours in the body of the pancreas) 10, 11d and p, and 18 in DP[11, 86] (Figure 5). But are all regional Ln's equally important? There are studies indicating that some regional Ln's (e.g. LN 8a) are associated with short overall survival[87]. The clinical relevance of such a survival-predicting property of the engagement of separate Ln's has, however, so far not been confirmed.

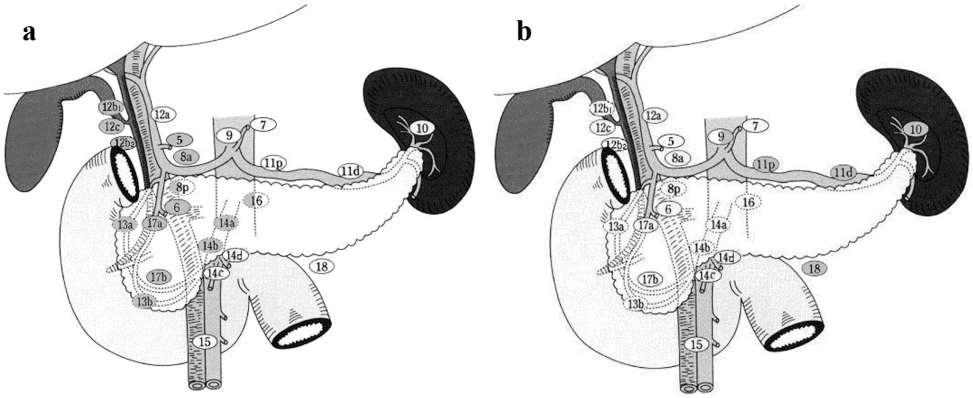

Figure 5. Japan Pancreas Society nomenclature of peripancreatic lymph nodes and the ISGPS recommendation of lymph nodes to resect in a. PD and b. DP. Reprinted with permission, Japan Pancreas Society. Classification of pancreatic carcinoma. 2003.

Postoperative management

Postoperative care after pancreatic surgery varies worldwide. Current trends in postoperative care are dominated by ERAS® (Enhanced Recovery after Surgery) protocols and this concept is now applied in several types of cancer surgery[88]. In recent years, interest in similar systematic postoperative care after PD has gained ground[89]. The concept includes, among other things, epidural analgesia, early mobilization, use of laxatives, earlier removal of nasogastric tube and resumption of oral food intake, most of which are already in use but not strictly defined[90, 91]. Apart from proven benefits to the patients in applying ERAS, it may also lead to an update and possibly a

higher grade of international consensus on what is important in the postoperative care of patients with pancreatic resections[92].

Weight gain and elevation in plasma glucose are controlled for and treated, since they can negatively affect recovery after surgery[93, 94]. Output from abdominal drains is, if used at all, checked for volume and type of content in order to detect signs of leakage from the anastomoses and they are removed if no sign of POPF is present on postoperative day three (POD3)[91]. The need for routine abdominal drain is currently the target of a national Swedish study randomizing between having a drain or not having a drain after PD. A nasogastric tube is often used for the first one to three days and oral feeding is then gradually started[91].

Surgical Complications

Overall postoperative results have improved considerably regarding both mortality and morbidity over the last 30 years[21]. Morbidity, however, still remains high with figures from 45-69%[21, 95-97]. The potentially most harmful complication after PD is POPF whereas the most frequent complications are delayed gastric emptying (DGE), wound infections and intra-abdominal abscesses.

DGE consists of gastric paralysis without mechanical obstruction, and has been defined by ISGPS[98]. It is an innocuous complication in itself but can be a sign of more severe complications[99] and markedly affects patient quality of life, recovery and length of hospital stay[98, 100, 101]. It occurs in 14-44%[102 21, 100, 101, 103] after pancreatic surgery. POPF and infections dominate in DP[21, 102, 104].

Specific postpancreatectomy hemorrhage (PPH) is also defined and classified by ISGPS[105] according to time of onset (early/late), location (intra/extra

luminal) and severity. The incidence is 1-10%, the occurrence intimately linked to POPF and mortality is high, especially in late hemorrhage[106, 107].

The ISGPS seeks to create a uniform and universally accepted description and classification of postpancreatectomy complications (DGE, PPH, and POPF) that will facilitate international comparisons of research reports.

POPF

This is the potentially most harmful complication after pancreatic surgery and deserves some extra attention. It may promote intra-abdominal tissue damage, DGE, abdominal abscesses or sepsis and bleeding from central abdominal arteries in the region, e.g. the common hepatic artery, as a result. This can cause longer hospital stay, increased costs, delayed recovery and mortality[103, 108]. DP was previously considered a minor operation but is now recognized as having high morbidity dominated by POPF[109, 110]. The uniform definition of POPF, based on clinical presentation and graded A to C, was published by ISGPF (International Study Group for Pancreatic Fistulas) in 2004 and was revised and updated in 2017[1, 111] (Figure 6). The incidence of clinically relevant POPF (CR-POPF), B and C fistulas, is 12-14% in most series[97, 112, 113 103].

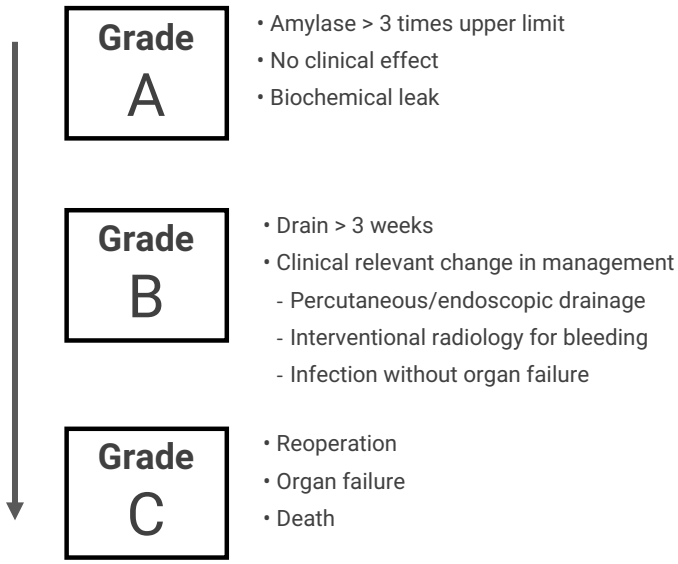

Figure 6. Postoperative pancreatic fistula grading, according to the ISGPF[1].

Many risk factors for developing a CR-POPF are reported in the literature[108] and some of the most accepted are non-dilated pancreatic duct and soft/normal pancreatic texture[103, 112, 113], high body mass index (BMI)[114], intraoperative blood loss[115], long operating time[116] and high-risk pathology, such as ampullary, duodenal and cystic malignancies[110, 112, 113, 115, 116]. The secretion inhibitor somatostatin (and analogues) has been tested to prevent POPF but studies show conflicting results where a Cochrane review recommends the use of somatostatin analogues[117] and the ISGPF states that it may have a role in high-risk patients but not otherwise[66].

Perioperatively discovered unresectable disease

In patients planned for curative surgery, 8-20% are diagnosed during the operation with previously undetected, locally advanced or metastasized disease, precluding resection and cure[118, 119]. With a life expectancy of three to 11 months[13, 120] it is of major importance to provide the best quality of life during patients' short remaining lifetime. Previous studies have shown that

75% will develop biliary obstruction and up to 25% will develop gastric outlet obstruction (GOO)[121, 122] and recommend prophylactic gastric by-pass with a concomitant biliary bypass since this procedure prevents recurrent obstruction and mortality and morbidity do not increase[123, 124](Figure 7).

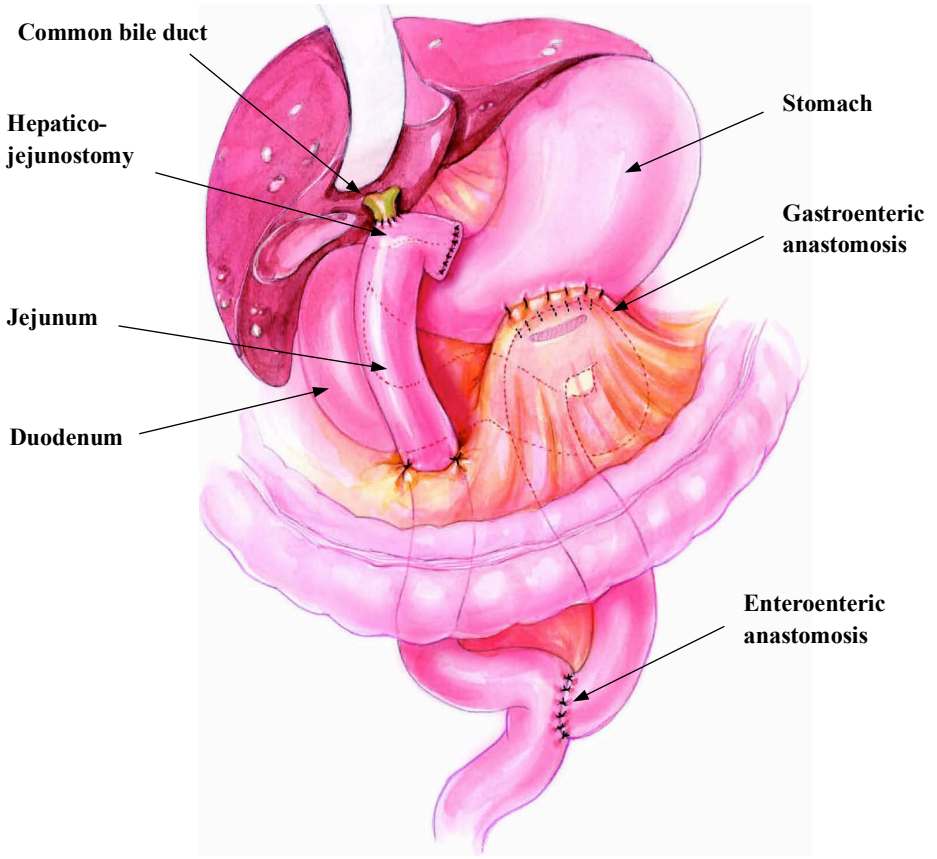

Figure 7. Palliative double bypass with hepaticojejunostomy, gastroenteric anastomosis and enteroenteric anastomosis. Reprinted with permission, © Corinne Sandone, Johns Hopkins University

Critics of this strategy claim that 98% of these patients could be handled without surgery[125]. Since then we have seen the development of self-expanding metallic stents (SEMS) and there are studies that indicate similar reintervention frequency and number of in-hospital days prior to death,

regardless of the initial procedure (surgical bypass or endoscopic stenting)[126] and an indication that prophylactic duodenal bypass does not protect from future GOO (Spanheimer-14).

Palliation by non-surgical techniques is standardized practice when unresectable cancer is found during work-up. The double bypass procedure has a morbidity and mortality rate of 31–56% and 0–5%, respectively, and can decrease the likelihood of receiving systemic treatment[123, 124, 126-130]. Considering that not all patients will develop biliary or gastric obstruction, a bypass may even be unnecessary.

As mentioned before, 75% of pancreatic cancers develop biliary obstruction with symptomatic jaundice. Recent studies have shown that biliary SEMS are superior to plastic stents regarding dysfunction frequency, complication rate, quality of life, patency, need for reintervention and even survival, at the same cost[131-133]. Duodenal SEMS, used in treating patients with advanced disease, are today a safe and effective alternative to surgical bypass with at least as good quality of life as surgery, and shorter length of stay and time to chemotherapy[134-137]. As of today, no trial exists that directly compares endoscopic SEMS for both biliary and duodenal obstruction with prophylactic double bypass surgery.

Oncology

Adjuvant chemotherapy

Adjuvant chemotherapy with gemcitabine or fluorouracil, for six months after surgery, has a significant survival benefit as compared to no chemotherapy (5% vs. 21% five-year survival) in patients resected for pancreatic and periampullary cancer[138-140]. Furthermore, very recently published data show the superiority of a combination of gemcitabine and

capecitabine, as compared to only gemcitabine, in pancreatic cancer (28.8% vs. 16.3% five-year survival) and this treatment is now recommended as first-line[141].

Palliative chemotherapy

In reasonably fit patients (ASA classification ≤2) with pancreatic cancer, preferably with locally advanced, and not metastatic, pancreatic and periampullary cancer, chemotherapy should be offered after an initial discussion in a multidisciplinary board[142]. In locally advanced pancreatic cancer, the addition of chemoradiotherapy or erlotinib to gemcitabine treatment has not shown improved survival[143, 144]. Although in metastatic pancreatic cancer several small studies using combination therapy with two to three drugs have not shown a better effect[145]. In 2013, Von Hoff et al. showed a 1.8 month longer survival with the addition of nab-paclitaxel, at the cost of increased toxicity[146]. Due to this toxicity and the frailty of patients with pancreatic cancer, monotherapy is currently recommended, with gemcitabine, fluorouracil or capecitabine, or participation in a clinical drug trial [147].

Prognosis

There are several tools to prognosticate in cancer disease and for solid tumours the TNM staging system, developed and maintained by The Union for International Cancer Control (UICC), is one of the most frequently used[148]. It relies on anatomical extent of the tumour growth, where T stands for size of the tumour, N describes spread to regional lymph Nodes and M stands for distant metastases. These three (TNM) put together give a stage that correlates to prognosis.

In pancreatic cancer, even among patients who undergo tumour resection, recurrence rates are high and long-term survival is scarce. Why is this? There

are studies on mutations in pancreatic cancers, using mathematical models, showing that the development of a cancer takes ten to 20 years to develop from the initiation of tumorigenesis in a cell into a metastatic cancer[149]. In this model the vast majority of patients are diagnosed in the phase where the tumour cells have acquired the ability to metastasize. Various tumour-related factors have been identified as predictors of survival, in addition to the TNM system, after potentially curative resection. These factors include tumour size, lymph node disease, tumour grade and vascular invasion[150].

On diagnosis, 50-60% have distant metastases, up to a third have borderline resectable or locally advanced disease (some resectable with neoadjuvant treatment and some not) and 15-20% are potentially curable[151-153]. For the entire group, including non-resectable stages, the five-year survival is 6-8% and the median survival 25 months[31, 154] whereas the median survival in locally advanced cancer is six to 11 months and in metastatic disease three to six months[13, 120]. After surgery and adjuvant chemotherapy, the five-year survival is 14-26%[8, 9, 11, 155], the median survival time is 14-22 months[12-14] and, looking at the subgroups of periampullary cancer, extrahepatic bileduct cancer has a five-year survival of 25% and a median survival of 29 months[11, 21] ampullary cancer 44-48% and 29-36 months[11, 14] and duodenal cancer 48-73% five-year survival[11, 21].

There are several known prognostic factors of survival where some of the most important are age[156], tumour stage[156], tumour size[157, 158], resection margins[11, 156], number of metastatic Lns[67, 159, 160] and Ln ratio (metastatic/total number Lns resected)[11, 156]. These factors are not accessible preoperatively and can therefore not be used in treatment decision-making. Interest has been drawn to the location of Ln metastasis and its impact on prognosis. Extended Ln resection, including para-aortic Lns, has not conveyed prolonged survival

but possibly increased morbidity[11, 85, 161, 162]. Metastases to second-order Lns are associated with decreased survival[67, 80, 87, 163]. However, metastatic Lns are not readily identified on radiologic imaging and they are not always obvious during surgical dissection[85]. A useful prognostic factor would be one that is assessable before resection, e.g. via diagnostic laparoscopy, when it can be included in staging and the planning of treatment modality.

2 Aims

As mentioned above, there are several knowledge gaps in the field of surgical treatment of pancreatic tumours, and this thesis project focuses on some of them. The overall aim was to investigate whether modification of existing surgical techniques and routines can improve postoperative outcome in patients.

The specific aims were

- to evaluate whether prophylactic surgical double bypass or endoscopic treatment on demand, with stents, is better for patients with perioperatively unresectable periampullary cancer.
- to investigate whether tumour involvement of the regional lymph node 8a is of prognostic importance for overall survival in patients operated with PD for suspected pancreatic and periampullary cancer.
- to analyse whether a biodegradable reinforcement material, of the stapler line on the pancreatic stump after distal pancreatectomy, can reduce the frequency of postoperative pancreatic fistulas.
- to assess whether pancreatogastric anastomosis reduces the postoperative pancreatic fistula rate, after pancreatoduodenectomy, as compared to pancreatojejunal anastomosis.

3 Methodological considerations

3.1 Common definitions and tools

Postoperative complications are graded according to the Clavien Dindo classification[164] where the therapy used to correct a specific complication defines the severity of the complication. The highest rank scored is the one used on a five-grade scale (I-V). This was registered 30 days postoperatively or at discharge.

The ISGPF classifications of POPF[1, 111] and the ISGPS classification of DGE[98] were used in papers I, III and IV.

Ln stations were resected, in PD and DP, as defined by the ISGPS and the JPS[11, 86, 165].

Postoperative day 1 (POD1) was the first day after surgery.

Postoperative length of stay (LOS) was the total number of in-hospital days after the operation.

Mortality was specified as in-hospital or within 30 days of surgery in papers I, III and IV.

In paper II, deaths were recorded until the last day of follow-up (≥five years).

Collection of data on demographics, histopathology and peri- and postoperative outcome was made from medical records and surgical planning software at the hospitals involved, as described below.

3.2 Paper I

To answer the question in the study reported in Paper I an RCT was started, but it turned out to be difficult to include patients. Thus the study was halted and we searched for an alternative approach. At Sahlgrenska University Hospital, unresectable disease found during surgery was treated with prophylactic double bypass (DoB), hepaticojejunostomy and gastroenterostomy. At Skåne University Hospital, Lund, symptomatic biliary obstruction and/or gastric outlet syndrome (GOO), at the time of surgery, were treated with surgery or endoscopy (with SEMS). Non-symptomatic patients were observed and treated when they exhibited symptoms of biliary obstruction or GOO (Wait-and-See, WaS). This presented us with the alternative of a retrospective cohort study in seeking an answer to the question of which treatment strategy was best for these patients. With this study design, however, causality can not be demonstrated and there is risk of bias, such as missing data or patients lost to follow-up, and confounding, e.g. differences in the demographics of the two groups. The two study groups were also from two different hospitals, potentially adding to difficulties comparing the groups. To minimize this the authors decided on definitions for the different study parameters in a consensus meeting and two of the authors then collected the data from hospitals in the Västra Götaland Region and Region Skåne, one at each hospital.

All patients with interrupted PD, because of locally advanced or metastasized disease, at Sahlgrenska University Hospital and Skåne University Hospital, Lund, between 2004 and 2013, were included. Benign disease and endocrine cancers were excluded. Patients at the two hospitals were compared regarding complications, short and long-term postoperative outcome, including re-interventions and re-admissions due to biliary obstruction and/or GOO,

length of stay and overall survival. The groups were analysed with Intention to Treat (ITT). Endpoints were complications and long-term follow-up.

The differences between the groups were discussed so that the potential effect of this on outcome would at least not lead to an overestimation of results. Regarding the comparison of the two hospitals, no differences in postoperative treatment and outcome have been shown between the two in the yearly reports from the Swedish National Pancreatic and Periampullary Cancer Registry (SNPPCR)[166].

3.3 Paper II

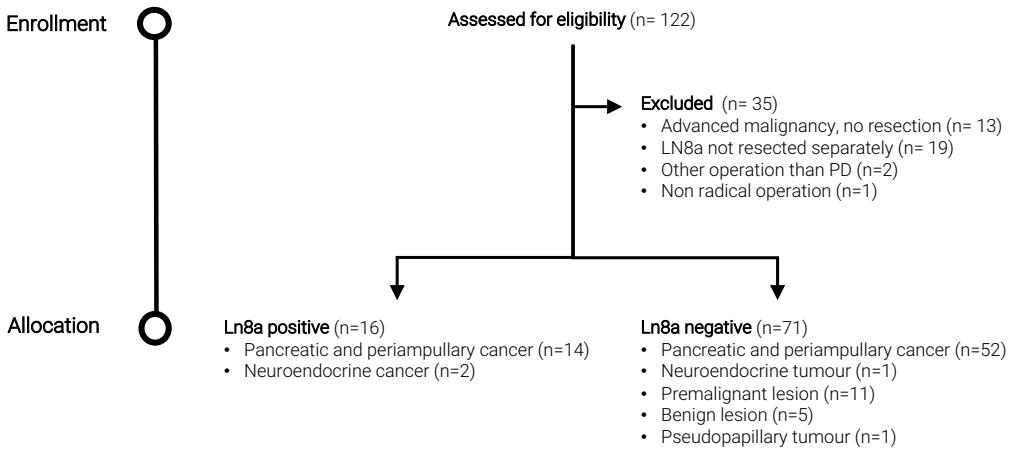

Figure 8. Flow chart on patients in paper II. Ln, lymph node; PD, pancreatoduodenectomy.

In this study we used a prospective cohort study design including patients operated with PD between 2008 and 2011 at Sahlgrenska University Hospital, see the flow chart (Figure 8). Only patients operated with suspicion of malignant disease were included.

A standard PD was performed but Ln8a was resected and sent as a separate specimen to the Pathology Department, where it was stained according to routine (haematoxylin and eosin) to find metastases and analysed with immunohistochemistry to detect micro-metastases. The two groups were defined by tumour status in Ln8a, noted as + or – for tumour growth, and compared. A survival analysis was performed comparing the two groups. The adenocarcinomas were then analysed separately, looking for independent predictors of short survival, with uni and multivariate analysis.

The primary endpoint was overall survival (OS) according to the tumour status of Ln8a.

Since the exposure is relatively uncommon (Ln8a+) we both had few numbers and skewed group sizes to work with. We used statistical methods allowing for this and the outcome of the study is clearly significant. To check for bias with regard to the excluded group, their demographics were analysed and were not found to differ from the study group.

3.4 Paper III

A multicentre RCT design was used, randomizing patients planned for DP from 2014 to 2016 to stapler division of the pancreas with or without a biodegradable reinforcement material (Biodesign® Staple Line Reinforcement, COOK® Medical). A power calculation was made on a previously observed POPF frequency of 25% and an expected reduction of 20% of the POPF rate in the intervention group. To detect this, 100 patients, 50 in each arm, were needed (Figure 9). The randomization was carried out using opaque envelops in bundles of ten at each centre, drawn at the time of surgery when resection was deemed feasible. There was no systematic blinding, as it was not deemed to interfere with study outcome.

Reason for resection, operative technique used (open/laparoscopic), splenectomy or not and the use of prophylactic Somatostatin did not interfere with the study protocol but were registered. All patients were followed until drain removal.

Sahlgrenska University Hospital, Karolinska University Hospital at Huddinge, Skåne University Hospital at Lund and Linköping University Hospital participated in the study. Fistulae were diagnosed and graded according to the ISGPF classification of 2004[111]. Day of drain removal, LOS, re-interventions and re-admissions were recorded. The stapler-only group and the group with reinforcement on the stapler-line were compared.

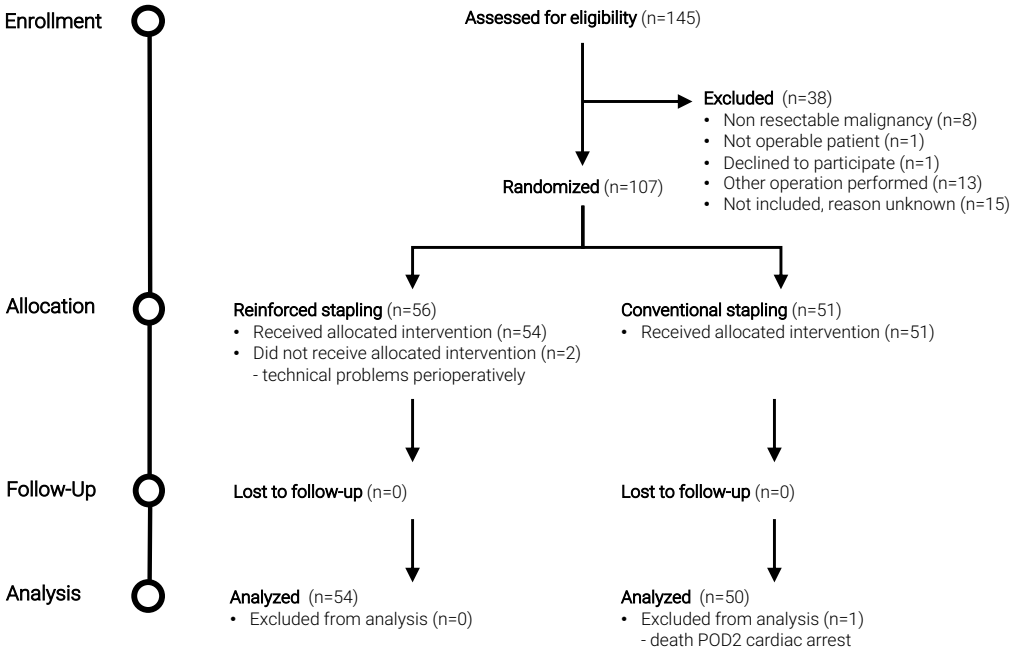

Figure 9. Flow chart on patients in paper III. POD2, postoperative day 2.

The primary endpoint was the development of a POPF and secondary endpoints were morbidity, mortality and LOS.

One possible weakness worth mentioning is that in this study the pancreatic texture and duct width were not registered in this study and since these characteristics are known risk factors of POPF, this may have introduced a selection bias. Patients of all ages, all diagnoses and any operative approach (open or laparoscopic) were included, rendering external validity to the data.

3.5 Paper IV

This study was registry based using prospectively gathered data from the SNPPCR. The study included patients operated with PD and reconstructed with either PG or PJ between 2010 and 2016. Pylorus preserving PDs (PPPD) were not included, in order to achieve a more homogenous study group. The reason for resection was noted but did not interfere with the study protocol. The material was divided and compared with regard to the two different pancreatic reconstructions, PG and PJ. Parameters used to assess POPF were pancreatic leakage, drain amylase on POD3, postoperative bleeding, DGE and re-operation.

The primary endpoint was the development of a CR-POPF and secondary endpoints were other complications and their severity grade, according to the Clavien Dindo classification, and LOS.

Data collection was restricted to parameters included in the registry, and there is a risk of information bias both regarding missing data and how

parameters are interpreted when registered. In Paper IV some of the demographic differences between the groups, such as ASA classification and the frequency of preoperative biliary drainage, are believed to stem from regional interpretational differences and traditions, respectively. We have within the frame of this study not been able to address the characteristics of the missing group, potentially introducing a bias, but the extent of missing data in this material ranges from 0.1 to 10.1%. Some parameters, often used in the study of pancreatic complications, such as pancreatic consistency and pancreatic duct width, are unfortunately not included in the registry, and not stratifying for this can possibly have introduced a bias. The coverage of the registry is 85-99% (forms A-D) and the coverage rate of malignant patients for the time period, as compared to the national Swedish cancer registry, is 86%. For these reasons validity is judged to be good.

3.5.1 Swedish National Pancreatic and Periampullary Cancer Registry

The Swedish National Pancreatic and Periampullary Cancer Registry (SNPPCR) contains data concerning treatment of patients with pancreatic and periampullary tumours.

From 2010, data on patients are prospectively registered and in 2015 and 2016 the Registry was validated and showed good results. For resected patients, the parameter coverage is more than 85%, making it possible to draw conclusions on trends over regions and time[31].

3.6 Statistics

Power calculations are made with a two-sided α-level of 5% and a power of 80%.

Continuous data are presented as mean, median and range or IQR and categorical variables as numbers/frequencies and percentages, as appropriate.

For comparison between two groups, the Mann–Whitney U-test was used for continuous variables and the Chi-square, Fisher exact and Mantel Haenszel Chi-square tests for dichotomous variables. All significance tests were two-sided and conducted at the 5% significance level.

Survival analysis was made using Kaplan Meier curves (papers I and II). Univariate analysis was made using the Log-rank test for dichotomous variables. Hazard ratios were calculated with Cox proportional hazards regression model. Multivariate Cox analysis was performed to find independent predictors of OS (paper II).

In paper IV an adjusted analysis was made, using logistic multivariate regression, for factors potentially influencing fistula formation, apart from PG/PJ.

Statistics software: SAS System Version 9, Cary, NC, USA and SPSS statistical package, v22.0-24.0, SPSS Inc.®, Chicago, Ill

3.7 Ethical considerations

All study protocols were approved by the Regional Medical Ethics Committee, papers I, II and IV by the Committee in Gothenburg and paper III by the Committee in Stockholm.

In paper III, patients were provided with verbal and written information regarding the study and intended intervention prior to giving their written consent for participation and the study was registered on clinicaltrials.gov (NCT02149446).

4 Summary of Results

4.1 I. What to do when unresectability is discovered peroperatively?

This retrospective cohort study included 143 patients, 73 from Sahlgrenska University Hospital constituting the DoB group and 70 from Skåne University Hospital Lund constituting the WaS group.

The WaS group was significantly older (70 vs. 66 years, p=0.013) and had a significantly higher ASA score (p=0.049). The two groups were comparable regarding tumour characteristics: histopathology, tumour size and stage, reason for non-curative surgery, and postoperative palliative chemotherapy (60-64%). The DoB group had a significantly higher blood loss (600 ml (100–5000) vs. 200 ml (0–900), $p < 0.001$) and a need for blood transfusion (32% vs. 14%, $p = 0.017$) than the WaS group, but operation duration did not differ. Reconstructions performed and postoperative outcome are presented in Table 2.

Table 2. Initial procedure and postoperative outcome. WaS, wait and see; DoB, double bypass; DGE, delayed gastric emptying. n (% / range)

	WaS (n=70)	DoB (n=73)	p-value
Operative procedure			
DoB	12 (17)	59 (81)	
Hepaticojejunostomy	0	12 (16)	
Gastroenterostomy	10 (14)	2 (3)	
WaS	48 (69)	0	
Postop. Complications	22 (31)	48 (67)	< 0.001
DGE	12 (17)	26 (36)	0.017
Clavien Dindo IIIa - V	3 (4)	17 (23)	0.001
Primary length of stay	8 (2-36)	14 (6-71)	0.001

The significant difference in DGE probably influences the difference in the Clavien Dindo score and LOS.

When followed over time, the two study groups had the same requirement of re-admission for biliary or gastric outlet obstruction (WaS 61% vs. DoB 67%, p=0.491) but, when adding up the total hospital stay (primary and subsequent), the difference in LOS remained (18 days (3–74) for WaS vs. 24 days (8–53) in the DoB group, p = 0.001). The stented group was separated in the analysis of bile duct related complications according to stent material, plastic or SEMS, revealing a greater need for in-hospital care in the plastic stent group and equal outcome for SEMS vs. DoB (Table 3).

Table 3. Outcome regarding hospital stay and re-interventions due to biliary complications. ERC, endoscopic retrograde cholangiography; PTC, percutaneous transhepatic cholangiography; SEMS, self-expanding metal stent. n (% / range).

	WaS plastic (n=25)	WaS SEMS (n=23)	DoB (n=73)	p-value
Readmission due to cholangitis/cholestasis	17 (68)	6 (26)	11 (15)	0.001
Hospital stay due to biliary problems	10 (0-36)	4 (0-27)	4 (0-42)	0.001
ERC/PTC after initial intervention	37	13	10	0.001

When looking at morbidity related to gastric outlet obstruction (GOO), the WaS group and the DoB group developed GOO to a similar extent and needed in-hospital care and re-intervention for GOO to a similar extent, meaning that DoB did not prevent GOO (Table 4).

Table 4. Outcome regarding Gastric outlet obstruction. n (% / range).

	WaS (n=70)	DoB (n=73)	p-value
Gastric outlet obstruction	13 (18)	9 (12)	0.350
Endoscopic stent	7 (10)	5 (7)	0.550
Surgical bypass	6 (8)	1 (1)	0.060
Hospital stay due to Gastric outlet obstruction	15 (8-46)	17 (7-92)	0.473

In conclusion, DoB is associated with higher postoperative morbidity and longer in-hospital stay as compared to the WaS strategy. The results thus support the use of the latter strategy.

4.2 II. Can lymph node 8a predict advanced disease?

A prospective protocol was applied from 2008 to 2011. During the study period, 122 patients were eligible for separate assessment of Ln8a. Thirty-five patients were excluded, as presented in the flow chart (Figure Y). The study groups consisted of 16 patients with metastatic growth in Ln8a (Ln8a+) and 71 patients with a normal Ln8a (Ln8a-).

The immunohistochemistry revealed another three metastatic Lns except for the 13 found on routine staining, and the origin of the cancer could also be diagnosed in the Ln analysis (adenocarcinoma or neuroendocrine cancer).

There were no significant differences in demography between the groups (age, gender, ASA score) even when only the subgroup of adenocarcinomas was considered (14 vs. 52 patients) and they received adjuvant chemotherapy to the same extent. The median follow-up was 6.7 (5.3-8.2) years or until the time of death.

In the survival analysis, there was a significant difference between the Ln8a+ and the Ln8a- groups (0.74 years (95% CI 0.26–1.26) versus 5.91 years (95% CI 2.91–), $p < .001$), shown in Figure 10. The one long-time survivor in the Ln8a+ group had an endocrine tumour. When comparing only adenocarcinomas, there was still a significant difference (0.74 years (95% CI 0.23–1.26) versus 2.93 years (95% CI 2.00–), respectively, $p < .001$) and, when further comparing Ln8a+ adenocarcinomas with Ln8a- but Ln+

adenocarcinomas (standard Ln stations), there was also a significant difference.

The OS in the Ln8a+ group resembled that of unresectable disease; 8.3 months in our material and three to 11 months in the literature[13, 120].

Furthermore, the uni- and multivariate analyses of the adenocarcinomas, searching for independent predictors of short OS, showed that Ln8a+ is an independent predictor.

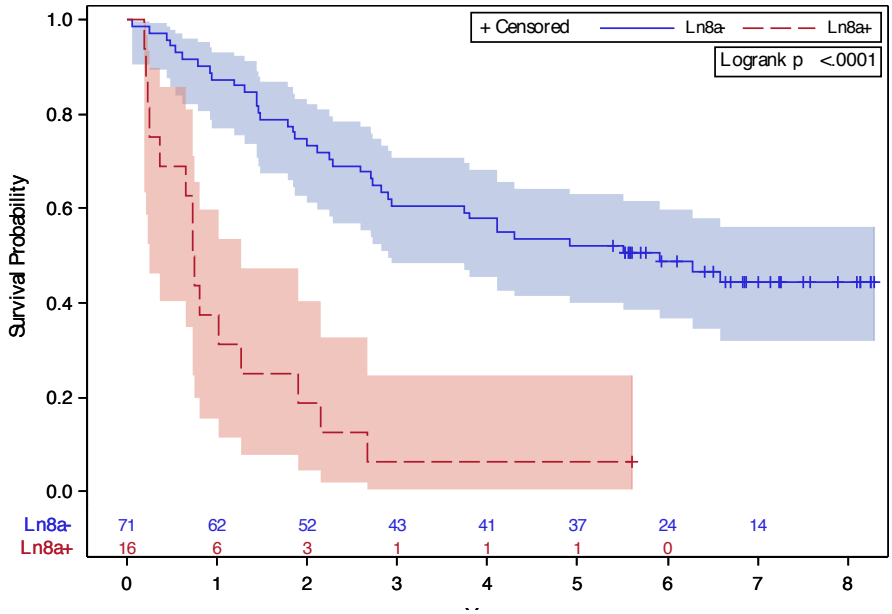

Figure 10. Kaplan Meier curve on overall survival in Ln8a+ and Ln8a- patients. Ln, lymph node.

Taken together, the results confirm previously published results from Connor et al.[87], that tumour involvement in Ln8a is associated with significantly reduced overall survival.

4.3 III. Does mesh reinforcement of the pancreatic stump, after distal pancreatectomy, reduce fistula formation?

To address the question we adopted an RCT design involving four centres. During the study period, 145 patients were eligible, of which 38 were excluded, for different reasons (Figure Z: flow chart) and 107 randomized, resulting in an intervention group of 56 patients and a control group of 51 patients. In the intervention group, two patients did not receive the allocated treatment, reinforcement on the stapler line, because of technical problems during the operation, and one patient in the stapler-only group died on POD2 from myocardial infarction, before assessment of POPF was possible, and was excluded from final analysis. The study group consisted of 104 patients (71.7%), 54 patients allocated to stapling with reinforcement (51.9%) and 50 patients allocated to stapler division only (48.1%). The groups were comparable regarding demography (BMI, ASA score etc.) previous abdominal surgery, use of prophylactic somatostatin and final histopathology.

Table 5. Operative data, paper III. n (% / range)

	Stapling with reinforcement (n=54)	Stapling (n=50)	p-value
Type of operation			0.795
Open	43 (80)	41 (82)	
Laparoscopic	11 (20)	9 (18)	
Duration of operation	150 (64-400)	152 (54-327)	0.795
Splenectomy	14 (26)	16 (32)	0.495

The two groups were also equal in perioperative outcome such as surgical approach (laparoscopic/open), multivisceral resection, operation duration and perioperative blood loss (Table 5). The development of POPF did not differ between the two groups, nor did development of CR-POPF. The overall morbidity (79%) in the study group was quite high but severe complications (Clavien Dindo IIIb-V) were uncommon and no grade IV or grade V morbidity was registered in either group (Table 6).

In accordance with already mentioned results, there was no difference regarding different major surgical complications (bleeding, DGE, abdominal fluid collections) or time to drain removal. Nor were there any differences in LOS, re-admission or re-intervention rate.

Table 6. Postoperative outcome, paper III. POPF, postoperative pancreatic fistula. n (% / range)

	Stapling with reinforcement (n=54)	Stapling (n=50)	p-value
Grade of POPF			0.980
0	32 (59)	21 (42)	
A	16 (30)	21 (42)	
B + C	6 (11)	8 (16)	
Clavien Dindo			0.627
0	32 (59)	21 (42)	
I – IIIa	46 (85)	40 (80)	
IIIb - V	2 (4)	4 (8)	
Length of stay	9 (2-35)	9 (2-114)	0.695

In conclusion, our results showed no difference in fistula rates. In other words stump reinforcement does not appear to convey an outcome advantage.

4.4 IV. Does choice of reconstruction influence fistula formation following pancreatoduodenectomy?

Data were collected from the SNPPCR. During the study period, from 2010 to 2016, a total of 2051 PDs with a pancreatic reconstruction (PG or PJ) were registered. Of those 36 (1.8%) were miscoded and had to be omitted. Pylorus preserving PDs (PPPD) were not included leading to the exclusion of another 330 operations (16.1%). This resulted in a study group of 1685 patients (82.2%), 567 with PG reconstruction (33.6%) and 1118 with a PJ reconstruction (66.4%).

The groups were comparable regarding age, gender, BMI and comorbidity. The ASA score was higher in the PJ group ($p<0.001$). Preoperative biliary drainage and prophylactic use of Somatostatin were more frequent in the PG group compared to the PJ group (69.5% vs. 61.4%, $p<0.001$; 70.1% vs. 29.2%, $p<0.001$, respectively). Histopathology, metastatic Lns and tumour stage were comparable in the two groups with the exception of the total number of Lns resected, where PG had a median of 18 (0-54) and PJ a median of 21 (0-99) resected. Operation time was significantly longer for PG, with a median of 410 (183-840) min, compared to PJ, 373 (96-820, $p<0.001$) min, and a lower frequency of venous resections (13.1% vs. 22.0%, $p<0.001$). The group differences were considered not to affect the results and will be further discussed in the general discussion below.

The postoperative outcome showed a significantly lower rate of POPF after PG compared to PJ (18.1% vs. 28.5%, $p<0.001$) as well as rate of CR-POPF (fistulas grade B and C) (11.1% vs. 19.8%, $p<0.001$), presented in Table 7.

Table 7. Postoperative outcome, paper IV. PG, pancreatogastrostomy; PJ, pancreatojejunostomy, CR-POPF, clinically relevant postoperative pancreatic fistula; DGE, delayed gastric emptying. n (%).

	PG (n=567)	PJ (n=1118)	p-value
Surgical complications	237 (43.0)	586 (56.7)	<0.001
Wound infection	69 (12.5)	65 (6.3)	<0.001
Intraabdominal abscess	52 (9.4)	117 (11.3)	0.27
CR-POPF	61 (11.1)	205 (19.8)	<0.001
DGE	76 (13.8)	258 (25.0)	<0.001
Bile leakage	22 (4.0)	53 (5.1)	0.38
Postoperative bleeding	37 (6.7)	109 (10.5)	0.014
Wound dehiscence	16 (2.9)	41 (4.0)	0.32
Other	26 (4.6)	148 (13.2)	<0.001
Re-operation	46 (8.3)	127 (12.3)	0.018
Clavien Dindo			<0.001
0	270 (49.0)	369 (35.7)	
I - IIIa	223 (40.5)	403 (48.6)	
IIIb - V	58 (10.5)	162 (15.7)	
Mortality	7 (1.3)	25 (2.4)	0.14

Postoperative bleeding, DGE and reoperations were also less frequent in the PG group whereas wound infections were more common in PG. Mortality was comparable in the two groups, 1.3% vs. 2.4%, p=0.14.

In addition to anastomotic technique two other parameters had significantly lower POPF rates, biliary drainage and use of somatostatin. An analysis,

using logistic multivariate regression, was performed to evaluate the effect that the pancreatic anastomosis (PG and PJ) had on fistula development when adjusting for biliary drainage and somatostatin use. The result remained significant meaning that type of anastomosis still had a significant effect on POPF development.

On the basis of these results, it appears that pancreatogastrostomy is a safer reconstruction after pancreatoduodenectomy.

5 Conclusions

- Patients with unresectable periampullary cancer at laparotomy, without obstructive symptoms can safely be managed endoscopically, with metallic stents, on demand. This strategy has significantly lower morbidity and shorter length of hospital stay compared to prophylactic surgical double bypass. Prophylactic duodenal bypass does not prevent future gastric outlet obstruction.

- Tumour involvement of lymph node 8a, in suspected pancreatic or periampullary carcinoma, is associated with significantly reduced overall survival, indicating a possible role in the preoperative workup ahead in these patients.

- Reinforcement with a biodegradable mesh in the stapler closure of the pancreatic remnant, in distal pancreatectomy, does not decrease the rate of overall or clinically relevant pancreatic fistulas.

- Pancreatogastrostomy appears to be a safer pancreatic reconstruction than pancreatojejunostomy, after pancreatoduodenectomy, due to significantly less risk of developing clinically relevant pancreatic fistulas.

6 General discussion

6.1 Surgery in a palliative setting (Paper I)

A majority of patients with pancreatic cancer are beyond cure at diagnosis but, with a fairly good performance status, they can have prolonged survival with palliative chemotherapy. In spite of the current work-up for pancreatic cancer, with high quality imaging, patients are still found to have unresectable disease at surgery with curative intent, due to metastatic or locally advanced disease. These patients have an aggressive tumour and short life expectancy. The tumour is prone to obstruct the biliary outflow and the duodenum as it progresses. Optimal palliative treatment is of the utmost importance, including maintaining biliary and intestinal patency and providing prompt chemotherapy.

It has previously been shown that double bypass surgery, performed at initial laparotomy, is a safe and effective treatment in avoiding future obstruction[123, 124]. But this means preventing obstruction in 20% of the patients and an unnecessary operation in 80% of patients. Data from other studies say that non-curative surgery is associated with high morbidity, potential mortality and a patency of surgical bypasses that does not exceed endoscopic SEMS alternatives[122, 126-128]. It may also lead to less chemotherapy and shorter survival[128, 167]. SEMS is already the treatment of choice in patients with known palliative disease[168].

Results reported in paper I show that the DoB group resumed oral feeding later, had twice as many complications and longer hospital stay compared to the WaS group. During the study period, there was a shift from plastic stents

to SEMS in our material, in analogy with results from others demonstrating improved patency for SEMS[169]. When comparing biliary complications in our study, the group with SEMS (subgroup in WaS) and the DoB group had an equal frequency of re-admissions and re-interventions, suggesting that DoB does not protect from future hospitalization, as shown by others[126]. In this paper, plastic stents were inferior to both metallic stents and surgical bypass with respect to re-interventions and re-admissions.

Regarding GOO related complications, the DoB group was in similar need of re-admission and re-intervention as the WaS group, indicating that DoB does not protect from future GOO, parallel to results presented by Spanheimer[128].

Paper I supports a current strategy of only treating symptomatic patients and when doing so using metal stents as the primary strategy, saving surgery for cases not suitable for endoscopy.

6.2 Looking for a diagnostic tool (Paper II)

The potential cure for patients with pancreatic and periampullary cancer is PD, which is a major operation with a recovery of several months. In patients with early tumour recurrence (<12 months) after a PD, which is correlated to a poor prognosis[170], there is a risk of not benefiting from the resection and of not receiving chemotherapy. This group would perhaps have had better effect of chemotherapy from the start. In a retrospective study, Connor et al. found that tumour involvement of Ln8a was a predictor of short overall survival in patients resected for pancreatic cancer[87]. This Ln station is accessible without major dissection or adding surgical trauma to the patient, presenting it as a possible staging tool.

In our prospective cohort (paper II) we show that metastasis to Ln8a is associated with a significantly shorter OS compared to patients with tumour

free Ln8a, regardless of tumour engagement of other regional Lns. Other studies on this subject also present a short OS whereas some do not find a difference between Ln8a engagement and Ln engagement overall[87, 171, 172].

The Ln8a+ patients and the unresectable patients, not included in the study, had a similar survival time in both our and Connor's data[87]. Others have seen a shorter OS but still longer than without surgery, for which reason they still propose resection for these patients[173].

Both routine staining and immunohistochemistry were used to detect metastases, resulting in three patients diagnosed only with the latter method. The relevance of detecting metastases with immunohistochemistry has been previously demonstrated by Bogoevski et al. who also found metastatic engagement of Ln8 (common hepatic artery in their study) to be a prognostic factor of short OS[174].

In our Ln8a+ group there were 14 adenocarcinomas and 2 neuroendocrine cancers and the different diagnoses could be made from the Ln8a specimen, making it even more useful as a potential prognostic tool.

We have included all patients where pancreatic or periampullary cancer cannot be ruled out preoperatively, regardless of what postoperative diagnosis they had. This mirrors the clinical situation we are faced with and for which we need a prognostic tool. Other studies only present adenocarcinomas[87, 171-173, 175] and in our subgroup analysis, only adenocarcinomas, OS is still significantly shorter in the Ln8a+ group.

Paper II shows that Ln8a is a strong predictive factor of reduced OS. This could perhaps play a role in characterizing tumours in the pancreatic and periampullary region preoperatively, e.g. by resecting the node during diagnostic laparoscopy.

6.3 Operative technique in pancreatic surgery

As described above the problem with a high burden of complications, potentially of a severe character, accompanies pancreatic surgery and so do efforts to improve outcome. An important parameter in post pancreatectomy complications is the formation of POPF, caused by leakage from the pancreatic anastomosis (in PD) or the divided pancreatic stump (in DP), which can lead to further complications. Hence much effort has been devoted to optimizing the pancreatic anastomosis and division techniques.

6.3.1 Minimizing POPF in Distal Pancreatectomy (paper III)

Numerous methods have been tested to minimize POPF formation after DP, as described above, but very few have shown significant differences. Promising results presented from a study using prosthetic mesh reinforcement of the stapler line showed a POPF frequency of 1.9% in the reinforcement group as compared to 20% in the non-reinforced group.

In paper III we investigate whether this effect would hold for a biodegradable reinforcement, considering potential complications related to prosthetic material. We could however not show any difference in POPF frequency between the reinforced and the non-reinforced group, neither for overall POPF nor for CR-POPF. And there was no difference in any of the postoperative outcome parameters. These results are concurrent with findings of others, trying different techniques at the stump of the pancreas[69, 72, 74, 75, 109], even if there are exceptions[77, 176]. We can currently not recommend the use of reinforcement on the stapler in DP.

The reason for the low success rate of different surgical techniques in decreasing POPF frequency is still unknown but, from described experiences, it is possible that the answer lies elsewhere. There are studies indicative of

pancreatitis and ischemia, combined with intrinsic characteristics of the gland, being mechanisms behind the development of POPF, triggered by the trauma the surgery inflicts on the pancreas[103, 177, 178].

6.3.2 Minimizing POPF in pancreatoduodenectomy (paper IV)

In paper IV, comparison of the two most common anastomotic techniques, PG and PJ, shows that PJ has significantly more CR-POPF and a higher overall morbidity. Others have found PJ to be associated with higher POPF frequency[62, 179, 180], but there are also studies showing no difference[61, 63, 181] or the opposite[182].

Furthermore, the PJ group had more post pancreatectomy hemorrhage (PPH), more often DGE and more re-operations. This is not surprising and most likely a consequence of the higher frequency of POPF after PJ. In contrast, several studies with a significant difference in POPF, often in favour of PG, do not show a difference in morbidity or mortality[183-185]. This may be explained by inclusion of all POPF, not only CR-POPF.

In analogy with the above one would expect a longer hospital stay in the PJ group, which we did not show. There are however data showing that significantly more PJ patients were discharged to another hospital ward compared to PG patients, who were significantly more often discharged to the home.

The use of Somatostatin to prevent POPF is much debated. No international consensus has been reached[117, 186] and there are consequently no recommendations. The present study showed that Somatostatin was used significantly more often in the PG group, possibly affecting fistula formation. However, when adjusted for in the regression analysis, it did not affect

POPF. Since the effect of Somatostatin in POPF development is not universally agreed upon, it has been suggested that it be regulated in future RCTs minimizing heterogeneity[64].

Our two study groups differ regarding preoperative biliary drainage, possibly reflecting different local regimens in the treatment of jaundice. The parameter was adjusted for in the regression analysis and did not interfere with the effect that anastomosis had on POPF development. However it still remained significant indicating a role in fistula formation.

The differences seen in ASA classification and perioperative blood loss between the groups are difficult to explain but may stem from differences in interpretations of parameter definitions: in the former, and absence of a standardized method of measurement, in the latter, when filling in the registry forms. Low correlations in some registry parameters were observed in the validation of the Registry, performed in 2015 to 2016, which overall showed good results (submitted manuscript). Over the years, continuous work has been done in, from the Registry Steering Committee to harmonize interpretations of parameters and simplify registry forms in order to improve the quality of data, which can be seen in the yearly reports from the Registry[31]. The work of further developing the registry must however go on.

7 Future perspectives

The majority of the papers in this thesis is the result of Swedish collaborations; paper I, III, IV. They have come about thanks to years of work with founding and developing the Swedish National Pancreatic and Periampullary Registry and the Swedish Study Group for Pancreatic Cancer. The nearby future lies in continuing and expanding these collaborations in order to generate ideas and increase population size.

We have come a long way in optimizing perioperative care in order to minimize postoperative complications and this will continue not only through registry data and collaborations but also with the help of data from the ERAS® database.

In spite of results described above and throughout this thesis fistula frequency is still, at best, 11% telling us that the answer must lie elsewhere. Further research on fistula formation should address questions of inflammation and ischemia caused by the surgical trauma and inherent properties of the pancreatic tissue predisposing of pancreatic leakage.

Furthermore the vast majority of our patients will be faced with recurrent disease, in spite of curative surgery. And we are still faced with the large group of patients that have a disease beyond cure from the start. This implies a need for shift of focus. Further development of surgical techniques will not be the solution for our patients. The next step must be the development of systemic treatments for this systemic disease. Surgery will be an important part of the treatment but whom to take to surgery and when will maybe change in a new chemotherapy era. And this future also demands national and international collaborations, with surgeons, oncologists as well as radiologists.

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Errata

Paper II

Methods, page 226; A uni- and multivariate analysis was also performed, on the adenocarcinomas, to look for predictors of short OS.

Figure 4, page 228: The Kaplan Meier curve is erroneous. A correct version is presented in the Chapter 4.2, Figure 10, page 34.

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Appendix

Paper I - IV