# Perioperative aspects of pancreaticoduodenectomy

Williamsson, Caroline

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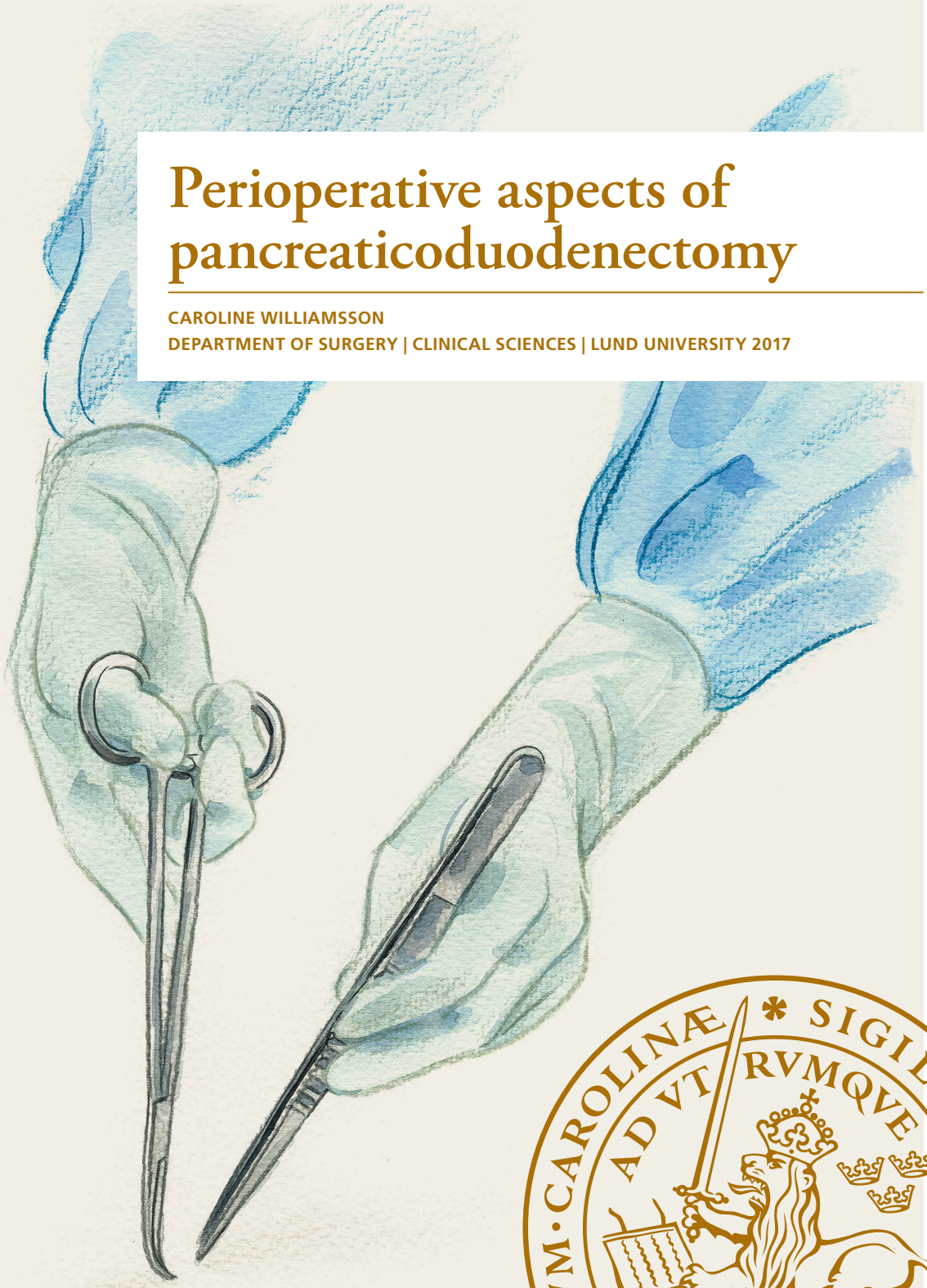

# Perioperative aspects of pancreaticoduodenectomy

Caroline Williamsson


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*Faculty opponent*
Associate Professor Kristoffer Lassen, Oslo University Hospital

Supervisor: Associate Professor Bobby Tingstedt

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Abstract

Background: About 1200 are yearly diagnosed with cancer in the periampullary region in Sweden. Only 10-15% can be offered potential cure by pancreaticoduodenectomy (PD). The perioperative challenges are great. The overall morbidity can be as high as 70%, of which 15-20% are major complications. Some 8-20% are unexpectedly irresectable at laparotomy due to advanced disease. The best intraoperative approach for them is unclear. The general aim of this thesis was to investigate and modify different elements of the perioperative care for PD patients, with the intent to improve outcome for patient with less morbidity and better use of healthcare utilities.

Method: Paper I and IV were retrospective studies investigating the effects on perioperative outcome and clinically relevant postoperative pancreatic fistula (CR-POPF) during transition to a high-volume center. The effect of implementing a fast track program for PD was studied in paper II, by comparing a prospective cohort of 50 patients with an equally sized historical control group. Safety, clinical outcome, costs and health-related quality of life were analyzed. In paper III, the short- and long-term outcome after prophylactic surgical bypass and endoscopically placed biliary stent and duodenal stent on demand were retrospectively assessed. Two equally sized cohorts with perioperatively finding of unresectable cancer from Sahlgrenska University Hospital (surgical strategy) and Skåne University Hospital, Lund (endoscopic strategy) were compared. Paper V was a follow-up study on sustainability of the enhanced recovery (fast track) program, with evaluation of compliance to the protocol and postoperative outcome for 160 patients.

Result: The transition from a low- to a high-volume institution resulted in decreased operating time and intraoperative blood loss and hospital length of stay. (paper I) The fast track program for PD was followed by less delayed gastric emptying (DGE), shortened lenght of stay (LOS) and diminished costs for care. Despite earlier discharge, readmissions did not increase and health-related quality of life was not impaired. (paper II) There are more postoperative complications and longer hospital stay correlated with surgical palliative double bypass, than endoscopic treatment of stents for biliary and duodenal obstruction. A prophylactic gastroenterostomy does not prevent future gastric outlet obstruction. (paper III) The total rate of CR-POPFs was 12% in all patients. There was no decrease over time nor correlated costs, despite an increase of hospital volume. (paper IV) The postoperative benefits with an ERP were maintained and adherence rates to different protocol items were increased in the post implementation phase. (paper V)

Conclusion: The centralization process resulted in improved perioperative parameters and shortened hospital stay for the whole PD cohort, but did not decrease the rate of CR-POPF nor its subsequent impact on LOS or costs. Fast track program for PD was safe. It reduced DGE, hospital stay and costs. The positive outcome was sustained, with increasing compliance to the protocol, after initial implementation. Patients with unresectable periampullary cancer can safely be managed with endoscopic drainage on demand, with lower morbidity and shorter hospital stay than with surgical prophylactic bypass.



Key words: pancreaticoduodenectomy, enhanced recovery, perioperative care, centralization, palliative surgery

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# Perioperative aspects of pancreaticoduodenectomy

Caroline Williamsson


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UNIVERSITY

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Faculty of Medicine, Clinical Sciences, Lund University

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*To my family*

*Dan, Ellen och Julia*

# Content

# List of publications

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

I. Ansari D, Williamsson C, Tingstedt B, Andersson B, Lindell G, Andersson R. Pancreaticoduodenectomy – the transition from a low- to a high-volume center. Scand J Gastroenterology 2014;49:481-4

II. Williamsson C, Karlsson N, Sturesson C, Lindell G, Andersson R, Tingstedt B. Impact of a fast-track programme for pancreaticoduodenectomy. Br J Surg. 2015 Aug;102:1133-41

III. 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(Oxford). 2016 Jan;18:107-12

IV. Williamsson C, Ansari D, Andersson R, Tingstedt B. Postoperative pancreatic fistula- impact on outcome, hospital cost and effects of centralization. HPB(Oxford). 2017. Febr 1. Doi: 10.1016/j.hpb.2017.01.004

V. Williamsson C, Karlsson T, Westrin M, Ansari D, Andersson R, Tingstedt B. Sustainability of an enhanced recovery program for pancreaticoduodenectomy. Submitted World J Surg. 2017-02-02.

# Thesis at a glance

| | Question | Method | Results | Conclusion |
|---|---|---|---|---|
| **I** | Have the postoperative outcome been improved during the transition from a low- to a high-volume institution? | Retrospective analyze of perioperative course for 221 patients from 2000 until 2012. | Operating time, blood loss and transfusion decreased. Hospital stay decreased. | The transition to a high volume center improved perioperative parameters. |
| **II** | How will an enhanced recovery program for PD effect outcome and quality of life? | A prospective cohort of 50 patients compared with historical controls, combined with HRQoL questionnaires. | DGE was reduced (26% vs. 48%). LOS shortened by 4 days. Costs decreased by 30%. No differences in HRQoL. | Enhanced recovery program was safe and decreased DGE, hospital stay and costs. HRQoL was not impaired by the ERP. |
| **III** | Is prophylactic double bypass or endoscopic biliary stent and duodenal stent on demand, better for unexpectedly unresectable patients? | Retrospective comparative study of 143 patients from two high volume institutions. | Double bypass had more postoperative complications and longer hospital stay. Prophylactic gastroenterostomy does not prevent gastric outlet obstruction. | Unresectable patients can be safely managed with endoscopic drainage on demand, with lower morbidity, than with a prophylactic double bypass. |
| **IV** | Has the incidence of clinically relevant POPF changed by the transition from a low- to a high-volume institution? | Retrospective analyze of 322 patients in three different volume groups. | The incidence of CR-POPF and correlated costs and LOS were equal in the three groups. | Centralization of pancreatic surgery has not decreased the incidence of CR-POPF nor its subsequent impact on LOS or costs. |
| **V** | How well is the postoperative outcome of the enhanced recovery program sustained and what is the compliance rate? | With the group from study II as controls, two follow-up groups were compared regarding outcome and compliance. | Adherence rates increased from 64% to 71%. Postoperative complications or LOS did not change. | The positive outcome of ERP for PD were sustained and compliance has increased. |

# Abbreviations

| | |
|---|---|
| ASA | American Society of Anesthesiology |
| BMI | Body mass index |
| DFS | Disease free survival |
| DGE | Delayed gastric emptying |
| DoB | Double bypass |
| EORTC | European Organization for Research and Cancer |
| -QLQ30 | Quality of life questionnaire (30 questions) |
| -PAN26 | Pancreatic cancer module questionnaire (26 questions) |
| ERAS® | Enhanced recovery after surgery |
| ERP | Enhanced recovery program |
| FT | Fast track (synonym for enhanced recovery) |
| GE | Gastroenterostomy |
| GOO | Gastric outlet obstruction |
| HRQoL | Health-related quality of life |
| ISGPF | International study group of pancreatic fistula |
| ISGPS | International study group of pancreatic surgery |
| LOS | Length of stay |
| OS | Overall survival |
| PD | Pancreaticoduodenectomy |
| PG | Pancreaticogastrostomy |
| PJ | Pancreaticojejunostomy |
| POD | Postoperative day |
| POPF | Postoperative pancreatic fistula |
| -CR-POPF | Clinically relevant POPF |
| PPH | Postpancreatectomy hemorrhage |
| RCT | Randomized controlled study |
| WaS | Wait-and-see |

# Introduction

## Periampullary cancer

The concept of periampullary cancer comprises all primary cancers that emanates in the proximity of the ampulla of Vater, without consideration of histopathology. Most common are the primary adenocarcinomas, which can originate from the pancreatic head, distal bile duct, ampulla and duodenum. Neuroendocrine tumors, solid pseudopapillary neoplasms or gastrointestinal stromal tumors are more infrequent. Figure 1 displays an overview of the periampullary area and adjacent anatomical structures.

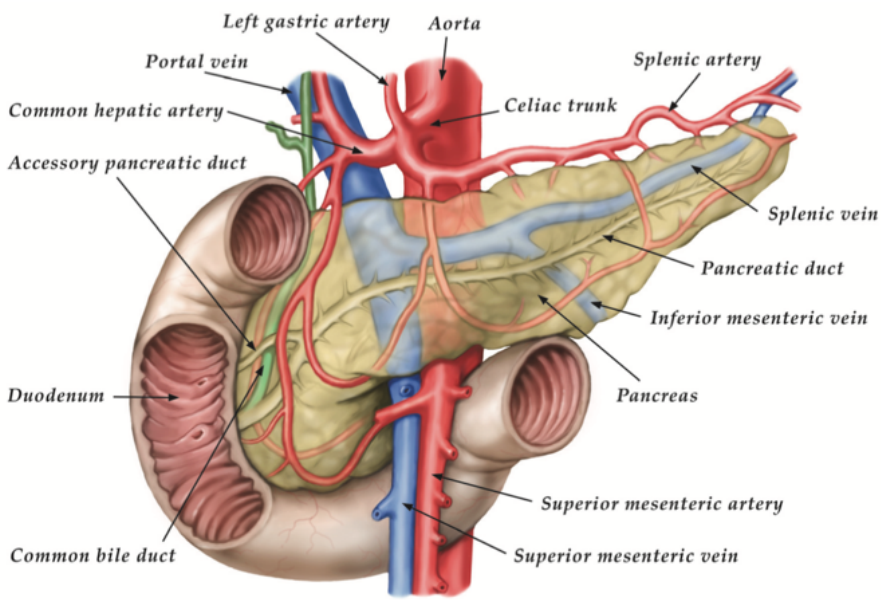


**Figure 1**
Anatomy of the pancreas and periampullary region. The ampulla of Vater is where the bile duct and pancreatic duct end in the duodenum. (Reprinted with permission dr. Daniel Ansari[1], © Anders Flood.)

*Epidemiology*

Pancreatic cancer is the most common type of the periampullary adenocarcinomas in the western world. Pancreatic cancer accounts for 7% of all cancer-related deaths, and it is currently the fourth-leading cause of death by cancer in the western world[2,3]. With increasing incidence, it is expected to be the second cause of cancer death by 2030 in the United States[4].

In Sweden, the annual incidence of periampullary tumors is approximately 1200. The majority is the pancreatic cancers, but only the tumors located in the pancreatic head are included in the periampullary cancers[5]. The tumors in the pancreatic body and tail, around 400 annually, will not be discussed in this thesis. (table 1)

**Table 1**
Proportion and distribution of periampullary tumors diagnosed in Sweden 2015.

| Anatomical position | Patients diagnosed 2015, n (%) |
|---|---|
| **Pancreas** | |
| **Head** | 697 (42.6) |
| **Body** | 245 (15) |
| **Tail** | 182 (11.1) |
| **Other location/multifocal** | 227 (13.8) |
| **Duodenum** | 99 (6.1) |
| **Distal bile duct** | 159 (9.7) |
| **Ampulla of Vater** | 27 (1.7) |
| | Total 1636 (100) |

The incidence of periampullary cancer increases with age. Environmental exposures for periampullary cancers are mostly studied for pancreatic cancer. The risk for pancreatic cancer is increased for smokers[6], in obese[7] and for persons with heavy alcohol intake[8]. Chronic pancreatitis moderately excesses the risk for pancreatic cancer[9]. Type 2 diabetes mellitus is associated with an increased risk for pancreatic cancer, which decreases with duration of diabetes, but still persists decades after diagnosis[10]. Since diabetes type 2 can be both cause and consequence of pancreatic cancer, the relationship is somewhat difficult to apprehend. Diabetes and chronic pancreatitis is also associated with extrahepatic cholangiocarcinoma (CCC)[11]. Additionally, liver flukes, chronic biliary inflammation and congenital bile duct cysts increases the risk for CCC[12]. There is a strong predisposition for the familiar adenomatous polyposis (FAP) syndrome and duodenal and ampullary neoplasia, with a risk of up to 200% higher than general population[13,14]. Approximately 10% of pancreatic cancer are hereditary and genetic alterations (p16/CDKN2A, BRCA2, PRSS1) are identified for some of these patients[15].

*Diagnosis*

The initial symptoms are often vague, with malaise, weight loss, epigastric pain and nausea, which contributes to a late diagnosis. For the majority of patients, palliative treatment is then the only choice, due to advanced disease. Periampullary tumors may compress the bile duct, causing jaundice, or obstruct the duodenum, causing gastric outlet obstruction[16]. Ampullary and bile duct cancers present earlier in the course of the disease due to biliary obstruction.

Radiology has an important role for the initial diagnosis, but also in determining resectability and treatment monitoring. Ultrasonography is frequently the first-line diagnostic tool, and can have a sensitivity and specificity of about 90%[17], but it is user dependent[17,18]. Computed tomography (CT) is more appropriate for a reliable evaluation of resectability, with information on local extension, vascular involvement and distant metastases[18,19]. Additionally, endoscopic ultrasound with fine-needle aspiration for histopathological diagnosis, or magnetic resonance imaging (MRI) with its benefits on characterizing pancreatic masses and ductal structures, can give further valuable information[18,20]. Moreover, MRI visualizes small metastases in the liver better than CT[21]. CT-PET (18F-fluorodeoxyglucose positron emission tomography), with its wide anatomic coverage, can be suitable for detection of metastases and, much-disputed, for treatment monitoring[22]. A thoracic CT is standard to exclude pulmonary metastases[23]. Despite optimal preoperative radiology, liver or peritoneal metastases are found in more than 10% of patients at time of surgery[24,25].

The only serum tumor marker available on the market for periampullary adenocarcinoma is CA 19-9. It has a sensitivity and specificity of approximately 80%[26] and can be falsely elevated by cholestasis.

A majority of patients with periampullary cancers presents with jaundice. If the tumor is resectable and surgery can be scheduled within a few weeks, preoperative bile duct stenting should be avoided since it increases morbidity[27]. ERC-related (endoscopic retrograde cholangiography) complications such as pancreatitis, bleeding or cholangitis contributes to increased morbidity, however, there are no clear evidence for increased postoperative complications compared with non-stented patients[28]. In presence of cholangitis, planned neoadjuvant therapy or delay to surgery, the bile duct should be stented[28,29]. Metal stents carries less risk for obstruction and need for re-intervention than plastic stents[30,31], and if placed well below the confluence of left and right bile duct, it does not restrain the surgical resection[29].

*Differential diagnosis*

There are premalignant or benign disorders that can mimic a periampullary tumor. Chronic or autoimmune pancreatitis can present with an expansive mass in the

pancreatic head. An elevated immunoglobulin G4 (IgG4) or histopathology can diagnose the autoimmune pancreatitis[32]. Other lesions in this area can be intraductal papillary mucinous neoplasia (IPMN), cystadenoma or cysts[33,34]. Sometimes diagnostic uncertainty remains despite optimal work-up, which might result in a pancreaticoduodenectomy (PD) for a benign cause, evoked by the fear of omitting a resectable periampullary cancer[35].

*Prognosis*

Despite advances in surgical technique and new chemotherapy, long-term survival for periampullary cancers has just slightly increased during the last decades. The worst prognosis of them all, with 5-year survival of 6-8% in Europe and United States, is the pancreatic ductal adenocarcinoma[2,5,36]. Patients with locally advanced tumors have a median overall survival (OS) of 9-13 months[16,37] and for patients with metastatic disease, the survival is a mere six months[38]. After resection and following adjuvant chemotherapy, the median OS is around 23-28 months[5,39,40], with a distinct division depending on presence of invaded lymph nodes. A radical resected node negative tumor results in a five-year OS of 41%[34].

Prognoses for the other periampullary cancers are somewhat less vicious. The 5-year OS for all stages of extrahepatic bile duct cancer in Europe is 11%[41]. The median OS for resected distal bile duct cancer is 37 months, with a median disease-free survival (DFS) of 14.6 months[42].

For ampullary cancer, the 5-year survival is 40-45% overall[43], more favorable if intestinal histopathological differentiation is present (60%) and less if pancreaticobiliary type exists (20%)[44]. The favorable prognosis after ampullary carcinoma could be attributed to early presentation and subsequent high resectability rates[45].

The relative 5-year OS for all stages of duodenal and small intestine cancer in the Nordic countries is 50-60%[3]. The median OS for resected duodenal cancer is 84 months, with a DFS of 53 months[46]. For unresectable disease the survival is 2-8 months[47].

The 5- and 10-year survival for 890 patients resected for periampullary adenocarcinoma from 1970 until 1999, at the Johns Hopkins Institution, Baltimore, is presented in figure 2[48].

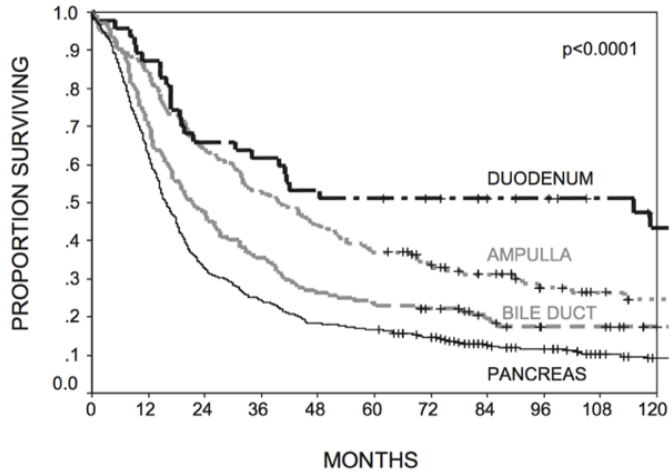


**Figure 2**
The Kaplan-Meier actuarial 10 year survival by site of tumor origin for a cohort of 890 patients treated by pancreaticoduodenectomy (pancreas n=564, ampulla n=144, bile duct n=135, duodenum n=47). The 5 year acual survival 17% pancreas, 37% ampulla, 23% bile duct and 51% duodenum. Ten-year actuarial survival rates: 9% pancreas, 25% ampulla, 17% bile duct and 44% duodenum. Reprinted with permission from Elsevier, Riall et al.[48]

Patients should be offered adjuvant chemotherapy after PD, unless contraindicated. Adjuvant chemotherapy, gemcitabine for pancreatic and distal bile duct cancer, increases the 5-year survival rate, 21% vs. 10% for observation alone[40,49]. The recently published ESPAC-4, shows an increased median OS of 2.5 months for combined gemcitabine and capecitabine compared with gemcitabine alone[39]. For patients with duodenal cancer, especially nodal metastases, current practice is to give oxaliplatin-based chemotherapy as adjuvant therapy[47].

# Pancreaticoduodenectomy

Surgical resection offers the only possibility of cure, but is associated with a high risk for postoperative complications.

## The evolution of pancreatic surgery

The first attempts to resect parts of pancreas and duodenum were explored during the end of the 19th and the beginning of the 20th century. The progress was entirely dependent on brave surgeons, active during a time of initial diagnostic understanding of pancreatic disease and development of modern anesthetic and aseptic techniques. The limited techniques for hemostasis or adequate resuscitation restricted major abdominal surgery[50]. Some misconceptions hampered the progress in pancreatic surgery; one that duodenum was essential for life and must not be resected, and another that re-introduction of pancreatic secretions into the gastrointestinal lumen were hazardous for survival[51,52].

The Italian surgeon Alessandro Codivilla, made the first reported PD in 1898 for a tumor involving the stomach and the pancreatic head. The patient did however not survive the postoperative period[50,52]. In the same year, William Stewart Halsted undertook the first transduodenal papillectomy, for resecting an ampullary tumor. No pancreatic parenchyma was resected. Felix Franke, a German surgeon, made a subtotal duodenum-sparing pancreatectomy in 1900, and was the first to use thermocautery technique for hemostasis. His fellow citizen Walther Kausch, is credited to the first successful partial PD 1909, as a part of a two-stage procedure[50].

During the first years of the 20th century a few PDs were made, of which four can be considered successful, since the patient survived the perioperative period. The continued progress was slow, and interest first revived in 1935, when Allen Oldfather Whipple (figure 3) presented the result of his three first PDs[53], a procedure that became eponymously associated with his name.

Until this time, a one-stage procedure was practically impossible due to bleeding disorder that come with obstructive jaundice. Vitamin K became available on the market 1939[51]. The first part of the two-stage procedure was to restore bile flow to the gastrointestinal tract by a cholecystogastrostomy, and deviate gastric content by a gastroenterostomy. The second stage completed the resection of duodenum and pancreas. The evolution to a one-stage procedure avoided the hazards with two anesthetic procedures and risk for troublesome adhesions[54,55].

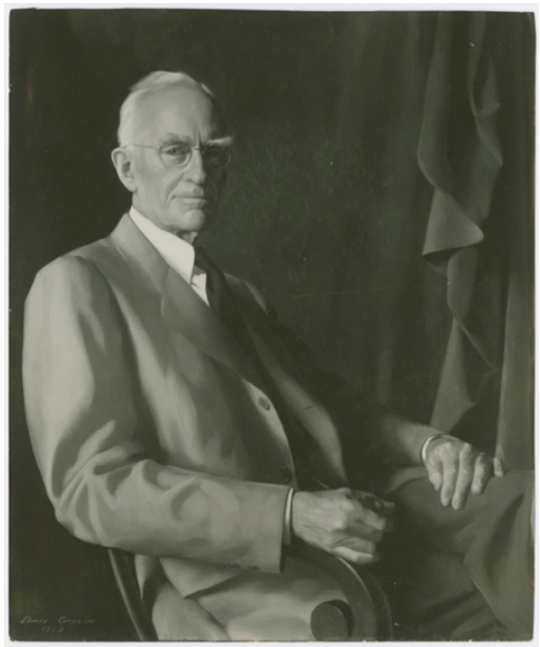

**Figure 3**
Allen O. Whipple. With courtesy of Archives & Special Collections, Columbia University Health Sciences Library.

Whipple performed in total 37 PDs during his career and based on his experiences he drew some important conclusions; the importance of radical resection for prognosis[51]; the superiority of a pancreaticoenteric anastomosis over pancreatic duct ligation as part of reconstruction and the advantage of choledochoenterostomy compared with cholecystogastrostomy concerning postoperative cholangitis[52,55].

Most surgeons continued the Whipple procedure, as described by Whipple, for decades, besides from experimenting with different reconstruction techniques, mainly focusing on management of the pancreatic duct. Isolation of the pancreaticojejunal anastomosis on a separate Roux-limb, different techniques of pancreaticogastrostomy, injection of the duct with occlusive material were all developed and tested, and none produced the desired decrease of pancreatic fistulas[51]. In 1978 the pylorus preserving PD was presented by Traverso and Longmire[56].

## Resectability and surgical considerations

Clinical staging for periampullary cancers are based on diagnostic work-up and the TNM classification system which describes the disease by its local extension (Tis-

T4), with or without lymph node metastases (N0-1) and with or without distant metastases (M0-1)[57]. Based on the TNM grading, a valuation of the disease stage (0-IV) is made. The disease stage has implications for treatment and prognosis.

All patients should be assessed at a multidisciplinary tumor board and a shared decision, based on radiological findings and considerations of risk and benefit grounded on performance status, will be taken individually for all patients. Special attention will be taken to the extension of engagement of adjacent major vessels and the presence of metastases.

At time of diagnosis, approximately 20% of the patients have a resectable tumor, 20-25% have a locally advanced disease and 50-55% have distant metastases[58]. In recent years, an intermediate group between upfront resectable and technically unresectable have emerged. They are found among the locally advanced tumors and are classified as borderline resectable, defined as a technically resectable tumor, but with a high risk for positive surgical marginal[59]. The details of the borderline resectable tumor has been debated, but moderate consensus exists, as displayed in table 2. Resectable tumors are all tumors with less vascular involvement, and locally advanced are tumors with more extensive vascular engagement. The presence of distant metastasis states the tumor as unresectable, regardless of local extension[58].

**Table 2**

Definition of borderline resectable tumors, as defined by the International study group for pancreatic surgery (ISGPS)[58].

| Borderline resectable tumor |
|---|
| Occlusion or narrowing of the portal vein/superior mesenteric vein for a short segment, with a suitable vein in the surroundings for reconstruction |
| Encasement of the gastroduodenal artery, with a short encasement or abutment of the hepatic artery, but without involvement of the celiac trunk |
| Tumor abutment of $\leq 180^0$ of the superior mesenteric artery circumference. |

There is convincing evidence of the survival benefit of PD for patients with resectable periampullary cancer compared with no operation. Bilimoria et al reviewed 9559 patients with early pancreatic cancer in the United States. Nearly 40% of these patients were not offered surgery. These patients had 1- and 5-year survival rates of 27% and 3% respectively, compared with 70% and 25% for the resected patients[60]. There is no convincing evidence regarding survival benefits for resection of metastatic pancreatic disease compared to palliative chemotherapy, although some data suggests an association with long-term survival in selected patients, particular those with only aortocaval lymph metastases[61,62].

*Surgical technique*

The resection can be a standard Whipple (here referred to as pancreaticoduodenectomy, PD), with the resection of the pancreatic head, gallbladder, common bile duct, duodenum and the distal part of the stomach. The other alternative is a pylorus preserving PD (PPPD). (figure 4) The PPPD is associated with shorter operative time and decreased blood loss. Postoperative mortality, overall survival and total morbidity is equal, but the rate of delayed gastric emptying is favored by standard Whipple[63].

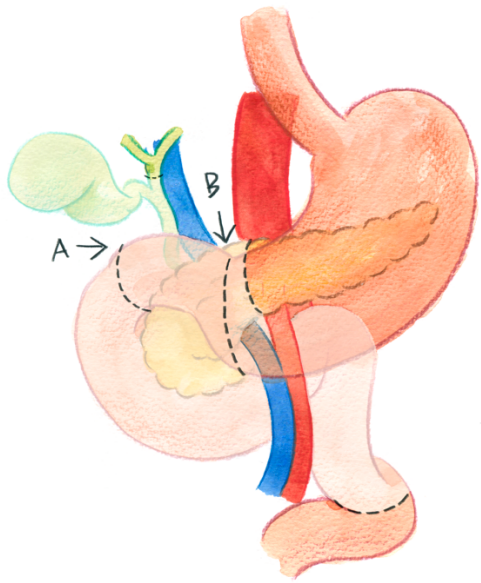


**Figure 4**
The area to be removed at surgery displayed in pale colours. A and B illustrates the different types of resection. **A** pylorus preserving PD, and **B** standard PD. © Elin Fahlstedt.

There are several alternatives for the reconstructive part. The pancreaticoenteric anastomoses that are most frequent are pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG). (figure 5) Currently, no technique is proven better regarding the postoperative pancreatic fistulas (POPF)[64]. Furthermore, neither fibrin glue or transanastomotic duct stent have proven its benefits on POPF[64,65].

The various techniques of PJ include end-to-side invagination, duct-to-mucosa and the "binding technique" using one or two-layer of sutures. Some studies have

implied that the duct-to-mucosa anastomosis is correlated with a lower incidence of POPF, however, others show contradictive results[64]. PG has been suggested to be technically easier[66], and anatomically more accessible for postoperative treatment of intraluminal hemorrhages[67]. Some randomized controlled trials have compared PG and PJ, albeit most fail to find any difference in POPF rate at all[66,68-70], however some studies suggests a reduced rate of POPF for PG, 10-11% vs. 24.5-33%, compared with PJ[71,72]. Two recent meta-analyses presented contradictive results, one in favor of PG and one showed equal rate of fistulas[73,74].

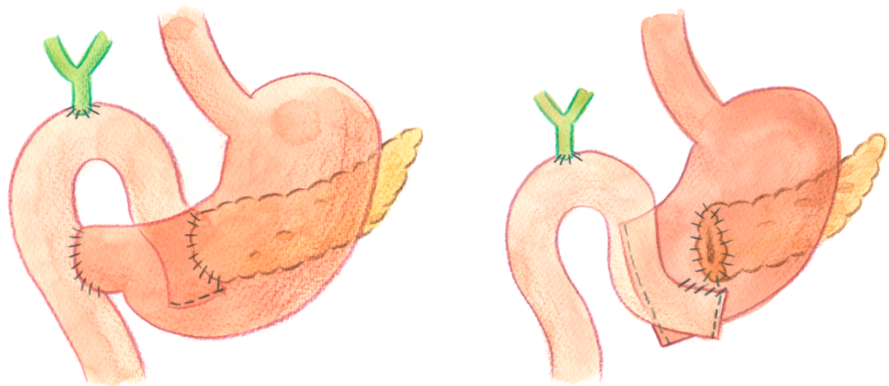

**Figure 5**
Schematic illustration of different recontructive techniques. **Left**: Pancreaticojejunostomy, gastroenterostomy and hepaticojejunostomy after a PPPD. **Right**: Pancreaticogastrostomy, gastroenterostomy and hepaticojejunostomy after a PD. © Elin Fahlstedt.

Based on the absence of standardization of the surgical technique, inadequate study design and various confounding factors, there are insufficient evidence to make clear conclusions[64]. However, high volume surgeons use both techniques with good outcome. It has been suggested that a standardized and consistent practice of a single technique might reduce the fistula incidence[75].

*The importance of radical resection*

Increasing tumor size[76] and extension of lymph node involvement correlates with a poor prognosis[43,77,78]. Poorly differentiated tumors display an aggressive behavior[79] and invasion of the vascular, lymphatic and neural system also worsen the prognosis[80], specifically perineural invasion[81]. These are all factors that cannot be influenced by the surgeon.

The surgeon's ambition, which is to remove the tumor radically, will give the patient an opportunity for cure. The anatomical intimacy of essential vessels may interfere with the surgeon's mission.

A radical resection refers to the term R0, indicating that no tumor cells are existing at the resection margins. R1 is a microscopic presence of tumor cells at the margins, and R2 is an incomplete resection where macroscopic tumor is left in the patient.

Comparisons of the true resection margins between institutions have been difficult, since both a marginal of 0 mm and 1 mm were used for definition of R0. There are now standardized protocols for histopathological assessments of the pancreaticoduodenal specimen accepted at high-volume institutions, which have increased the rate of R1 resections to around 76-85%, since 1 mm marginal is obliged for R0[82,83].

R0 resections have an improved survival compared with R1 resections, and R1 resected patients have an improved survival compared with patients with locally advanced unresectable pancreatic adenocarcinoma[84]. A survival benefit is seen if the resection margin increases beyond 1mm[85]. Regarding R1, the most commonly involved margin is the posterior margin and venous margin (portal vein/superior mesenteric vein [PV/SMV])[82,86].

*Vascular resections*

To achieve a radical resection, a vascular resection might be necessary. (figure 6) Resection of the PV/SMV can be performed safely, with comparable short and long-term outcomes as for standard resection without vein resection[87]. There is no evidence for neoadjuvant therapy for isolated venous involvement[58].

Striving for R0-resections, a systematic resection of the PV/SMV has been proposed. Patients with pancreatic adenocarcinoma without venous involvement who had a PV/SMV resection had significant longer overall survival than patients in a matched control group without vein resection, 42 vs. 22 months[88].

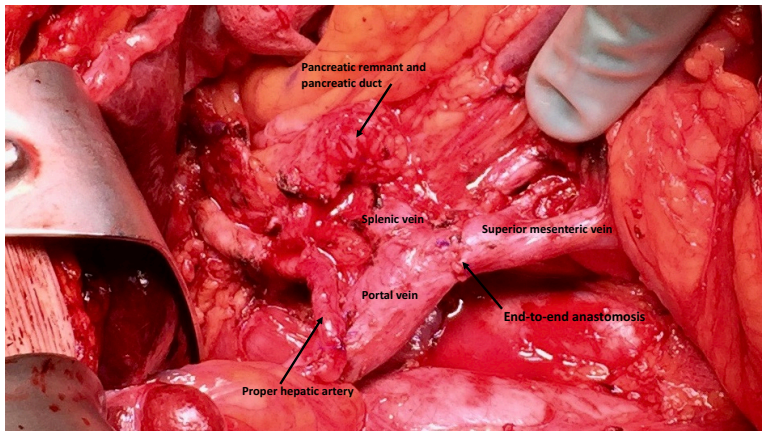


**Figure 6**
Picture of the surgical area after pancreaticoduodenectomy, displaying an end-to-end vein anastomosis. Photo dr. B Tingstedt.

Arterial resection is burdened with more than a fivefold increased perioperative mortality and a halved 1-year survival, than patients with comparable tumor situation[89], and is therefore not recommended routinely by the International study group for pancreatic surgery (ISGPS)[58]. These patients should be treated within a clinical trial. It can be delicate to classify these patients correctly, while it is difficult to differentiate true tumor growth from inflammation around the tumor. Therefore, the recommendation is that borderline resectable patients should undergo surgical exploration. Neoadjuvant chemotherapy or chemoradiotherapy are advocated for these situation, for the potential improvement of resectability and the rate of clear resection margins[58].

*Lymphadenectomy*

The classification of the nodal stations in pancreatic surgery is derived from the Japan Pancreas Society nomenclature, as displayed in figure 7[90]. A standard lymphadenectomy involves resection of pancreaticoduodenal lymph nodes (in figure below; 13, 17), lymph nodes along the hepatoduodenal ligament (5, 6, 12b, 12c), right side of SMA (14a, 14b) and the lymph nodes at the common hepatic artery (8a and debated 8p)[90]. As an attempt to improve overall survival, extended lymphadenectomy, which includes resection of lymph nodes around the celiac trunk (9), splenic (11d, 11p) and left gastric arteries (7), as well as along the left side of SMA (14c, 14d) and paraaortic nodes (16), has been studied. As of today, there are no evidence of survival benefits, but increased morbidity[91] and the ISGPS does not recommend extended lymphadenectomy[90].

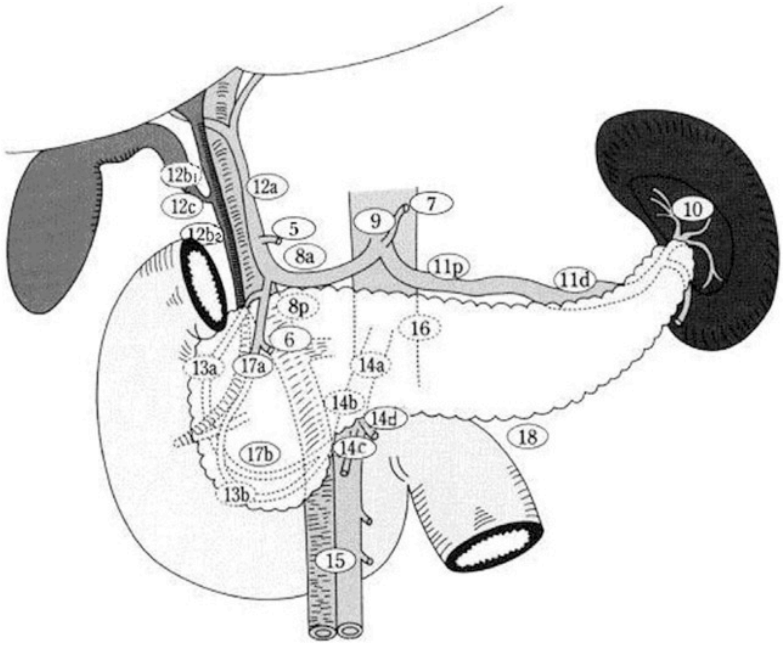


**Figure 7**
Japan Pancreas Society nomenclature of peripancreatic lymph nodes. (Reprinted with permission, Japan Pancreas Society. Classification of pancreatic carcinoma. 2003.)

## The postoperative course and complications

*High volume effect*

In the first years of experimenting with pancreatic surgery, the patient had an almost equal chance of survival or death from the surgery itself. With increasing experience the mortality fell, although with a disappointing pace. Prior to 1940 there were 41 PDs reported with an overall mortality of 34%, and during the beginning of the 1940s, 60 PDs with a mortality of 22%[50]. Hemorrhage was the most common cause of death. Still in the 1970s the mortality was approximately 20%[51,92]. There was a widespread skepticism to the procedure due to the high mortality. It was even suggested that for resectable pancreatic tumor, a palliative surgical bypass had equal or better outcome than an attempted resection[93]. In the beginning of the 1980s, the nihilistic attitudes changed as high-volume centers arose. Luft et al, presented as early as 1979 the relationship between high volume, increased experience and lower mortality[94]. Hospital mortality fell to less than 5%[95,96], operative times and blood loss decreased[34,97,98]. There was also substantial benefit in long-term survival[99-101].

The growing superiority of the high-volume institutions was based on a variety of factors including standardization of perioperative care, around the clock availability of experienced staff, mandatory review at multi-disciplinary tumor board, advances of surgical technique, intensive care support and interventional radiology, resulting in a safer procedure[34,96,102,103]. Large volume became a surrogate marker for improved outcomes. Birkmeyer reported in 2003, that much of the positive outcome in high volume centers, could be explained by the individual surgeon volume, since it correlated inversely with operative mortality[104]. The learning curve for PD is proposed to be around 60 operations, which is reachable only at high volume institutions[105]. In 2014, Schneider et al demonstrated that although patients at high volume centers have more medical comorbidities, the overall morbidity as well as failure to rescue after major complications are lower in high volume contra low-volume hospitals, following complex hepato-pancreatico-biliary surgery[106].

The organization to centers of excellence is an ongoing process. More recent reports from both the United States and Europe show a difference in perioperative mortality from 12-24% at low volume hospitals to 3-4% at high volume centers[107-110]. Higher hospital volumes explains a large proportion of decline in mortality associated with pancreatic surgery[111]. Median OS is prolonged (18 vs. 16 months) for patients in high volume centers[112].

The skeptics take time to convince. In 2007, Bilimoria et al reviewed 9559 patients with early, resectable, pancreatic cancer in the United States[60]. Nearly 40% of these patients were, for unknown reasons, not offered surgery. They also noted that patients were more likely to be offered surgery in combination with chemotherapy if they were diagnosed at a university hospital versus a community hospital.

*Surgical complications*

While mortality has decreased, the morbidity remains high. Some present a total morbidity around 50%[33,34,97,113], but also figures of 65-69%[114-116] is seen. The heterogeneity probably relay on how strict the review was in terms of reporting minor complications, as major complications are rather constant around 15-20%[114,115,117]. The most common complications are delayed gastric emptying (DGE) and postoperative infections, superficial wound infections or deep abscesses. The most serious complications are the postoperative pancreatic fistulas (POPF) and the postpancreatectomy hemorrhage (PPH).

There has been a change from operative to non-operative management of the various complications after PD. Interventional radiology has gained an important role[118] and most patients can now be successfully treated without reoperation[119,120].

*Postoperative pancreatic fistula*

Postoperative pancreatic fistula (POPF) is the major cause of serious morbidity after PD[121-123] and consequently correlates to increased hospital stay, mortality and costs[118,124]. Previously, the incidence of reported fistulas varied greatly due to a lack of uniform definition. Bassi et al demonstrated in 2004, that the rate of fistulas varied between 9.8% and 28.5% depending which definition they used[125]. In 2005, the International Study Group of Pancreatic Fistula (ISGPF) established a definition for POPF, based on a drain amylase elevated 3 times above normal serum level from the third postoperative day. The three grades, (table 3), represent an escalating clinical impact and economic sequelae[126]. Since then, it has been validated[121] and is the most used classification[127]. ISGPF just recently published their updated recommendation, where the former grade A is now called a biochemical leak, and no longer a true fistula[128].

**Table 3**
The definition of postoperative pancreatic fistula according to ISGPF[128].

| Postoperative pancreatic fistula | |
|---|---|
| **Grade A** | Biochemical leak. No need for altered management, no clinical or economical impact. |
| **Grade B** | Intermediate terapeutic interventions (medication, nutritional support), prolonged need for drainage, moderate increase of hospital stay, complications and costs. |
| **Grade C** | Aggresive intervention that dramatically impact the postoperative course (reoperation, intensive care for sepsis treatment), significant increase of hospital stay, morbidity and costs. |

The total rate of fistulas associated with PD is 19-26% and 11-12% consists of the clinically relevant fistulas (CR-POPF), grades B and C[127,129].

Patients with fistulas are more prone to have bile leak, deep abscesses and wound infections[122]. Furthermore, deep abscesses are most frequently associated with fistulas[130]. The cost for patients with CR-POPF are 1.3 times higher than the cost for those without CR-POPF[115].

There are many reports on predisposing factors for POPF which can be divided into patient, tumor and operative features. Obesity[131], increased operating time[113,122,123], increased blood loss[132], intraoperative transfusions[122], soft parenchyma and a gracile pancreatic duct[122,132-134] are some recognized risk factors. The ampullary, duodenal and bile duct cancers correlate with a higher rate of POPF compared with the pancreatic adenocarcinoma, explained by their less obstructing effect on the pancreatic duct[113,132]. Fistula rates of 5% in chronic pancreatitis, 12% in pancreatic cancer, 15% in ampullary cancer and 33% in bile duct cancer have been reported[135]. Predictive risk scores originating from risk factors have been presented. Roberts et al[136] use body mass index (BMI) and pancreatic duct size, whereas Callery et al[134] use pancreatic texture, location of tumor, pancreatic duct diameter and intraoperative blood loss, to calculate a risk percentage for postoperative fistula. As

mentioned previously, none of the techniques for pancreatic anastomosis are definitely superior to another[64].

Despite extensively studied, controversy exists regarding the prophylactic effect of somatostatin analogues, such as octreotide. Several European studies states that octreotide may prevent postoperative fistulas and support routine use, whereas North American studies conclude the opposite.[64] A Cochrane review summarized that somatostatin analogues may decrease postoperative complications but not mortality[137].

*Delayed Gastric Emptying*

Delayed gastric emptying (DGE) without mechanical obstruction is common after pancreatic surgery, reported to affect 19%-57% of all patients[33,138,139]. A variation of definitions existed, but the validated[140] consensus definition presented by ISGPS in 2007, has aided comparisons of studies onwards[141]. A DGE is defined by the need of nasogastric tube after postoperative day (POD) 3, or the inability to tolerate solid food on POD 7. (table 4)

**Table 4**
Delayed gastric emptying as defined by IPGPS[141].

| Delayed gastric emptying | |
|---|---|
| **Grade A** | NGT for 4-7 days or reinsertion >POD 3, unable to eat at POD 7 |
| **Grade B** | NGT for 8-14 days or reinsertion >POD 7, unable to eat at POD 14. |
| **Grade C** | NGT for > 14 days or reinsertion >POD 14, unable to eat at POD 21 |

The mechanism of gastroparesis is not entirely understood. Decreased plasma motilin levels caused by resection of the duodenum[142], lymph node dissection along the common hepatic artery causing a disruption of vagal and sympathetic innervation to the antropyloric region and devascularization of the pylorus after PPPD are some of the factors accused to induce DGE[143]. The various techniques of gastroenterostomy have been suggested to affect the rate of DGE, but two recent meta-analyses could not reveal any differences in DGE between the antecolic or retrocolic route of the gastrojejunostomy[143,144]. However, DGE is often associated with intra-abdominal collections from an unsatisfactory drained POPF or an intraabdominal abscess[139,143,145]. A patient BMI ≥35 and an increased operating time have been suggested as risk factors for DGE[139].

DGE is not a life-threatening complication but can prolong hospital stay[139,140] and decrease quality of life[141].

*Postpancreatectomy hemorrhage*

Postpancreatectomy hemorrhage (PPH) is a potentially life-threatening complication of PD. The frequency of gastrointestinal or intraabdominal hemorrhage following pancreatic resection, is approximately 1-8% and accounts for 11%-44% of overall mortality[146-149]. An international consensus definition was established by ISGPS also for PPH, where it is classified according to onset, severity and location of bleeding (intra-/extraluminal)[149]. (table 5)

**Table 5**

Postpancreatectomy hemorrhage, intra- or extraluminal bleeding, as defined by ISGPS[149].

| Postpancreatectomy hemorrhage | |
|---|---|
| **Grade A** | Early (<24 hours) mild, no or little clinical impact |
| **Grade B** | Early severe, moderate/severe clinical impact, radiology/reoperation<br>Late (>24 hours) mild, little/moderate impact on clinical course, observation/radiology/endoscopy |
| **Grade C** | Late severe, life-threatening, need for aggressive intervention: interventional radiology/reoperation/intensive care |

The grading system has been validated and correlates well with increased morbidity, mortality and hospital stay[148,150]. Early PPH is largely caused by surgical failure with inadequate hemostasis, and late PPH is often correlated with a POPF or a deep abscess, which have an erosive effect on blood vessels[150]. Late PPH is preceded in around half of the cases with a sentinel bleed, which is a minor bleeding from surgical drains or the gastrointestinal tract, and should instantly lead to an intense search for the source of bleeding with CT angiography or angiography[151].

Wellner et al presented a cohort of 1082 patients with an overall rate of PPH of 7.2%. The mortality was 4.1% for patients with PPH grades A/B and 31% for patients with PPH grade C. Most common were the intraluminal bleedings, followed by bleeding from the visceral artery branches. Intraluminal PPHs were associated with less mortality compared with the extraluminal bleedings (7.7% vs 20.5%).[146]

*Intra-abdominal abscess and prophylactic drain*

Intra-abdominal abscess occurs in 3-14% after PD[130,152]. It is a frequent cause of re-hospitalization and is associated with POPF or biliary fistulas[120]. There are contradictive data on the correlation of abscesses and preoperative biliary stents. While some have proposed that intraabdominal collections can be superinfected by colonized bile after biliary stenting[120], other report similar frequency of intra-abdominal abscesses between stented and non-stented patients[153]. Another source of infection is translocation of colon bacteria, as described in acute pancreatitis[154]. Risk factors for postoperative infectious complications are age >70, BMI >25, operative time >7 hours, bile contamination and a soft pancreas[152].

Prophylactic drain insertion allows monitoring for postoperative bleeding and detection and drainage of a pancreatic fistula. Prolonged usage of drain (>POD 4) is shown to correlate with increased incidence of intraabdominal abscesses[155]. Furthermore, some studies failed to show reduction of complications in presence of drains[156,157]. However, omitting drain was also demonstrated to increase morbidity and mortality in unselected cases[158]. Currently there are indications that a prophylactic drain can be avoided in patients with low-risk for POPF[159,160], and that a long-lasting drain is associated with increased complications, hospital stay and costs[161].

## Pancreaticoduodenectomy at Skåne University Hospital, Lund

Due to policy changes, pancreatic surgery has been transferred from several hospitals in the region to Skåne University hospital during the last decade, resulting in the organization of a tertiary referral center.

The technical aspects of pancreaticoduodenectomy have mainly remained constant since 2000, except for a change in the reconstruction of the gastroenterostomy (GE) and hepaticojejunostomy. Between 2000 and 2009 the hepaticojejunostomy was performed on a single Roux-en-Y, followed by the gastroenterostomy and enteroenterostomy on an antecolic omega loop. After 2009, the GE and hepaticojejunostomy was performed on the same Roux-en-Y, as presented below.

After access by a bilateral subcostal incision and subsequent exclusion of metastatic disease, PD is performed including resection of the pyloric region and a standard lymphadenectomy. The reconstruction is made by pancreaticogastrostomy, with two layers of interrupted sutures to invaginate the pancreatic remnant into the posterior gastric wall. The gastrointestinal tract is reconstructed on a single retrocolic jejunal limb, with a side-to-side gastrojejunal anastomosis and distally an end to side hepaticojejunostomy. (figure 8) No sealants, patches or duct stents are used. A nasogastric tube and one or two intra-abdominal drains are inserted at operation. Prophylactic low molecular weight heparin, octreotide, proton pump inhibitor and antibiotics are used routinely.

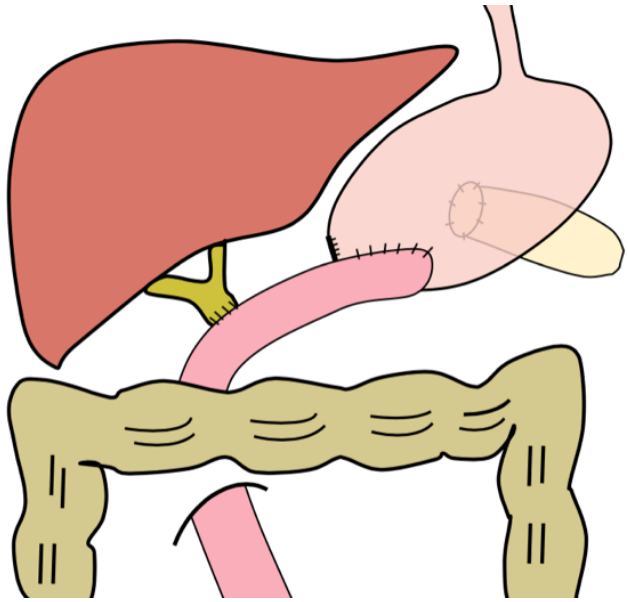

**Figure 8**
Schematic figure of the method of reconstruction, with a pancreaticogastrostomy and a gastroenterostomy and hepaticojejunostomy on a single jejunal limb.

## When resection is not possible

*Surgical bypass versus endoscopic treatment*

For 8-37% the tumor is unexpectedly found to be unresectable at time of the intended resection laparotomy, due to occult peritoneal or hepatic metastases[162-164]. Techniques for palliation of obstructive pancreatic tumors developed in the early 20th century, in absence of successful resections. Cholecystogastrostomy, eventually changed to hepaticojejunostomy, was used for biliary diversion and gastroenterostomy for gastric decompression, later on used in reconstruction after PD[92].

Historically, staging of patients with periampullary cancers was made with laparotomy. Prior to the development of modern imaging technique in the 1990s, 30-40% were found to have unresectable disease during exploration[165,166]. The anticipated high rate for biliary and gastric obstruction due to progressive disease, led to prophylactic bypasses. Amongst patients with periampullary cancers, biliary obstruction affects up to 75%[167] and around 13%-25% will develop gastric outlet obstruction (GOO)[98,167,168] during their remaining life-time.

The traditional biliary bypass, hepaticojejunostomy, was supplemented by a prophylactic gastroenterostomy, based on reports showing that perioperative

morbidity or mortality did not increase, for patients with an estimated life time that exceed 6 months[169-171]. (figure 9) Surgical bypass is reported to prevent recurrent biliary and delayed duodenal obstruction[169-172].

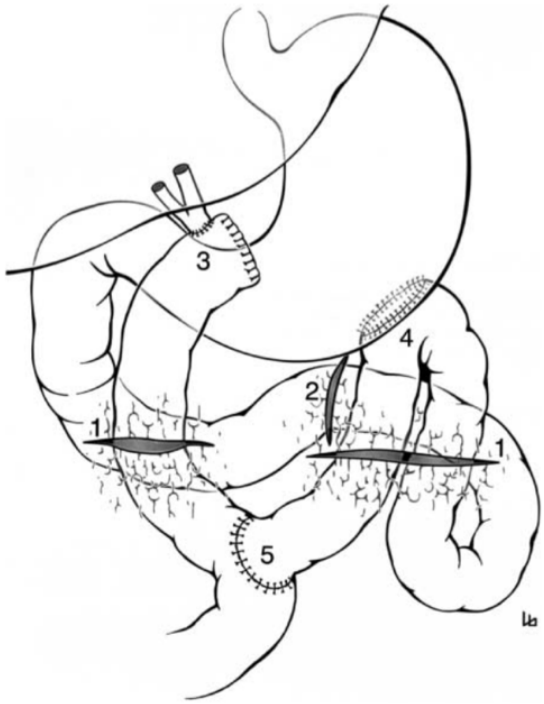


**Figure 9**
Schematic picture of a palliative double bypass, retrocolic hepaticojejunostomy and a gastroenterostomy by Heinicke et al[173]. **1**: Two openings in the transverse mesocolon, **2**: Ligament of Treitz, **3**: Efferent loop, retrocoloc, end-to-side hepaticojejunostomy, **4**: Afferent loop, side-to-side gastroenterostomy at the posterior gastric wall, **5**: End-to-side enteroenterostomy (reprinted with permission Copyright © 2002 Karger Publishers, Basel, Switzerland.)

The survival time for these patients are however limited, and a non-therapeutic laparotomy can be associated with substantial morbidity, potential mortality, decreased likeliness of palliative chemotherapy and diminished quality of life, making less invasive alternatives attractive[167,174]. An operation with a double bypass is burden with a morbidity of 31-56% and a mortality of 0-5%[165,169,170,175-177]. Since not all patients develop obstructive symptoms, the operative bypass might be unnecessary.

With the evolution of laparoscopic technique for staging, the assessment of stage was improved and some 14-35% unnecessary laparotomies prevented[178-180]. There are though reports on a limited detection ability of laparoscopy, just 35% of the total proportion of unresectable patients were found at laparoscopy[164] and with improved radiological technology for staging, the benefit of laparoscopical staging has

decreased[178,180]. The advantage of laparoscopy for pancreatic tumors are higher than for other periampullary cancers, 14% vs. 4%[178]. A recent Cochrane review conclude that diagnostic laparoscopy would avoid 21 unnecessary laparotomies in 100 patients, where CT scan shows resectable disease[181].

When biliary, duodenal or double bypass procedures recently were compared with laparotomy alone, their value was questioned. The proportion of patients requiring invasive postoperative interventions and the total number of in-hospital days was similar regardless of initial procedure, although the indication varied according to performed procedure. Following a double bypass, 40% of the patients required additional procedures[175]. A prophylactic duodenal bypass did not eliminate future GOO[176].

The modern endoscopic treatments challenge operative bypass procedures. There has been a significant evolution in the field of self-expanding metallic stents (SEMS) and their use in malignant obstruction symptoms. When unresectable cancer is detected during workup, palliation of symptomatic jaundice by placement of a biliary stent during endoscopic retrograde cholangiopancreatography (ERCP) is standard practice[182,183]. Besides, Espat et al have shown that 98% of the patients without surgical bypass at initial laparoscopic staging operation, were managed by endoscopic techniques without subsequent surgery[184].

There are no differences in technical or therapeutic success when comparing plastic biliary stents with operative bypass, but there is a significant higher risk for recurrent obstructive symptoms in the use of plastic stents[185]. Successful stent placement and efficiency is around 90%. SEMS are superior to plastic stents regarding patency (3-4 months vs. 7-10 months) and reduced risk for recurrent biliary obstruction[30,31,186,187]. Plastic endoprothesis are recommended if expected lifespan is less than 4 months[185,188], and SEMS when longer survival is expected[189]. SEMS are cost effective compared with plastic stents in locally advanced disease[189]. Lower costs and higher quality of life has been demonstrated for SEMS compared with surgical bypass[183]. In case of endoscopic failure, successful relief of bile obstruction can be reached with percutaneous transhepatic cholangiography (PTC) to the price of higher morbidity and mortality[190,191].

Duodenal stent is a safe and effective nonsurgical option for GOO[192]. Compared with surgery, endoscopic duodenal stent placement has benefits of shorter length of stay, lower costs[193-196] and faster relief of symptoms[192] to a better extent[194,195]. The rates of technical success and delayed complications[192,193,195] are comparable with the surgical alternative, as well as quality of life[197]. The need for re-interventions is higher, due to the more common recurrences of GOO after endoscopically placed stents[195]. However, in 75% of the patients, a single stent is effective and sufficient for the remaining lifetime[198].

Overall, endoscopic palliation is associated with shorter hospital stay and lower morbidity compared with surgical palliation[172,199]. Figure 10 displays combined biliary and duodenal stents.

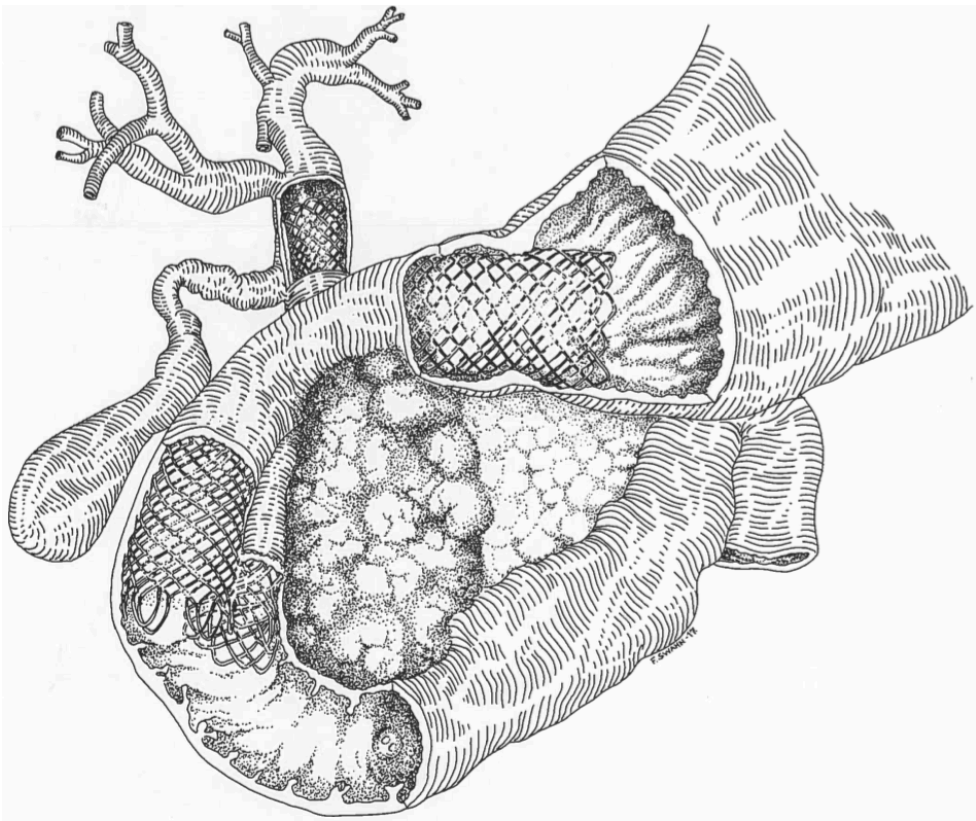

**Figure 10**
An illustration of the combination of a biliary and duodenal metal stents, for treatment of pancreatic tumor stricture. With courtesy of dr Fredrik Swahn. (© F Swahn)

Another aspect to consider, is that some data suggest that surgical trauma leads to shorter survival. Spanheimer et al showed that the overall survival was significantly shorter after surgical palliation compared with laparotomy alone[176]. Postoperative complications have a significant impact on long-term survival[117,177]. Long-term survival may be affected by the degree of systemic immune response to infection or surgical trauma[200,201].

For the palliative patient, it is of great importance to give sufficient support and adequate symptom relief. A contact nurse should be allocated and pain controlled

with opioids, steroids[202] or celiac plexus block[166,203]. Pancreatic enzyme replacement can increase body weight[204], which can improve quality of life and prolong survival[205].

Palliative chemotherapy for pancreatic cancer is gemcitabine or FOLFIRINOX (combination of fluorouracil, leucovorin, irinotecan and oxaliplatin), with a median survival time of 6.8 months vs. 11.1 months. FOLFIRINOX should, due to toxicity, be limited to patients with very good performance status[38]. Generalized duodenal cancer is treated in line with generalized colon cancer and ampullary cancers and cholangiocarcinomas are sometimes offered a combination of gemcitabine and oxaliplatin. The combination with radiotherapy has not shown any additional benefits for locally advanced disease[37], but additional irreversible electroporation (IRE) has been reported to nearly double median survival to around 23 months[206].

# Enhanced recovery

Enhanced recovery programs (ERP), also called Enhanced Recovery After Surgery (ERAS®) or fast track programs, are multimodal, evidence-based approaches to optimize patient outcome after surgery. The main objective is to reduce stress response to surgery and subsequently accelerate functional recovery. This is achieved through, among others, optimal pain control, early reintroduction of normal food and early mobilization[207].

The concept was first introduced by Professor Kehlet in Denmark in the 1990s[208]. Ideally, elective surgery should not affect the patient adversely, but in reality, it is associated with the risk of pain, infectious complications, nausea and gastrointestinal paralysis, among other unwanted factors that might prolong time to recovery and discharge[208,209]. An approach to avoid and minimize these factors is crucial. Apart from surgical and anesthetic failures, the key pathogenic factor in postoperative morbidity is the surgical stress, which is the systemic response to surgical trauma, regulated by endocrine, neural and immunological mechanisms[210]. Kehlet proposed multimodal interventions to modify postoperative pathophysiology, involving not only surgeons but also anesthesiologists, nurses and physiotherapists. Surgical wards were rearranged to rehabilitation units with focus on early mobilization, nutrition and pain relief, and restrictive attitude to recovery-limiting procedures such as iv fluids, catheters, drains and tubes[208].

The care programs are packages of evidence-based items, either general or specific to the contemplated surgery. Each item is suggested to contribute to a favorable outcome, but it is hard to determine the importance of each item's specific impact on outcome. The general principles are displayed in table 6.

**Table 6**
General principles of an enhanced recovery program[211].

| Preoperative | Perioperative | Postoperative |
|---|---|---|
| Information and counseling | Stress reduction: effective pain relief, regional anestesia, minimally invasive surgery | Opioid-sparing analgesia |
| Optimization of organ function | Short-acting opioids | Prevention of nausea |
| Abstinence of smoking and alcohol | Zero-balance of fluids | Prevention of paralytic ileus |
| No bowel preparation | Maintenance of normothermia | Early resumption of food |
| Carbohydrate loading | Oxygen therapy | Early mobilization |
| | Antimicrobial prophylaxis | Early removal of catheters, drains and tubes |
| | Thromboembolic prophylaxis | Discharge criteria |

Preoperative counseling reduce fear and improves compliance and postoperative recovery[212]. Preoperative organ optimization including abstinence of alcohol and tobacco influence the rate of postoperative cardiorespiratory, infectious and bleeding complications[209]. Bowel preparation may lead to dehydration and are not recommended[212]. Overnight fasting increases insulin resistance and discomfort after surgery[213], both well prevented by use of preoperative carbohydrate-rich drinks[214,215]. Epidural analgesia is superior to parenteral opioids in control of postoperative pain and return of gastrointestinal function[216]. Short-acting opioids are recommended perioperatively and an opioid-sparing regime postoperatively to minimize adverse opioid effects[209]. A zero-fluid balance is desirable, since intravenous fluid overload increase the risk for postoperative complications and delays the return of gastrointestinal function[217,218]. Normothermia and oxygen therapy may decrease the risk for anastomotic complications, wound infection[219] and normothermia may also diminish blood loss by minimizing coagulopathy[209]. Minimal invasive surgery reduces wound size and minimizes the adverse inflammatory response[220]. Antimicrobial and thromboembolic prophylaxis reduces postoperative infections and thrombosis[219]. Postoperative nausea and paralytic ileus are key factors in recovery and quality of life, and several other components of the enhanced recovery strategy have the goal of reducing postoperative paralytic ileus, such as epidural analgesia, laxatives and avoidance of fluid excess and nasogastric intubation[220].

Postoperative use of nasogastric tube increases the risk of fever, atelectasis and pneumonia, as well as delays return of bowel function[221]. Allowing normal food directly postoperative, at the patients' discretion, is safe and does not increase morbidity[222]. A transurethral catheter can be removed already on POD 1, even in the presence of a thoracic epidural, which reduce urinary tract infections compared with continued catheterization[223]. Prolonged bed rest is harmful, and increases muscle loss, impairs pulmonary function and predisposes to thromboembolic complications[208]. There are no clear suggestions on extent of mobilization, but decreased length of stay, earlier return of gastrointestinal function and better

postoperative performance have been demonstrated to correlate with mobilization[224].

ERPs were early adopted for colorectal surgery, but despite interest from several surgical areas, the implementation beyond colorectal surgery has been slow[211]. An enhanced restoration of organ functions has been demonstrated, and a decrease of primarily medical complications[219]. A Cochrane analysis of randomized controlled studies (RCT) of ERPs in colorectal surgery has demonstrated the reduction in morbidity and hospital length of stay[225]. A meta-analysis from 2014, including 38 randomized trial across different surgical areas, concluded that ERP reduces morbidity by 30% and postoperative length of stay (LOS) by 1 day overall[226].

There are currently several reports, but no RCTs, that supports enhanced recovery programs after PD, of which the majority were published in recent years. The described protocols are different. Some data show reduction of the DGE rate[227-229], although not supported by a meta-analysis from 2013[230]. Without compromising safety, a decrease of postoperative length of stay[231-238] and earlier recovery, mobilization and feeding[237,238] have been demonstrated. The programs are also safe for elderly[239,240]. Their impact on health-related quality of life (HRQoL) after PD has not been evaluated in pancreatic surgery setting. The anticipated decrease of overall morbidity as seen for colorectal surgery, has not clearly occurred.

In 2013, the ERAS® Society published guidelines for perioperative care for PD[241]. They include recommendations for the preoperative, perioperative and postoperative course, affecting a multidisciplinary team of surgeons, anesthesiologists, ward nurses and physiotherapists. In addition to the general recommendation above, some specific recommendations for PD are presented. Avoidance of preoperative biliary drainage unless necessary, early drain removal after 72 hours of perianastomotic drain unless indication of POPF, no use of somatostatin analogues and abstain enteral and parenteral nutrition in favor of normal food for patients without complications. The ERAS-group concludes at last, that a follow-up after implementation is essential for success. Additionally, it is important to evaluate achieved effects, and to be able to identify possible need for modification[241].

*Adherence to protocol items*

There is a proposed association between adherence to protocol and clinical outcome, as shown in colorectal surgery. Increasing compliance is shown to correlate with less complications and shorter hospital stay[242].

Another aspect is that a decrease in compliance have been demonstrated in the post implementation phase, when the sustainability of ERPs has been evaluated in colorectal surgery[243,244].

Reports on the PD patients' ability to adhere to protocol items have been scarce[231,232,239,240,245]. Two studies analyze adherence to preoperative, perioperative and postoperative elements more systematically[229,237]. Both presented high adherence rates to the preoperative and perioperative items, 84-100%, but for the postoperative items Braga et al showed a compliance rate of 38-66%[237] and Zouros et al compliance rates of 75-96%[229]. In accordance, they proposed that low adherence may be associated with postoperative complications, as uneventful patients in the latter study had a significant higher adherence, 88% vs. 41%, than those with complications[229], and all uneventful patients in the study by Braga had a postoperative compliance >60%.[237]

# Aims

The general aim of this thesis was to analyze strategies to improve the perioperative care for patients planned for pancreaticoduodenectomy, with less morbidity and better use of healthcare utilities.

Specific aims were

- To evaluate if the perioperative outcome after pancreaticoduodenectomy have been improved by the transition from a low- to a high-volume center.
- To develop an enhanced recovery program for perioperative care of pancreaticoduodenectomy and analyze its effect on outcome, with special focus on morbidity, length of stay, costs and quality of life.
- To investigate whether a surgical double bypass procedure or endoscopic treatment with stents (biliary and duodenal) on demand is better for patients with perioperative unresectable periampullary malignancies.
- To assess how the incidence, management and costs for clinically relevant postoperative pancreatic fistula (CR-POPF) have changed during the centralization process.
- To estimate the adherence rate to the different items in the enhanced recovery protocol and to evaluate its sustainability after the implementation phase.

# Methods

The study population mainly consists of consecutive patients planned for elective PD at the Department of Surgery, Skåne University Hospital at Lund, from 2000 and forward. Depending on the individual study that follows, there are some variations in inclusion criteria, based on year or diagnosis.

*Definitions*

Postoperative complications were graded according to the Clavien-Dindo classification system[246] at 30 days after surgery or within the primary admission. Grades I-II were regarded to be minor complications, and grades IIIa-V to be major complications. In paper V, complications were additionally classified according to the comprehensive complication index (CCI), to assess the burden of all complications, instead of solely the most severe one[247,248]. The open access calculator was used for CCI score estimation[249].

The complications specific to pancreatic surgery; delayed gastric emptying (DGE)[141], postpancreatectomy hemorrhage (PPH)[149] and postoperative pancreatic fistula (POPF)[126], were defined according to international consensus advised by the International Study Group of Pancreatic Surgery (ISGPS) and International Study Group on Pancreatic Fistula (ISGPF). They are graded in A-C, according to clinical severity, time of onset and management. POPF grade A is a biochemical fistula with no impact on patients' postoperative course, why the subgroup clinically relevant POPFs (CR-POPF), consisting of POPF grades B and C, was used. These procedure specific complications and their management were noted within 90 days.

Mortality was specified as in-hospital or within 30 days of PD in paper I, III and IV, and within 90 days in paper II and V. Postoperative day 0 was the day of surgery. Postoperative length of stay (LOS) was the total number in-hospital days after the operation.

In paper III, the definition of metastatic disease was a histologically proven liver or peritoneal metastases. A stage III tumor was always considered locally advanced. In presence of extensive vein involvement without reconstructive possibilities, a stage IIB tumor was also locally advanced. (table 7)

**Table 7**
Clinical stage in relationship with TNM for pancreatic cancer, which are the majority of unresectable patients.

| | T (Primary tumor) | N (Regional lymph nodes) | M (Distant metastaseis) |
|---|---|---|---|
| **Stage 0** | Tis | 0 | 0 |
| **Stage IA** | T1 | 0 | 0 |
| **Stage IB** | T2 | 0 | 0 |
| **Stage IIA** | T3 | 0 | 0 |
| **Stage IIB** | T1-3 | 1 | 0 |
| **Stage III** | T4 | 0/1 | 0 |
| **Stage IV** | T1-4 | 0/1 | 1 |

Tis: carcinoma in situ, T1: tumor ≤2 cm confined to pancreas, T2: tumor >2 cm confined to pancreas, T3: tumor growth outside pancreas without arterial involvement, T4: tumor growth outside pancreas with extensive arterial involvement.

The fast track program, which was implemented in 2012, changed name in 2014 to enhanced recovery program.

# Paper I

A retrospective observational study based on medical records analyzing outcome after PD, in relation to hospital volume.

Patients undergoing PD from January 1, 2000 until December 31, 2012, were identified from a computerized search in hospital records. A review of the medical records was conducted, and a database with details on patient demographics, tumor characteristics, surgical parameters and postoperative course was constructed. The annual hospital volume for PD were noted and thereafter categorized in three different volume groups based on cut-off values important for outcome, defined by others[250].

# Paper II

A prospective cohort study with a historical control group, evaluating safety, clinical outcome, costs and the impact on health-related quality of life of a fast track (FT) program for PD.

Consecutive patients undergoing PD were followed before (control group) and after (fast track group) implementation of the FT routine in October 2012, and their outcome were compared. Information on the FT group were prospectively collected

and data for controls were retrospectively collected from medical records. During the study time, there were no changes in the surgical technique.

Differences between traditional care and fast track program are outlined in table 8.

Total costs were calculated and included ward costs (healthcare personnel, laboratory tests and nutrition) as well as costs for operation, anesthesia and radiological examinations.

*Quality of life*

European Organization for Research and Treatment of Cancer (EORTC) is a multinational organization assembling research to improve management of cancer and its related problems. They have elaborated a validated questionnaire (QLQ-C30 version 3.0)[251] to assess the general quality of life of cancer patients, both functions and symptoms. Disease specific modules, with respect of tumor site and treatment, can be administrated in addition to the core questionnaire. The pancreatic cancer module (QLQ-PAN26)[252] measures gastrointestinal symptoms, pain and emotional problems, and addresses patients at all disease stages.

Health-related quality of life (HRQoL) was, in this study, measured by questionnaires two weeks before and four weeks after surgery. The two questionnaires were distributed to the participating patients, and collected, at the outpatient clinic.

**Table 8**
Parameters in fast track program versus traditional care.

| | Fast track pathway | Traditional care |
|---|---|---|
| **Before surgery** | Written and oral information to patient about operation and perioperative care | Oral information about operation |
| **Day of admission** | Pre-operative nutritional drink<br>Antithrombotic prophylaxis<br>Solid food until midnight | Antithrombotic prophylaxis<br>Fasting after midnight before procedure |
| **Day of surgery, POD 0** | Drinks until 6 am<br>Pre-operative nutritional drink at 6 am<br>Antimicrobial prophylaxis<br>Epidural analgesia<br>Secondary antimicrobial prophylaxis if operative time > 6 hours<br>Insertion of intra-abdominal drain, nasogastric tube and urinary catheter<br>Antiemetics at end of anaesthesia<br>Administration of PPI and pancreatic secretion inhibitor<br>Transfer to intermediate care unit and light mobilization and respiratory training<br>Sipping on clear fluids, 300 ml | Antimicrobial prophylaxis<br>Epidural analgesia or patient controlled analgesia (PCA)<br>Insertion of two intra-abdominal drains, nasogastric tube and urinary catheter<br>PPI and pancreatic secretion inhibitor<br>Intermediate care unit |
| **POD 1** | Transfer to ward<br>Nasogastric tube removal if < 300 ml/day<br>Oral intake of fluids, 500 ml<br>Mobilization (sitting at least 1+1 hour, 1 walk at the ward)<br>Respiratory training<br>Sample of amylase from intra-abdominal drain<br>Sample taking of blood glucose x 4, continuous until discharge | Transfer to ward<br>Respiratory training<br>Sample of amylase from intra-abdominal drain<br>Sample taking of blood-glucose x 4 |
| **POD 2** | Increased mobilization (sitting 2+2 hours, 2 walks around the ward)<br>Respiratory training<br>Oral intake of 1000 ml of fluids and yoghurt | Mobilization according to patient's ability<br>Respiratory training |
| **POD 3** | Increased mobilization (sitting 2+2 hour, 4 walks around the ward)<br>Respiratory training<br>Removal of nasogastric tube unless contraindicated<br>No limit of per oral fluids, yoghurt and toast<br>Sample of amylase from intra-abdominal drain, removal if amylase < 8 µkat/l* and fluids <200ml/day | Removal of nasogastric tube if accepted by operating surgeon<br>300 ml clear fluid<br>Sample of amylase from intra-abdominal drain on day 3 and 5.<br>Mobilization and respiratory training according to patient's ability |
| **POD 4** | Full mobilization<br>Respiratory training<br>Normal diet | Mobilization and respiratory training according to patient's ability<br>Stepwise increase of oral intake at the discretion of consulting surgeon |
| **POD 5** | Cancellation of EDA, substitution to oral analgetics | Drain removal at the discretion of the consulting surgeon. |
| **POD 6-7** | Removal of urinary catheter (POD 6)<br>Depending on previous day, with continuously step up of oral intake and mobilization | Removal of EDA and urinary catheter |
| **POD 8-9** | Discharge | |

Criteria for discharge: no fever, no need for intravenous fluids, satisfactory pain control with oral medication, passage of flatus or stool, full mobilization and patient agreement to discharge. EDA: epidural analgesia, POD: postoperative day, PPI: proton pump inhibitor.

# Paper III

A retrospective study investigating short- and long-term outcome after surgical double bypass compared to a "wait and see"-strategy with endoscopically placed stents on demand, for perioperative unresectable periampullary malignancy, during 2004 until 2013.

The approach to perioperative finding of unresectable cancer has at Sahlgrenska University Hospital been to perform a surgical double bypass, hepaticojejunostomy and gastroenterostomy. In contrast, at Skåne University Hospital Lund, the approach has been to surgically treat only patients with symptoms of dysfunctional biliary drainage and/or gastric outlet obstruction (GOO) at time of laparotomy. The bile duct was secured in all patients, either by a preoperative or intraoperative placed endoscopic stent. The patients without a palliative surgical procedure were observed with a "wait-and-see" strategy, i.e. wait until symptoms of GOO or biliary dysfunction develop, before performing endoscopic drainage or bypass procedures.

Patient treated at Sahlgrenska University Hospital and Skåne University Hospital were compared. Data included were patient demographics, tumor characteristics, oncological treatment, operative data including reason for unresectability, short- and long-term postoperative outcome and overall survival. All re-admissions and re-interventions due to biliary and/or duodenal obstruction were noted. Only patients with a confirmed diagnosis of periampullary cancer were included, except for endocrine cancers, which were excluded due to the different life-expectancy.

# Paper IV

A retrospective observational study investigating the incidence of clinically relevant postoperative pancreatic fistula (CR-POPF) before and after centralization of PD and its impact on outcome and health care costs.

Consecutive patients undergoing PD from 2005-2015 were included and data were collected from medical records and radiology investigations. Surgical outcomes were analyzed in three volume groups, low-volume 2005-2009, high-volume 2010-2012 and after implementation of ERP. For estimation of the preoperative risk for POPF, the pancreatic fistula risk score described by Roberts et al was calculated from BMI and pancreatic duct width[136,253]. A comprehensive individual assessment was made to associate all patients with a correct POPF grade. Outcomes for patients with CR-POPFs were compared to patients without POPF or POPF grade A. Special attention was made to the postoperative management of CR-POPFs, such as medical treatment, interventional radiology and reoperations, and their associated costs.

# Paper V

A follow-up study on the sustainability of the enhanced recovery program for PD, with focus on adherence rates, postoperative length of stay and revised protocol parameters.

In April 2015, two parameters in the ERP were revised. Removal of the nasogastric tube was scheduled to POD 1, regardless of drainage volume, instead of removal POD 1-3 if drainage volume was below 300 ml. The allowed volume output for removal of the abdominal drain was increased from 200 ml to 400 ml, and if low amylase levels (<480 units/l [8 μkat/l]), the drain was removed earliest on POD 3 and by latest on POD 5.

This study evaluated if achieved benefits from implementing the ERP in October 2012, was maintained in the post-implementation phase, until August 2016. Patients in the prospective study (paper II) constitute the control group, and were compared with the subsequent patients following the same ERP (intermediate group) and patients following a modified protocol for ERP (modified group). Time span were 15 months for each group.

Data from medical journal for the two post-implementation groups were collected for evaluation of adherence to the protocol overall as well as individual elements and compared with the control group. The different items were also categorized into preoperative, perioperative and postoperative care elements. Postoperative course was registered to compare outcome between the three groups.

# Statistics

Data were generally not considered to be normally distributed in these studies. Continuous data were presented as median (range) and categorical variables were given as numbers/frequencies and percentages. Univariate analysis for continuous variables was conducted with the Mann-Whitney U test (for two groups) or the Kruskal-Wallis test (for more than two groups). Comparisons of categorical variables were made by Fisher´s exact test (for two groups) or the Mantel-Haenszel $\chi^2$ test (for more than two groups). Adherence rates (paper V) were given as mean, and evaluation of differences analyzed by ANOVA.

In paper II a multivariable linear regression analysis was performed to assess whether any variables influenced length of stay independently. Variables with $p<0.050$ in the univariable analysis were included in the multivariable analysis.

The survival analysis in paper III was performed with the Kaplan-Meier method.

Data were analyzed using the SPSS statistical package 20.0-23.0 (IBM, Armonk, New York, USA/// Inc.®, Chicago, IL, USA). A p-value of $<0.05$ was considered significant.

# Results

## Paper I

A total of 221 patients underwent PD during 2000-2012 and the annual hospital volume increased by eightfold, from 5 PDs in 2000 to 39 PDs in 2012. Hospital volume was categorized by the number of PDs performed annually into low-volume (<10 PDs/year), years 2000-2004, n=25, medium-volume (10-24 PDs/year), years 2005-2009, n=86 and high-volume (≥25 PDs/year), years 2010-2012, n=110, as presented in figure 11.

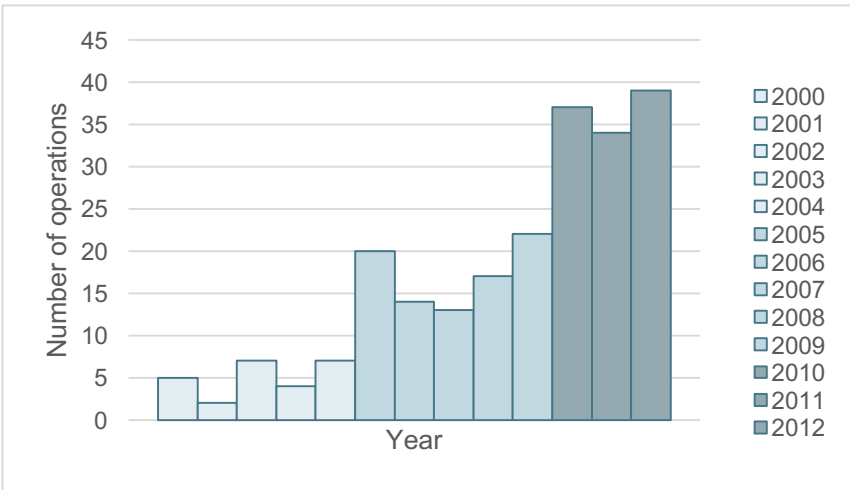


**Figure 11**
The increasing annual number of PDs presented, the three colors represent the volume classification, low-, medium- and high-volume.

Patient demographics did not change. Operative parameters improved from the low- to the high-volume period. The operative time decreased (median 523 min to 451 minutes), the intraoperative blood loss was reduced (median 1150 ml to 500 ml) and the subsequent need for blood transfusion was lower (57% to 10%), all clearly significant ($p<0.001$). There was a reduced incidence of postoperative hemorrhage

and reoperations, but the overall morbidity or intensive care did not change between the groups. The total number of patients with DGE did not decrease, but the proportion of severe DGEs had diminished in favor of the milder ones. Postoperative length of stay shortened significantly during this period, from 16 to 13 days.

The increased surgical volume resulted in benefits of the intraoperative parameters and reduced hospital stay.

# Paper II

A total of 100 consecutive patients underwent PD in the study interval, 50 patients before and 50 patients after implementation of the fast track program. The groups were comparable regarding demographics and co-morbidity. Patients in the fast track group had the nasogastric tube withdrawn and managed to resume a normal diet earlier than the control group. Postoperative length of stay was significantly reduced in the fast track group, and 80% of the patients were discharged by POD 14. There was no increase of readmissions within 60 days (3 patients in each group). There were fewer radiological examinations performed, especially the interventional procedures, in patients treated within the fast track program. The cost per patient was cut by almost 30%. (table 9)

**Table 9**
Postoperative parameters displayed for the control and fast track group.

| | Control (n=50) | Fast-track (n=50) | p-value |
|---|---|---|---|
| **Time to nasogastric tube removal** | 3.5 (1-34) | 1.5 (1-24) | 0.001 |
| **Tolerance of free fluids** | 6 (3-40) | 4 (2-24) | <0.001 |
| **Tolerance of solid food** | 8 (5-40) | 7 (4-25) | 0.024 |
| **Time to drain removal** | 7 (0-21) | 6 (0-32) | 0.061 |
| **Postoperative length of stay** | 14 (9-42) | 10 (6-35) | 0.001 |
| **Radiology** | | | |
| **All examinations** | 73 | 53 | 0.940 |
| **Interventioinal radiology** | 19 | 10 | 0.025 |
| **Cost (€)** | 14 576 (8 245-42 750) | 10 400 (6 519-39 558) | <0.001 |

Data presented as total numbers or median (range).

There was no difference in the overall morbidity between the groups, but the most common complication, DGE, was significantly reduced from 48% to 26% in the fast track group. Factors included in the regression analysis were the fast track program, variables that showed significant differences in the univariable analyses and age as

a co-variable. Factors that independently influenced LOS were the fast track program (p=0.049), DGE (p=0.012) and full tolerance of normal food (p=0.002).

All patients received HRQoL questionnaires, and 70% returned them completed in both groups. Most aspects of quality of life were impaired one month after PD. However, health status and function scales showed similar alterations, with no differences noted between the groups before or after surgery. Fatigue, loss of appetite and digestive symptoms were the predominant symptoms following the operation. (figure 12)

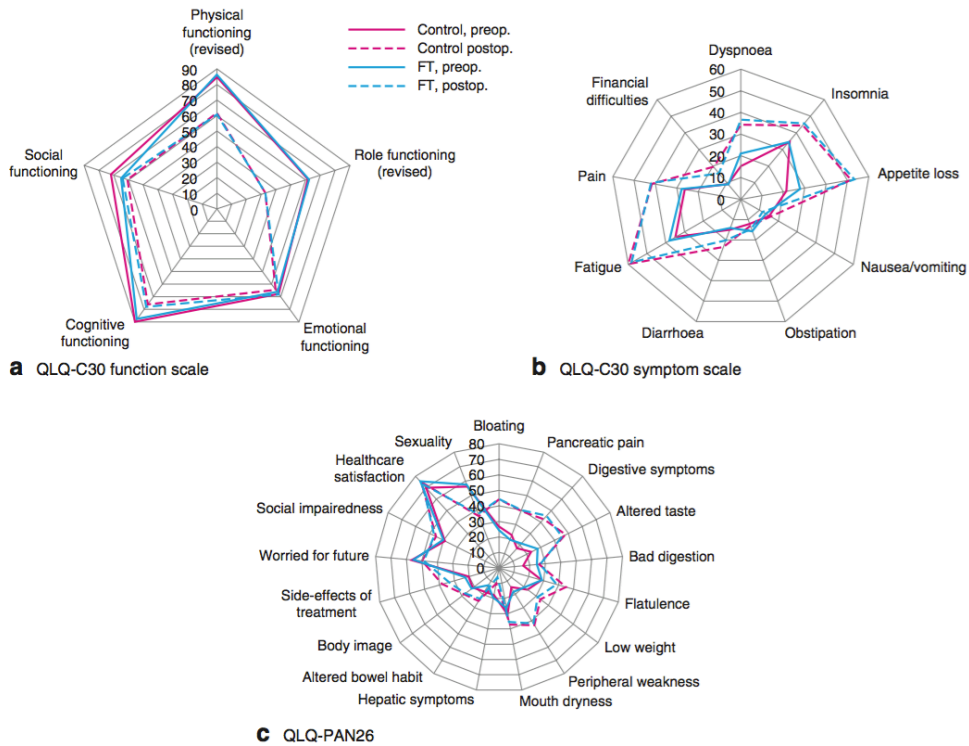


**Figure 12**
Quality of life 4 weeks before and after PD in control and fast track group. **a** QLQ-C30 function scale (100 is the best outcome), **b** QLQ-C30 symptom scale (100 is the worst outcome) and **c** QLQ-PAN26 (100 is the worst outcome).

In summary, the fast track program after PD resulted in shortened LOS and diminished costs, due to a faster postoperative recovery. Despite earlier discharge, readmission did not increase and HRQoL was not impaired.

# Paper III

A total of 143 patients were included in the study, 73 from Sahlgrenska University Hospital (Double bypass group, [DoB]) and 70 from Skåne University Hospital Lund (Wait-and-see group, [WaS]).

The patients in the WaS group were significantly older (70 versus 66 years) and had a higher ASA score than the patients in DoB. Tumor characteristics, such as histopathology, tumor size, stage and reason for unresectability, were similar between the groups. Palliative chemotherapy was administrated equally (60-64%) after the initial laparotomy. Initial procedure and postoperative outcome presented by strategy are showed in table 10.

**Table 10**
Proportion of different operative strategies and outcome, in the WaS and DoB group.

| | WaS n=70 | DoB N=73 | p-value |
|---|---|---|---|
| **Operative procedure** | | | |
| **Wait and see** | 48 (69) | 0 | |
| **Double bypass** | 12 (17) | 59 (81) | |
| **Gastroenterostomi** | 10 (14) | 2 (3) | |
| **Hepatikojejunostomi** | 0 | 12 (16) | |
| **Overall complications** | 22 (31) | 48 (67) | <0.001 |
| **Major complications** | 3 (4) | 17 (23) | 0.001 |
| **Removal of nasogastric tube** | 0 (0-22) | 2 (0-17) | <0.001 |
| **Tolerance of solid food** | 2 (1-31) | 7 (3-19) | <0.001 |
| **Delayed gastric emptying** | 12 (17) | 26 (36) | 0.017 |
| **Primary length of stay** | 8 (2-36) | 14 (6-71) | 0.001 |

Data presented as numbers (%) or median (range).

The operative time did not differ between groups, but the DoB group had a significantly higher intraoperative blood-loss (600 ml vs. 200 ml, $p<0.001$) and subsequent need for transfusions (32% vs. 14%) than WaS patients.

During their remaining lifetime, the two groups of patients were in similar need of readmission for biliary or gastric outlet obstruction, 61% in the WaS group and 67% in the DoB group, $p=0.491$. This results in a significantly shorter total length of stay for the WaS group, when both length of primary stay and readmissions are added together, compared to the DoB group (18 vs. 24 days, $p=0.001$).

Analyses to assess relapsing bile duct problems and delayed gastric outlet obstruction were made separately. The WaS group, primary treated with biliary stents, were divided into two groups depending on if they had a plastic or self-expanding metallic stent (SEMS), and were compared with the DoB group. Patients

with primary plastic stent had a significantly higher need for re-admittance and re-interventions, compared with both SEMS and DoB. (table 11)

**Table 11**
Outcome regarding hospital stay and reinterventions due to bile duct problems, ie. cholestasis and cholangitis.

| | WaS plastic n=25 | WaS SEMS n=23 | DoB n=73 | p-value |
|---|---|---|---|---|
| **Primary hospital stay** | 7 (3-39) | 7 (3-27) | 14 (6-71) | <0.001 |
| **Total hospital stay** | 18 (3-74) | 15 (5-73) | 24 (8-53) | 0.001 |
| **Patients readmitted due to cholangitis/cholestasis** | 17 (68) | 6 (23) | 11 (15) | 0.001 |
| **Hospital days due to biliary related problems** | 10 (0-36) | 4 (0-27) | 4 (0-42) | 0.001 |
| **ERC/PTC post initial intervention** | 37 | 13 | 10 | 0.001 |

Data presented as numbers (%) and median (range). WaS: wait and see, DoB: double bypass, SEMS: self expanding metallic stent, ERC: endoscopic retrograde cholangiography, PTC: percutaneous transhepatic cholangiography

Delayed GOO afflicted both group to similar extent, as well as corresponding need for hospital stay and re-interventions, as shown in table 12.

**Table 12**
Outcome regarding gastric outlet obstruction (GOO).

| | 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 GOO** | 15 (8-46) | 17 (7-92) | 0.473 |

Numbers (%) of patients and days in median (range).

There was a trend towards a longer overall survival in the WaS group, with a median of 330 days (15-1005) compared to 248 days (23-833) in the DoB group, albeit not significant, p=0.117.

This study demonstrates the higher rate of complications and longer hospital stay correlated with surgical double bypass, compared with endoscopic treatment with stents of biliary and duodenal obstruction.

# Paper IV

In total, 322 patients were included in the study. During the study period, the annual operation volume increased from 17 PDs/year in the low volume period, to 34/year in the high volume, up to 45/year in the ERP period.

Background data for the whole cohort showed mainly no differences in patient demographics or histopathology, except a higher frequency of smokers in the ERP group. The preoperative pancreatic fistula risk score was equal between the groups. There was a clear trend towards shorter length of stay (15 to 12 days, p=0.001) and decreased costs for PD care (€ 28 112 to 22 292, p<0.001) regarding all patients during this period.

The total incidence of CR-POPF was 12% during the study period, with no decline over the different volume groups. (figure 13) Regarding removal of nasogastric tube, resumption of normal food and the use of interventional radiology, no differences were noted. Furthermore, there was no decrease in intensive care utilization, overall length of stay or correlated costs for these patients. (table 13)

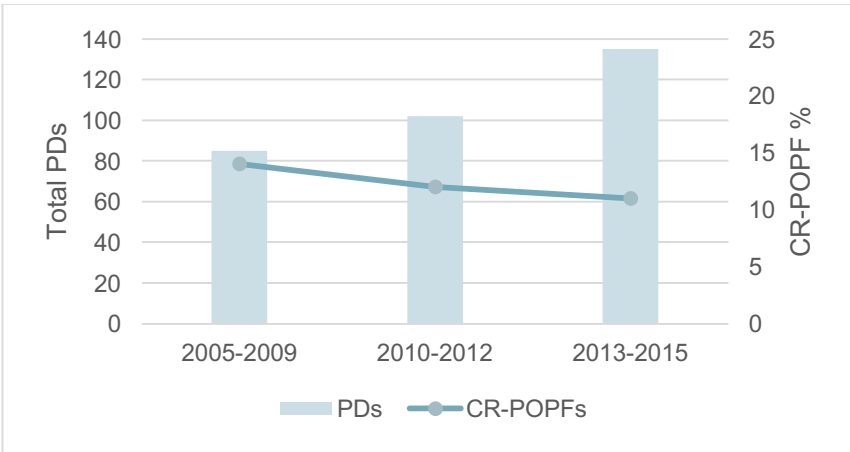


**Figure 13**
Evolution of total PDs and frequency of CR-POPFs in the different groups.

Patients with a CR-POPF, had a higher BMI (27.9 vs. 24.3, p<0.001), greater proportion of benign histopathology (23% vs. 8%, p=0.008) and had suffered a higher blood loss during surgery (650 ml vs. 500 ml, p=0.030), than patients without this complication. They were also more prone to other major complications (Clavien-Dindo ≥3a 59% vs. 11%, p<0.001) and subsequent therapeutic interventions (56% vs. 13%, p<0.001). The cost following their care is almost two-thirds higher (€ 34 061 vs. 22 181, p<0.001).

**Table 13**
Postoperative parameters for patients with CR-POPF.

| | Low-volume 2005-2009 n=12 | High-volume 2010-2012 n=12 | ERP 2013-2015 n=15 | p-value |
|---|---|---|---|---|
| **Posterative length of stay** | 30 (17-62) | 27 (8-78) | 24 (8-97) | 0.684 |
| **Removal of drain** | 16 (2-48) | 10 (5-36) | 7 (1-78) | 0.239 |
| **Removal of NGT** | 9 (5-27) | 7 (2-39) | 5 (1-78) | 0.632 |
| **Intensive care unit** | 22 (1.8) | 20 (1.8) | 20 (1.3) | 0.293 |
| **Interventional radiology** | 4 (33) | 5 (42) | 9 (60) | 0.382 |
| **Reoperation** | 2 (17) | 0 | 2 (13) | 0.357 |
| **Cost (€)** | 42 887 (30 572-80 263) | 30 810 (23 000-81 948) | 29 355 (20 112-141 246) | 0.075 |

Data presented as median (range) and numbers (%), exept for intensive care unit which is total days and mean.

Despite a continued increase of hospital volume and improved outcome for the overall PD cohort, the incidence of CR-POPF and associated costs have not decreased.

# Paper V

Overall 160 patients underwent PD during the study time, equally distributed in the three groups, control (n=50), intermediate (n=55) and modified (n=55). Preoperative and intraoperative variables were essentially unchanged, except a significant higher frequency of vascular resections in the modified group, (2%, 9% and 18% respectively).

Analysis of the postoperative course, showed a tendency over time to remove the nasogastric tube and abdominal drain earlier, which correlates with the changes made in the protocol. There was a higher frequency of nasogastric tube reinsertions, but there was no corresponding increase of postoperative complications. (table 14)

**Table 14**
Postoperative parameters for the three groups.

| | Control n=50 | Intermediate n=55 | Modified n=55 | p-value |
|---|---|---|---|---|
| **NG tube removal** | 1.5 (1-24) | 1 (1-8) | 1 (1-8) | <0.001 |
| **NG tube reinsertion** | 7 (14) | 18 (33) | 21 (38) | 0.017 |
| **Free fluids** | 4 (2-24) | 3 (2-78) | 2 (0-30) | <0.001 |
| **Solid food** | 7 (4-25) | 7 (4-80) | 6 (4-44) | 0.557 |
| **Drain removal** | 6 (0-32) | 7 (3-24) | 4 (2-74) | 0.001 |
| **Length of stay** | 10 (6-35) | 12 (7-97) | 13 (6-77) | 0.301 |
| **Clavien-Dindo ≥3a** | 7 (14) | 11 (20) | 16 (29) | 0.169 |
| **CCI** | 12.2 (0-54.2) | 12.2 (0-85.1) | 22.6 (0-100) | 0.123 |

Data presented as numbers (%) and median (range). NG tube: nasogastric tube. CCI: comprehensive complication index.

As shown in figure 14, overall protocol adherence increased over the groups, with the highest compliance to the pre- and perioperative parameters. Of the postoperative protocol items, adherence increased significantly to abdominal drain removal on POD 3 (from 17% to 42%) and normal food on POD 4 (from 8% to 31%). Overall adherence was further analyzed in 10%-intervals, i.e. ≥50% to ≥90%. The higher overall adherence rate a patient presented, the shorter median postoperative length of stay and less major complications for that group of patients.

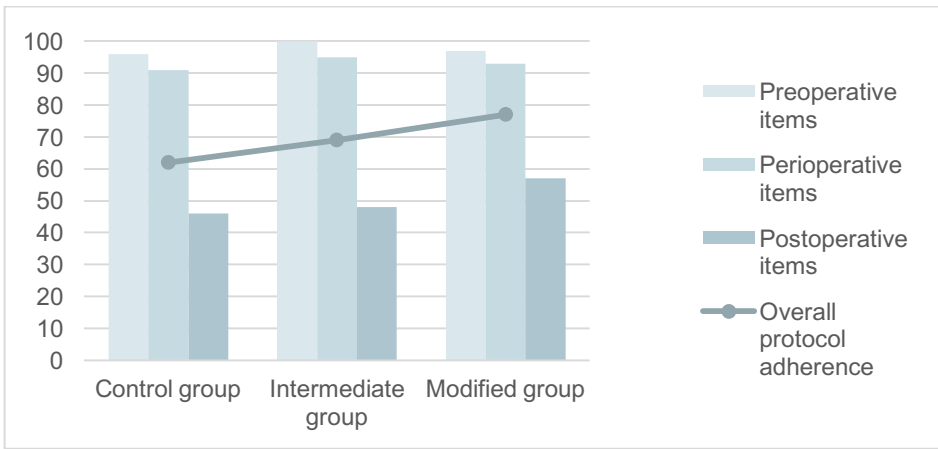


**Figure 14**
Adherence to the preoperative, perioperative and postoperatve items, and overall adherence, in the three groups.

As presented here, the postoperative outcome was maintained and adherence rates to the different ERP items have increased in the post implementation phase.

# Discussion

The results presented here will hopefully contribute to a better understanding of the perioperative elements that affect outcome after PD, and furthermore, improve the quality of life for unresectable patients. Considering most patients undergo PD for cancer, patients should be in better performance status to tolerate chemotherapy, if recovered well after the initial surgery.

## Aspects of centralization

Paper I serve as a detailed presentation of where we were standing at that point, and a stepping stone for the further studies in this thesis. With the structural changes in the region, and the eight-fold increase of hospital volume between 2000 and 2012, there was a need for a structural review of the change. The result basically verified what the team members had assumed, and provided a framework for identification of areas for possible improvements within the perioperative course.

The growth of experience that followed the major volume increase, resulted in improved quality parameters for PD such as decreased operating time and diminished blood loss during surgery. Furthermore, there were a decrease of some postoperative complications, such as PPH and a proportional change of the DGEs in favor of the less severe. Mortality was low overall, and there were no deaths in the high-volume era. Cameron et al[34], presented in 2006, a single institution, single surgeon's increasing experience with 1000 PDs, showing similar reduction of operating time, decreased blood loss and reduced LOS as in paper I.

The relationship between volume and mortality has been known for many years[107,111,250]. The outcome after PD can be influenced by other factors besides volume. Age, male gender and co-morbidity have been shown to increase risk for postoperative complications[254]. However, these factors did not differ between the volume groups in our study.

Alongside the increased case-load several other areas developed. The surgical instrument ultrascision was introduced, which might have affected operating time and intraoperative bleeding favorably. A core staff of few senior surgeons ensured a standardized consistent technique, which is proposed to improve outcome[75]. High

volume surgeons have been suggested to explain the better outcome at high volume centers[104]. Moreover, the ward staff, radiologists and interventional radiologists, acquired more experience following the volume-increase, which facilitated detection and management of complications, but also a more efficient postoperative care of the uncomplicated patient.

## Aspects of the perioperative course

*Enhanced recovery program*

The main reason for implementing the structural change in perioperative care with a fast track protocol, was the expectation of improved outcome for the patient. Apart from the stress reducing effect of the program, the standardized management intended to minimize unnecessary variation in care. “Fast track” will from now on solely be referred to as “enhanced recovery” or “ERP”.

The implementation of the program was safe, as no increase of total morbidity was disclosed. The overall decrease of morbidity, as seen in other surgical areas[226] and some meta-analysis with PD[230,255], was not seen. DGE however, the most common complication after PD, was reduced from 48% to 26%. Similar decrease of DGE has been presented by others[227,229], but was not confirmed in the meta-analysis mentioned above[230]. Early eating did not increase the rate of POPFs, in congruence with reports by others[222,227,233,238].

The implementation of ERP decreased LOS from 14 to 10 days, in line with other ERP reports[227,233,235,238,256], and was not associated with increased readmissions or impaired HRQoL. The reason for the decrease in LOS has been debated. The program itself have been suggested to be the single factor for reduced LOS[236], while early critics claimed the reduction is just an existing trend in healthcare systems, together with a selection of healthier patients[257,258]. With increasing experience of ERPs in different specialties applied for consecutive patients, there is however no longer any questions of the shortening effect on the hospital stay[226,255,259,260]. Our study showed that the program itself, reduced rate of DGE and earlier eating are independently associated with shortened LOS. The expectations from both patients and healthcare personnel also probably contributed to shorter LOS.

The evolution of perioperative care and subsequent shorter hospital stay, significantly reduced cost of care for PD patients, as shown in paper II and IV. An intention to decrease the cost of care, was never the purpose of the perioperative structural changes. It has to be looked upon, as a positive side-effect of the improved recovery and better performance status of the postoperative patients. Superior care for less expense, is indeed optimized use of healthcare resources. The cost-

effectiveness of ERPs is supported by many[233,261,262], but contradictive opinion exists[263].

This is the first, and to my knowledge, the only study evaluating quality of life for ERP after PD. There were no differences between the group with conventional or ERP care, in line with knowledge from colorectal surgery[264]. A deterioration in HRQoL one month after PD is expected[265]. One month after major surgery might have been too soon for evaluation. Our intention was to evaluate patients before possible side-effects of adjuvant chemotherapy.

The postoperative incidence of DGE was still quite high, but in concordance with figures presented by others (13-37%)[139,238]. The interpretation of DGE can be rather difficult and the DGE rate in the historic cohort was probably influenced by the forced use of nasogastric tube until POD 3. However, for both groups, the ISGPS criteria was used equally. As shown by Robertson et al, risk factors for DGE were operating time over 5.5 hours, prophylactic octreotide and patient BMI $\geq$35[139]. At least the two first-named factors were present for the majority of patients in paper II.

Paper II adds knowledge about the safety of ERP, not only related to PD, but also with the reconstruction by PG. There is insufficient knowledge on how well the evidence for PJ is transferrable to PG, regarding suitable management of nasogastric tube and eating. There is only one other study demonstrating that ERP for PD with PG is safe[228]. Today, many support the omission of nasogastric tubes, but they all perform a PJ[234,237,238]. The PG itself presents no increased risk for DGE[266]. However, the unpleasant thought, for which there is no evidence, of a gastric retention filled to the rim, stretching a new non-flexible anastomosis, influenced the decision of having an output limit for removal of the nasogastric tube in our program. At the time, that was also employed by others[227,231].

The enhanced recovery protocol developed for paper II corresponded well with the guidelines for PD published by the ERAS® Society during the study time. The main differences were the use of decompressing nasogastric tube, parenteral nutritional support and prolonged use for transurethral catheter[241].

*Follow-up and adherence to protocol*

After a successful implementation of a new routine, there is a risk for return to old traditions when the novelty effect fades out. The Hawthorne effect might enhance the difference in the result of implementation phase and post-implementation phase, because of the change of behavior, solely due to the study[267]. Introducing new programs can be challenging and require investments of personal time, devotion and financial investments[268]. Achieved benefits should be maintained, for the patients' best and to prevent a waste of valuable health-care resources[243]. Interpretation of the outcome of different ERP studies is problematic, without knowledge on how the

patients managed to adhere to the programs. A compliance of 70-80% has been suggested for improved outcome[259].

Encouraged by the support from guidelines[241], and the lack of adverse events in our program, the ERP was modified in 2015. The nasogastric tube was removed on POD 1, and the intraabdominal drain was removed on POD 3, if <400 ml and no signs of POPF. Changes of the protocol must be followed by an analyze of its impact[241,259].

Paper V presented the results of the ERP audit, including the modified protocol, showing that the early positive outcome was sustained, without any significant change in morbidity or LOS.

Moreover, the compliance to protocol items were more than 90% to preoperative and perioperative items, but lower rates, of 46-57%, to the postoperative elements. This result was in comparison with the studies by Zouros[229] and Braga et al[237], except for the higher postoperative adherence rates by Zouros. They both demonstrated an association for low compliance and postoperative complications. Likewise, our paper showed that a high compliance was correlated with fewer complications and shorter LOS. The postoperative items are logically more challenging to fulfil, since they are affected by adverse events, lack of patient motivation or wrong information from healthcare personnel.

This is the first paper which presents continuous adherence rates for PD, similar to standards used in colorectal surgery. The compliance with the program increased over time after implementation, from 64% to 71% overall, contrary to results from colorectal surgery[243,244]. The modification of the protocol might have brought new attention to the protocol, as any change were followed by repeated education. As shown previously, repeated training and dedicated personnel is crucial for optimal compliance rates[269].

Looking closer into some details, it was of no surprise that the nasogastric tube and intraabdominal drain were removed earlier in the modified program group, which were just according to the protocol. The reinsertion of nasogastric tubes increased significantly after the implementation group, and was considerably higher than reported elsewhere[227,234,270]. Several of the parameters showed indications of worse outcome, such as increase of DGE, reoperations, and increased primary LOS as well as the readmissions within 90 days. The incidence of major complications increased, both according to Clavien-Dindo and CCI. None of these were however significant, why no clear conclusions can be made. The background data for the groups were well comparable, except for significant more vascular resections in the modified group, suggesting that more advanced tumors were accepted for surgery in recent past. There is a possibility that more demanding resections and reconstructions, caused more adverse effects, but the size of the group was too small for significance. During data collection, it was noticed that, after the implementation phase, there

was a decreased tendency in discharging patients during weekends. Patients stayed hospitalized, despite fulfilling discharge criteria. This might depend on a waning compliance to protocol parameters by the health-care providers, and probably affected the LOS.

*Postoperative pancreatic fistula*

Paper IV demonstrated an overall CR-POPF incidence of 12%, which correlates well with international reports[127,129]. The incidence remained equal in the different volume groups, and their corresponding resource use have not declined. This indicated that the CR-POPFs were unaffected both by the increased volume of centralization and advancements in perioperative care with introduction of ERP. Similar results have been presented twice in cohorts preceding the ISGPF's definition[122,123].

With knowledge of the proposed risk factors for POPFs, an expected drop of incidence was based on reduced operating time and blood loss, repeatedly performed standardized surgical technique, and earlier removal of intraabdominal drain. On the other hand, the two validated, most used risk scores for POPF, are mainly based on endogenous uncontrollable factors. The risk score by Roberts et al[136], is derived from BMI and duct size, and the one by Callery et al[134], is calculated from pancreatic texture, pathology, duct size and intraoperative blood loss. Therefore, endogenous risk factors might be of more importance for outcome.

Knowledge of risk factors are important in the consultation with the patient, to present an estimation of the postoperative course. However, in reality there is, for the majority of patients, barely no time for optimizing unfavorable conditions. With the risk of a disseminating cancer, a high risk-taking is motivated for the majority of patients. In the setting of a premalign lesion, the estimation of risk-benefit relation is crucial. The preoperative pancreatic fistula risk scores by Roberts[136], might help the clinician individualize the risk assessment.

Even at an unaltered rate of CR-POPF, the high-volume team carries expectations of superior management to minimize its consequence for the patient. This was however not confirmed by paper IV. The hospital length of stay for these patients was not reduced. The following costs decreased over time, but not significant. The major expense item is the hospital length of stay and intensive care. Paper IV revealed a decrease use of intensive care, which could be a surrogate marker for fewer patients with organ dysfunction, but could also be an expression of a change in tradition of care level. Overall management of complications after PD has shifted from surgical interventions to percutaneous drainage, endoscopic or angiographic therapeutic interventions[119,120], which might decrease the number of in-hospital days[118]. In this study, the use of interventional radiology was also increased.

POPF rate varies among surgeons, partly explained by differences in pathology and risk factors for each cohort. However, the surgeon is proposed to be a significant variable for POPF[123,129] and high-volume surgeons have shown good outcome regardless of anastomotic technique[64]. Despite numerous attempts to modify the pancreatic anastomosis, none appears to be manifestly superior[64,74]. It is not likely, that a new method alone will solve the problem with CR-POPFs in the near future.

Octreotide, debated to be either increasing or decreasing the rate of POPF[129,137], is variously used globally, and the rate of CR-POPF seems to be principally consistent worldwide. Most probably, the somatostatin-analogues is not the key solution for the CR-POPFs.

# Aspects of surgical palliation

A non-therapeutic laparotomy is correlated with substantial morbidity, a non-negligible risk of postoperative mortality, a reduced chance of obtaining palliative chemotherapy and a deteriorated quality of life[167,174]. The routine bypass has been challenged by the minimally invasive non-surgical techniques, which are standard practice for palliation of unresectable cancers[182].

Paper III demonstrated that the DoB patients resumed eating later, had a longer primary LOS and had doubled risk for postoperative complications, compared with the WaS patients. Furthermore, both groups had equal number of readmissions prior to death, indicating that DoB does not prevent future hospitalization, as previously shown[175].

DoB has been shown to suffer from increased postoperative morbidity, but also shorter overall survival[176]. Survival disadvantages have been demonstrated for patients receiving a DoB compared with laparotomy alone[271]. The surgical trauma might influence survival unfavorably, as shown in experimental studies[272]. Additionally, postoperative complications can have a negative effect on survival[117,177]. Here, the DoB patients had a shorter median survival compared with WaS, but it did not reach significance.

The majority of patients in both groups had a preoperative biliary drainage. During the study time, there was a trend to exchange all plastic stents to metallic stents in the perioperative time, preferably during the same anesthesia as the laparotomy. As described previously, the metallic stents are superior regarding patency and reduced risk of obstruction[31,186].

Paper III showed that the outcome for metallic biliary stent were well comparable with the biliary bypass regarding biliary problems, with the advantages of earlier recovery after initial laparotomy. Patients with metallic stents had some additional

readmissions and re-interventions, but equal total LOS due to bile-related problems. The metallic stent is shown to be more cost-effective and improves HRQoL, compared with biliary bypass[183]. The plastic stents were inferior to both metallic stents and biliary bypass regarding re-interventions and readmissions in this paper.

Furthermore, parallel to results by Spanheimer et al[176], the two groups had similar proportions of late GOO and need for interventions, which suggests that prophylactic gastroenterostomy does not preclude future GOO.

Paper III supports the WaS strategy, if the biliary drainage is secured by a metallic stent, due to morbidity rates and hospital stay after DoB. Surgical bypass could be a secondary choice, if endoscopic stent placement fail. Gastroenterostomy, possibly performed laparoscopically, can be reserved for those with confirmed GOO, when duodenal stent is inappropriate.

# Aspects of methodology

*Retrospective studies*

General considerations with retrospective studies are the encountering of incomplete documentation, interpretation bias and difficulty establishing cause and effect relationship, when analyzing medical journals.

Most information on effects of centralization of PD originates from register based multi-institutional comparisons. There is a lack of studies describing the effects within the same unit. Most data are derived from administrative data and not medical records, giving information on mortality, hospital length of stay, but not detailed reports on perioperative parameters like blood loss, operating time and specified complications. The comparison within the same unit is a strength in paper I, since it minimizes the interpretation bias and the variation of care at different institutions. The medical journals were reviewed for details of the perioperative course, providing a lot of data for analysis.

Data for the control group in paper II was retrospectively collected, which might have given an underestimation of complications for that group. The favor of the prospectively recorded ERP group might be greater than demonstrated.

Data for paper III, were recruited from two different hospitals. Questions might rise regarding possible differences in postoperative treatment, and if the two cohorts can be compared. These two institutions, however, have not shown any differences in complications, LOS or overall management in the Swedish National Quality Registry for pancreatic cancer. Collection of data was made by two researchers, after a consensus meeting to define the study parameters.

In paper IV, to distinguish between a true fistula, deep abscess or an anastomotic leakage might be difficult, when analyzing a medical journal. One factor is the interpretation of the journal text itself and another factor is the dubiety of the interpretation made by the time of the attending surgeon, due to their comparable clinical appearance. To diminish the risk of missing CR-POPFs, an analysis was also made of the total group of patients affected by CR-POPF, deep abscess and anastomotic leakage. They were proportionally equal in all groups, which makes missing CR-POPF patients less likely.

*Enhanced recovery programs*

Some might argue that the lack of randomized controlled trials, make the evidence for enhanced recovery programs for PD unsatisfactory. Since the different items of the program are evidence-based, of which several have become standard care, it is problematic to perform a proper randomized trial. To withhold evidence-based parameters of care, is not acceptable, and health-care providers might be biased from already known evidence. Comprehensive cohort studies can provide trustful data regarding enhanced recovery programs.

The Hawthorne effect could have influenced the initial report of the ERP. It implicates that study participants or care givers will change their behavior due to the interest and attention of an ongoing study. This might have consequences when generalizing results of research to clinical practice. Following the extensive information and education of the program, healthcare providers might have been more observant and stringent with the protocol, causing a temporary improvement of outcome, when the ERP was implemented[267]. To perform a follow-up study can decrease this effect.

As paper II was a single center study, the external validity is limited, and its applicability in other health care settings unclear. Elements implemented at our center may not be generalizable.

It is also difficult to differentiate between the effects of implementation of the specific parameters of the ERP and the exclusive effects of standardization.

*Volume groups*

Analyzing different volume groups at a single institution, subsequently mean comparing different epochs. Low-volume is the most historic cohort and high volume the most recent one. During this time, not only surgical skills or postoperative care have improved. Cross sectional imaging has upgraded, both preoperative work up and identification of complications. Interventional radiology has become more available, and sepsis and intensive care treatments enhanced. The more historic group were more likely to undergo invasive management of complications then the recent group.

*Costs*

Costs of care are popular to present, but very hard to interpret in your own practice. Costs are influenced by the health-care system, governmentally or privately financed. A presentation of trends in costs, within the same financial system, is valuable anyhow, despite the actual figure on the last line.

# Conclusions

- The transition to a high-volume center significantly decreased operating time, intraoperative blood loss and need for transfusions, as well as the postpancreatectomy hemorrhages. The postoperative length of stay shortened significantly.
- The implementation of an enhanced recovery program was safe and significantly reduced delayed gastric emptying, length of stay and costs. The quality of life was not impaired.
- Asymptomatic patients with unresectable periampullary tumor at laparotomy, can safely be managed with endoscopic biliary metallic stent and subsequent treatment for duodenal obstruction on demand. Morbidity and length of stay was significantly decreased compared to double bypass surgery. Prophylactic gastroenterostomy does not prevent future gastric outlet obstruction.
- During transition to a high-volume center, the incidence of CR-POPF did not decline, nor its subsequent impact on hospital length of stay or costs.
- The benefits of the enhanced recovery program were sustained, and adherence rates have increased in the post-implementation phase.

## Errata

*In paper II:*

Table 1: termination of EDA is POD 5, instead of POD 4. Removal of urinary catheter is POD 6, instead of POD 5.

Table 2: N1, positive nodes is 32 in the fast track group, not 31 as displayed.

*In paper IV:*

Table 2: top left box should be empty, instead of “BC fistlar/abscess/läckage”.

# Future perspectives

Though we might do well today, we hope to do better tomorrow.

The concept of enhanced recovery program is acknowledged to improve outcome, but a continued development with refining each parameter and their combination, might have an additional positive effect. Parameters of specific interest to evaluate further, in our setting, would be the management of nasogastric tube, urinary catheter and the possible implementation of laparoscopic PD. Since the inflammatory response is correlated to the extent of surgical trauma, a laparoscopic PD will most likely induce a decreased the surgical stress. Repeated audits will ensure continued evaluation of the program components.

The management of the intraabdominal drain is debated. Prolonged use of drain increases the risk for deep abscesses[155]. It has been proposed that drains can be used selectively for patients with low risk for POPF[159,160]. A randomized prospective Swedish national multicenter study recently started, aiming to clarify if selective drain usage is safe and superior to prophylactic drain to all patients. Patients considered to have a low risk for POPF, a score of ≤10 calculated with the fistula risk score by Roberts, are randomized to receive an intraabdominal drain or not. Primary outcome is overall morbidity. This trial is monitored from our group.

Using data from the Swedish national register of pancreatic and periampullary cancer, POPF will be analyzed. Demographic, clinical and histopathological data will be evaluated for patients operated for periampullary cancer between 2010 until 2016. The aim of the study is to assess predictive factors, incidence and outcome of CR-POPF in a national perspective.

Using data from the same register mentioned above, the complication of DGE will be addressed. A special focus will be taken on a possible association between DGE and type of pancreatic anastomosis.

Hyperglycemia is correlated with worse postoperative outcome and increased risk for infectious complications[273]. Our group recently started a prospective study on improved postoperative blood glucose control for our PD patients. The aim is to evaluate if postoperative morbidity will decrease by a stable postoperative blood glucose between 7-10 mmol/l.

# Populärvetenskaplig sammanfattning

Varje år får ungefär 1200 patienter i Sverige beskedet att de har en ”periampullär” tumör, dvs en tumör belägen i bukspottkörtelhuvudet, nedre delen av gallgången, gallgångsmynningen till tolvfingertarmen eller tolvfingertarmen. (se figur 1) Operation ger en chans till bot, men kan endast erbjudas 15–20% av patienterna. Hos 80–85% av patienterna har tumören redan spridit sig, vilket innebär att operation av huvudtumören inte ska genomföras. Studier har visat att det inte ger någon överlevnadsvinst att operera en spridd cancer från denna region.

Operationen heter pankreatikoduodenektomi (PD), och innebär att man tar bort bukspottkörtelhuvudet, nedre delen av magsäcken, tolvfingertarmen, första biten av tunntarmen, gallblåsan och den gemensamma gallgången. (se figur 4) Tre ”anastomoser” (återkopplingar av organ) behövs, och kan utföras på några olika sätt. I Lund sys bukspottkörteln till magsäckens baksida och gallgången och magsäcken kopplas till tunntarmen. (se figur 8)

Utmaningarna kring PD är stora. Det är upp till 70% risk att få någon slags komplikation efter PD och 15–20% av dem är allvarliga. Med tanke på att de flesta behöver kompletterande behandling med cellgifter efter PD, är det viktigt att patienterna återhämtar sig snabbt efter operation.

Av de som planeras för PD, är det 8–20% som upptäcks ha en spridd cancer vid operation. De patienterna har traditionellt sett, opererats med ”bypass-operation” (förbi-koppling), av gallvägen och tolvfingertarmen, pga. att tumören förväntas tillväxa med tiden och ge stopp för både gallavflöde och födointag. På senare år har det utvecklats ”stentar” (plast- eller metallrör), som kan appliceras i gallgången och/eller tolvfingertarmen med hjälp av ”endoskopi” (slangkamera), och röntgen. Det mest fördelaktiga av dessa två alternativ har inte varit känt.

Under de senaste 10–15 åren har PD operationerna centraliserats till Skånes universitetssjukhus i Lund. Den ökade operationsvolymen har medfört att studier på PD-operationer, patienter och deras utfall kan göras.

Målet med avhandlingen var att undersöka och förändra olika aspekter av vården för PD patienter, med målet att förbättra den postoperativa vården för patienterna och på samma gång effektivisera användningen av hälso- och sjukvårdsresurser.

Studie I analyserade effekterna av centraliseringen av PD-kirurgin till Lund, genom att jämföra förloppet för de patienter som opererades mellan 2000 till 2012. Den årliga operationsvolymen ökade 8-faldigt. I samband med denna ökning, såg vi att operationstiden förkortades, blodförlusten och andelen som fick blodtransfusion under operation minskade. Likaså minskade allvarliga blödningar efter operation och vårdtiden förkortades med tre dagar.

Vi införde ett standardiserat vårdprogram, vilket kallades ”fast track”, som utvärderades i studie II. Det genomgick senare ett namnbyte till ”enhanced recovery program” (ERP). I studien, mellan 2011–2014, jämfördes 50 patienter som vårdades enligt traditionella principer, med 50 patienter som följde ett standardiserat vårdprogram. Den vanliga komplikationen ”fördröjd magsäckstömning” minskade med ca 50%. Vårdtiden förkortades från 14 dagar till 10 dagar, vilket resulterade i minskade sjukvårdskostnader. Antalet återinläggningar ökade inte och livskvaliteten minskade inte, trots att patienterna skrevs ut tidigare.

Studie III jämförde två behandlingsstrategier för de patienter där man inte kunde genomföra den tilltänkta canceroperationen. Två jämnstora grupper med totalt 143 patienter undersöktes, en från Sahlgrenska universitetssjukhuset, där man gör förebyggande kirurgisk ”bypass” på alla, och en grupp från Skånes universitetssjukhus, där endoskopisk behandling med stent är standard när symtom uppstår. Resultatet visade att det blev dubbelt så många komplikationer efter bypass-kirurgi, 67% jämfört med 31%. Vårdtiden i samband med operation var längre för bypass-gruppen, jämfört med den endoskopiska gruppen. Totalt var därför antalet sjukhusdagar fler för bypass-gruppen, eftersom behovet av sjukhusvård, under resten av livet, var lika stort i båda grupperna.

Komplikationen bukspottkörtelfistel undersöktes närmare i studie IV, hos patienter som opererades med PD från 2005–2015. Andelen med svåra bukspottkörtelfistlar var totalt 12%. Andelen fistlar minskade inte med tiden. Patienternas vårdtid och medföljande kostnad för fistelproblematiken minskade inte, trots att trenden för hela patientgruppen var minskad vårdtid och minskade kostnader.

I studie V genomförde vi en uppföljning av det standardiserade vårdförloppet, ERP, med 160 patienter från 2012 till 2016. Patienterna jämfördes i olika grupper, varav den sista gruppen följde ett förändrat program där magsäckssonden och bukhåledränaget skulle avvecklas tidigare. Resultatet visade att de positiva effekterna bestod, efter introduktionsfasens slut, då varken vårdtiden eller komplikationerna ökade statistiskt säkerställt. Följsamheten till programmet ökade i sin helhet med tiden, från 64% till 71%. Ju högre följsamhet till programmet patienterna uppvisade, desto kortare vårdtid och desto mindre komplikationer.

*Sammanfattningsvis visar avhandlingen att:*

- Centraliseringen av bukspottkörtelkirurgin förbättrade operationsparametrar, då operationstiden, blodförlust och behov av blodtransfusion minskade. Vårdtiden förkortades.
- Introduktion av ett fast-track program (ERP) var säkert. Fördröjd magsäckstömning, vårdtid och påföljande kostnader minskade statistiskt säkerställt. Trots att patienterna skrevs hem tidigare, påverkades inte deras livskvalitet negativt.
- Patienter med icke-operabel cancer kan på säkert sätt behandlas med endoskopiska stentar i gallgången och tolvfingertarmen, vid symtom på förträngning, istället för med kirurgisk bypass. Då minkar risken för komplikationer efter ingreppet och vårdtiden förkortas.
- Frekvensen av bukspottkörtelfistlar minskade inte trots centralisering av bukspottkörtelkirurgin. Vårdtiden eller kostnaderna för de drabbade patienternas vård minskade inte.
- Effekterna av ERP upprätthölls, då varken vårdtid eller komplikationer ökade. Följsamheten till ERP ökade med tiden.

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# References


1. Ansari D. Pancreatic Cancer. Early detection, prognostic factors, and treatment [Doctoral dissertation]: Lund University; 2014.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; **66**(1): 7-30.
3. Engholm G FJ, Christensen N, Kejs AMT, Hertzum-Larsen R, Johannesen TB, Khan S, Leinonen MK, Ólafsdóttir E, Petersen T, Schmidt LKH, Trykker H, Storm HH. . NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.3 08.07.2016 2016. http://www.ancr.nu/.
4. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014; **74**(11): 2913-21.
5. (RCC) RCis. Kvalitetsregister för tumörer i pankreas och periampullärt, årsrapport 2015. 2016: 6-8.
6. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010; **126**(10): 2394-403.
7. Aune D, Greenwood DC, Chan DS, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Ann Oncol* 2012; **23**(4): 843-52.
8. Wang YT, Gou YW, Jin WW, Xiao M, Fang HY. Association between alcohol intake and the risk of pancreatic cancer: a dose-response meta-analysis of cohort studies. *BMC Cancer* 2016; **16**: 212.
9. Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012; **23**(11): 2964-70.
10. Bosetti C, Rosato V, Li D, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. *Ann Oncol* 2014; **25**(10): 2065-72.
11. Welzel TM, Graubard BI, El-Serag HB, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2007; **5**(10): 1221-8.
12. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology* 2013; **145**(6): 1215-29.

13. Matsumoto T, Iida M, Nakamura S, et al. Natural history of ampullary adenoma in familial adenomatous polyposis: reconfirmation of benign nature during extended surveillance. *The American journal of gastroenterology* 2000; **95**(6): 1557-62.
14. Latchford AR, Neale KF, Spigelman AD, Phillips RK, Clark SK. Features of duodenal cancer in patients with familial adenomatous polyposis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2009; **7**(6): 659-63.
15. Del Chiaro M, Segersvard R, Lohr M, Verbeke C. Early detection and prevention of pancreatic cancer: is it really possible today? *World journal of gastroenterology : WJG* 2014; **20**(34): 12118-31.
16. Hidalgo M. Pancreatic cancer. *N Engl J Med* 2010; **362**(17): 1605-17.
17. Karlson BM, Ekbom A, Lindgren PG, Kallskog V, Rastad J. Abdominal US for diagnosis of pancreatic tumor: prospective cohort analysis. *Radiology* 1999; **213**(1): 107-11.
18. Lee ES, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. *World journal of gastroenterology : WJG* 2014; **20**(24): 7864-77.
19. Granata V, Fusco R, Catalano O, et al. Multidetector computer tomography in the pancreatic adenocarcinoma assessment: an update. *Infect Agent Cancer* 2016; **11**: 57.
20. O'Neill E, Hammond N, Miller FH. MR imaging of the pancreas. *Radiol Clin North Am* 2014; **52**(4): 757-77.
21. Holalkere NS, Sahani DV, Blake MA, Halpern EF, Hahn PF, Mueller PR. Characterization of small liver lesions: Added role of MR after MDCT. *J Comput Assist Tomogr* 2006; **30**(4): 591-6.
22. Jung W, Jang JY, Kang MJ, et al. The clinical usefulness of 18F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) in follow-up of curatively resected pancreatic cancer patients. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2016; **18**(1): 57-64.
23. Girvin F, Ko JP. Pulmonary nodules: detection, assessment, and CAD. *AJR Am J Roentgenol* 2008; **191**(4): 1057-69.
24. Schnelldorfer T, Gagnon AI, Birkett RT, Reynolds G, Murphy KM, Jenkins RL. Staging laparoscopy in pancreatic cancer: a potential role for advanced laparoscopic techniques. *Journal of the American College of Surgeons* 2014; **218**(6): 1201-6.
25. Beenen E, van Roest MH, Sieders E, et al. Staging laparoscopy in patients scheduled for pancreaticoduodenectomy minimizes hospitalization in the remaining life time when metastatic carcinoma is found. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2014; **40**(8): 989-94.
26. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2007; **33**(3): 266-70.
27. Fang Y, Gurusamy KS, Wang Q, et al. Pre-operative biliary drainage for obstructive jaundice. *The Cochrane database of systematic reviews* 2012; (9): CD005444.

28. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010; **362**(2): 129-37.
29. Tsuboi T, Sasaki T, Serikawa M, et al. Preoperative Biliary Drainage in Cases of Borderline Resectable Pancreatic Cancer Treated with Neoadjuvant Chemotherapy and Surgery. *Gastroenterol Res Pract* 2016; **2016**: 7968201.
30. Maire F, Sauvanet A. Palliation of biliary and duodenal obstruction in patients with unresectable pancreatic cancer: endoscopy or surgery? *J Visc Surg* 2013; **150**(3 Suppl): S27-31.
31. Garcea G, Ong SL, Dennison AR, Berry DP, Maddern GJ. Palliation of malignant obstructive jaundice. *Digestive diseases and sciences* 2009; **54**(6): 1184-98.
32. Crosara S, D'Onofrio M, De Robertis R, et al. Autoimmune pancreatitis: Multimodality non-invasive imaging diagnosis. *World journal of gastroenterology : WJG* 2014; **20**(45): 16881-90.
33. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Annals of surgery* 1997; **226**(3): 248-57; discussion 57-60.
34. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Annals of surgery* 2006; **244**(1): 10-5.
35. Kennedy T, Preczewski L, Stocker SJ, et al. Incidence of benign inflammatory disease in patients undergoing Whipple procedure for clinically suspected carcinoma: a single-institution experience. *American journal of surgery* 2006; **191**(3): 437-41.
36. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. *Lancet Oncol* 2014; **15**(1): 23-34.
37. Hammel P, Huguet F, van Laethem JL, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. *JAMA* 2016; **315**(17): 1844-53.
38. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**(19): 1817-25.
39. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017.
40. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; **304**(10): 1073-81.
41. Faivre J, Trama A, De Angelis R, et al. Incidence, prevalence and survival of patients with rare epithelial digestive cancers diagnosed in Europe in 1995-2002. *European journal of cancer* 2012; **48**(10): 1417-24.
42. Courtin-Tanguy L, Rayar M, Bergeat D, et al. The true prognosis of resected distal cholangiocarcinoma. *Journal of surgical oncology* 2016; **113**(5): 575-80.

43. Chen SC, Shyr YM, Chou SC, Wang SE. The role of lymph nodes in predicting the prognosis of ampullary carcinoma after curative resection. *World J Surg Oncol* 2015; **13**: 224.
44. Perysinakis I, Margaris I, Kouraklis G. Ampullary cancer--a separate clinical entity? *Histopathology* 2014; **64**(6): 759-68.
45. Panzeri F, Crippa S, Castelli P, et al. Management of ampullary neoplasms: A tailored approach between endoscopy and surgery. *World journal of gastroenterology : WJG* 2015; **21**(26): 7970-87.
46. Solaini L, Jamieson NB, Metcalfe M, et al. Outcome after surgical resection for duodenal adenocarcinoma in the UK. *The British journal of surgery* 2015; **102**(6): 676-81.
47. Cloyd JM, George E, Visser BC. Duodenal adenocarcinoma: Advances in diagnosis and surgical management. *World J Gastrointest Surg* 2016; **8**(3): 212-21.
48. Riall TS, Cameron JL, Lillemoe KD, et al. Resected periampullary adenocarcinoma: 5-year survivors and their 6- to 10-year follow-up. *Surgery* 2006; **140**(5): 764-72.
49. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013; **310**(14): 1473-81.
50. Schnelldorfer T, Adams DB, Warshaw AL, Lillemoe KD, Sarr MG. Forgotten pioneers of pancreatic surgery: beyond the favorite few. *Annals of surgery* 2008; **247**(1): 191-202.
51. Peters JH, Carey LC. Historical review of pancreaticoduodenectomy. *American journal of surgery* 1991; **161**(2): 219-25.
52. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2011; **13**(6): 377-84.
53. Whipple AO, Parsons WB, Mullins CR. Treatment of Carcinoma of the Ampulla of Vater. *Annals of surgery* 1935; **102**(4): 763-79.
54. Whipple AO. The Rationale of Radical Surgery for Cancer of the Pancreas and Ampullary Region. *Annals of surgery* 1941; **114**(4): 612-5.
55. Whipple AO. Pancreaticoduodenectomy for Islet Carcinoma : A Five-Year Follow-Up. *Annals of surgery* 1945; **121**(6): 847-52.
56. Traverso LW, Longmire WP, Jr. Preservation of the pylorus in pancreaticoduodenectomy a follow-up evaluation. *Annals of surgery* 1980; **192**(3): 306-10.
57. L.H. Sobin MKG, Ch. Wittekind. TNM classification of malignant tumours. 2009. http://www.inen.sld.pe/portal/documentos/pdf/educacion/13072015_TNM Classification.pdf (accessed 1602 2017).
58. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014; **155**(6): 977-88.

59. Abrams RA, Lowy AM, O'Reilly EM, Wolff RA, Picozzi VJ, Pisters PW. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Annals of surgical oncology* 2009; **16**(7): 1751-6.

60. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS. National failure to operate on early stage pancreatic cancer. *Annals of surgery* 2007; **246**(2): 173-80.

61. Hackert T, Niesen W, Hinz U, et al. Radical surgery of oligometastatic pancreatic cancer. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2017; **43**(2): 358-63.

62. Shrikhande SV, Kleeff J, Reiser C, et al. Pancreatic resection for M1 pancreatic ductal adenocarcinoma. *Annals of surgical oncology* 2007; **14**(1): 118-27.

63. Huttner FJ, Fitzmaurice C, Schwarzer G, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *The Cochrane database of systematic reviews* 2016; **2**: CD006053.

64. Shrikhande SV, Sivasanker M, Vollmer CM, et al. Pancreatic anastomosis after pancreatoduodenectomy: A position statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2016.

65. Lillemoe KD, Cameron JL, Kim MP, et al. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy? Results of a prospective randomized trial. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2004; **8**(7): 766-72; discussion 72-4.

66. Keck T, Wellner UF, Bahra M, et al. Pancreatogastrostomy Versus Pancreatojejunostomy for RECOnstruction After PANCreatoduodenectomy (RECOPANC, DRKS 00000767): Perioperative and Long-term Results of a Multicenter Randomized Controlled Trial. *Annals of surgery* 2016; **263**(3): 440-9.

67. Eckardt AJ, Klein F, Adler A, et al. Management and outcomes of haemorrhage after pancreatogastrostomy versus pancreatojejunostomy. *The British journal of surgery* 2011; **98**(11): 1599-607.

68. Yeo CJ, Cameron JL, Maher MM, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. *Annals of surgery* 1995; **222**(4): 580-8; discussion 8-92.

69. Bassi C, Falconi M, Molinari E, et al. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. *Annals of surgery* 2005; **242**(6): 767-71, discussion 71-3.

70. El Nakeeb A, Hamdy E, Sultan AM, et al. Isolated Roux loop pancreaticojejunostomy versus pancreaticogastrostomy after pancreaticoduodenectomy: a prospective randomized study. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2014; **16**(8): 713-22.

71. Topal B, Fieuws S, Aerts R, et al. Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy for pancreatic or periampullary tumours: a multicentre randomised trial. *Lancet Oncol* 2013; **14**(7): 655-62.

72. Figueras J, Sabater L, Planellas P, et al. Randomized clinical trial of pancreaticogastrostomy versus pancreaticojejunostomy on the rate and severity of pancreatic fistula after pancreaticoduodenectomy. *The British journal of surgery* 2013; **100**(12): 1597-605.

73. Menahem B, Guittet L, Mulliri A, Alves A, Lubrano J. Pancreaticogastrostomy is superior to pancreaticojejunostomy for prevention of pancreatic fistula after pancreaticoduodenectomy: an updated meta-analysis of randomized controlled trials. *Annals of surgery* 2015; **261**(5): 882-7.

74. Crippa S, Cirocchi R, Randolph J, et al. Pancreaticojejunostomy is comparable to pancreaticogastrostomy after pancreaticoduodenectomy: an updated meta-analysis of randomized controlled trials. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2016; **401**(4): 427-37.

75. Shrikhande SV, Barreto G, Shukla PJ. Pancreatic fistula after pancreaticoduodenectomy: the impact of a standardized technique of pancreaticojejunostomy. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2008; **393**(1): 87-91.

76. Forssell H, Proh K, Wester M, Krona H. Tumor size as measured at initial X-ray examination, not length of bile duct stricture, predicts survival in patients with unresectable pancreatic cancer. *BMC Cancer* 2012; **12**: 429.

77. Fischer LK, Katz MH, Lee SM, et al. The number and ratio of positive lymph nodes affect pancreatic cancer patient survival after neoadjuvant therapy and pancreaticoduodenectomy. *Histopathology* 2016; **68**(2): 210-20.

78. Elshaer M, Gravante G, Kosmin M, Riaz A, Al-Bahrani A. A systematic review of the prognostic value of lymph node ratio, number of positive nodes and total nodes examined in pancreatic ductal adenocarcinoma. *Annals of the Royal College of Surgeons of England* 2017; **99**(2): 101-6.

79. Crippa S, Partelli S, Zamboni G, et al. Poorly differentiated resectable pancreatic cancer: is upfront resection worthwhile? *Surgery* 2012; **152**(3 Suppl 1): S112-9.

80. Chen JW, Bhandari M, Astill DS, et al. Predicting patient survival after pancreaticoduodenectomy for malignancy: histopathological criteria based on perineural infiltration and lymphovascular invasion. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2010; **12**(2): 101-8.

81. Fouquet T, Germain A, Brunaud L, Bresler L, Ayav A. Is perineural invasion more accurate than other factors to predict early recurrence after pancreatoduodenectomy for pancreatic head adenocarcinoma? *World journal of surgery* 2014; **38**(8): 2132-7.

82. Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. *The British journal of surgery* 2006; **93**(10): 1232-7.

83. Esposito I, Kleeff J, Bergmann F, et al. Most pancreatic cancer resections are R1 resections. *Annals of surgical oncology* 2008; **15**(6): 1651-60.

84. Konstantinidis IT, Warshaw AL, Allen JN, et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? *Annals of surgery* 2013; **257**(4): 731-6.

85. Chandrasegaram MD, Goldstein D, Simes J, et al. Meta-analysis of radical resection rates and margin assessment in pancreatic cancer. *The British journal of surgery* 2015; **102**(12): 1459-72.
86. Delpero JR, Bachellier P, Regenet N, et al. Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a French multicentre prospective evaluation of resection margins in 150 evaluable specimens. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2014; **16**(1): 20-33.
87. Zhou Y, Zhang Z, Liu Y, Li B, Xu D. Pancreatectomy combined with superior mesenteric vein-portal vein resection for pancreatic cancer: a meta-analysis. *World journal of surgery* 2012; **36**(4): 884-91.
88. Turrini O, Ewald J, Barbier L, Mokart D, Blache JL, Delpero JR. Should the portal vein be routinely resected during pancreaticoduodenectomy for adenocarcinoma? *Annals of surgery* 2013; **257**(4): 726-30.
89. Mollberg N, Rahbari NN, Koch M, et al. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Annals of surgery* 2011; **254**(6): 882-93.
90. Tol JA, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). *Surgery* 2014; **156**(3): 591-600.
91. Orci LA, Meyer J, Combescure C, et al. A meta-analysis of extended versus standard lymphadenectomy in patients undergoing pancreatoduodenectomy for pancreatic adenocarcinoma. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2015; **17**(7): 565-72.
92. Clancy TE, Ashley SW. Pancreaticoduodenectomy (Whipple operation). *Surg Oncol Clin N Am* 2005; **14**(3): 533-52, vii.
93. Crile G, Jr. The advantages of bypass operations over radical pancreatoduodenectomy in the treatment of pancreatic carcinoma. *Surg Gynecol Obstet* 1970; **130**(6): 1049-53.
94. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. *N Engl J Med* 1979; **301**(25): 1364-9.
95. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. *Annals of surgery* 1995; **222**(5): 638-45.
96. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. *Annals of surgery* 1998; **228**(3): 429-38.
97. Schmidt CM, Powell ES, Yiannoutsos CT, et al. Pancreaticoduodenectomy: a 20-year experience in 516 patients. *Archives of surgery* 2004; **139**(7): 718-25; discussion 25-7.
98. Warshaw AL, Swanson RS. Pancreatic cancer in 1988. Possibilities and probabilities. *Annals of surgery* 1988; **208**(5): 541-53.
99. Riall TS, Nealon WH, Goodwin JS, et al. Pancreatic cancer in the general population: Improvements in survival over the last decade. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2006; **10**(9): 1212-23; discussion 23-4.

100. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. *Annals of surgery* 1995; **221**(6): 721-31; discussion 31-3.
101. Birkmeyer JD, Warshaw AL, Finlayson SR, Grove MR, Tosteson AN. Relationship between hospital volume and late survival after pancreaticoduodenectomy. *Surgery* 1999; **126**(2): 178-83.
102. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. *Annals of surgery* 1995; **221**(1): 43-9.
103. Delitto D, Black BS, Cunningham HB, et al. Standardization of surgical care in a high-volume center improves survival in resected pancreatic head cancer. *American journal of surgery* 2016; **212**(2): 195-201 e1.
104. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003; **349**(22): 2117-27.
105. Tseng JF, Pisters PW, Lee JE, et al. The learning curve in pancreatic surgery. *Surgery* 2007; **141**(5): 694-701.
106. Schneider EB, Ejaz A, Spolverato G, et al. Hospital volume and patient outcomes in hepato-pancreatico-biliary surgery: is assessing differences in mortality enough? *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2014; **18**(12): 2105-15.
107. Birkmeyer JD, Finlayson SR, Tosteson AN, Sharp SM, Warshaw AL, Fisher ES. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. *Surgery* 1999; **125**(3): 250-6.
108. Balzano G, Zerbi A, Capretti G, Rocchetti S, Capitanio V, Di Carlo V. Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. *The British journal of surgery* 2008; **95**(3): 357-62.
109. de Wilde RF, Besselink MG, van der Tweel I, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *The British journal of surgery* 2012; **99**(3): 404-10.
110. Lemmens VE, Bosscha K, van der Schelling G, Brenninkmeijer S, Coebergh JW, de Hingh IH. Improving outcome for patients with pancreatic cancer through centralization. *The British journal of surgery* 2011; **98**(10): 1455-62.
111. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011; **364**(22): 2128-37.
112. Gooiker GA, Lemmens VE, Besselink MG, et al. Impact of centralization of pancreatic cancer surgery on resection rates and survival. *The British journal of surgery* 2014; **101**(8): 1000-5.
113. de Castro SM, Busch OR, van Gulik TM, Obertop H, Gouma DJ. Incidence and management of pancreatic leakage after pancreatoduodenectomy. *The British journal of surgery* 2005; **92**(9): 1117-23.
114. Ansorge C, Lindstrom P, Strommer L, et al. Assessing surgical quality: comparison of general and procedure-specific morbidity estimation models for the risk adjustment of pancreaticoduodenectomy outcomes. *World journal of surgery* 2014; **38**(9): 2412-21.

115. Enestvedt CK, Diggs BS, Cassera MA, Hammill C, Hansen PD, Wolf RF. Complications nearly double the cost of care after pancreaticoduodenectomy. *American journal of surgery* 2012; **204**(3): 332-8.
116. McMillan MT, Christein JD, Callery MP, et al. Comparing the burden of pancreatic fistulas after pancreatoduodenectomy and distal pancreatectomy. *Surgery* 2016; **159**(4): 1013-22.
117. Kamphues C, Bova R, Schricke D, et al. Postoperative complications deteriorate long-term outcome in pancreatic cancer patients. *Annals of surgical oncology* 2012; **19**(3): 856-63.
118. Malleo G, Pulvirenti A, Marchegiani G, Butturini G, Salvia R, Bassi C. Diagnosis and management of postoperative pancreatic fistula. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2014; **399**(7): 801-10.
119. Sanjay P, Kellner M, Tait IS. The role of interventional radiology in the management of surgical complications after pancreatoduodenectomy. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2012; **14**(12): 812-7.
120. Lermite E, Sommacale D, Piardi T, et al. Complications after pancreatic resection: diagnosis, prevention and management. *Clin Res Hepatol Gastroenterol* 2013; **37**(3): 230-9.
121. Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, Vollmer CM, Jr. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. *Annals of surgery* 2007; **245**(3): 443-51.
122. Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2004; **8**(8): 951-9.
123. Schmidt CM, Choi J, Powell ES, et al. Pancreatic fistula following pancreaticoduodenectomy: clinical predictors and patient outcomes. *HPB Surg* 2009; **2009**: 404520.
124. Vollmer CM, Jr., Sanchez N, Gondek S, et al. A root-cause analysis of mortality following major pancreatectomy. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2012; **16**(1): 89-102; discussion -3.
125. Bassi C, Butturini G, Molinari E, et al. Pancreatic fistula rate after pancreatic resection. The importance of definitions. *Digestive surgery* 2004; **21**(1): 54-9.
126. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**(1): 8-13.
127. Harnoss JC, Ulrich AB, Harnoss JM, Diener MK, Buchler MW, Welsch T. Use and results of consensus definitions in pancreatic surgery: a systematic review. *Surgery* 2014; **155**(1): 47-57.
128. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery* 2017; **161**(3): 584-91.
129. McMillan MT, Soi S, Asbun HJ, et al. Risk-adjusted Outcomes of Clinically Relevant Pancreatic Fistula Following Pancreatoduodenectomy: A Model for Performance Evaluation. *Annals of surgery* 2016; **264**(2): 344-52.

130. Schulick RD. Complications after pancreaticoduodenectomy: intraabdominal abscess. *J Hepatobiliary Pancreat Surg* 2008; **15**(3): 252-6.

131. Fang CH, Chen QS, Yang J, Xiang F, Fang ZS, Zhu W. Body Mass Index and Stump Morphology Predict an Increased Incidence of Pancreatic Fistula After Pancreaticoduodenectomy. *World journal of surgery* 2016; **40**(6): 1467-76.

132. Pratt WB, Callery MP, Vollmer CM, Jr. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. *World journal of surgery* 2008; **32**(3): 419-28.

133. McMillan MT, Vollmer CM, Jr. Predictive factors for pancreatic fistula following pancreatectomy. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2014; **399**(7): 811-24.

134. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM, Jr. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *Journal of the American College of Surgeons* 2013; **216**(1): 1-14.

135. Bartoli FG, Arnone GB, Ravera G, Bachi V. Pancreatic fistula and relative mortality in malignant disease after pancreaticoduodenectomy. Review and statistical meta-analysis regarding 15 years of literature. *Anticancer research* 1991; **11**(5): 1831-48.

136. Roberts KJ, Hodson J, Mehrzad H, et al. A preoperative predictive score of pancreatic fistula following pancreatoduodenectomy. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2014; **16**(7): 620-8.

137. Gurusamy KS, Koti R, Fusai G, Davidson BR. Somatostatin analogues for pancreatic surgery. *The Cochrane database of systematic reviews* 2013; (4): CD008370.

138. Martignoni ME, Friess H, Sell F, et al. Enteral nutrition prolongs delayed gastric emptying in patients after Whipple resection. *American journal of surgery* 2000; **180**(1): 18-23.

139. Robinson JR, Marincola P, Shelton J, Merchant NB, Idrees K, Parikh AA. Peri-operative risk factors for delayed gastric emptying after a pancreaticoduodenectomy. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2015; **17**(6): 495-501.

140. Welsch T, Borm M, Degrate L, Hinz U, Buchler MW, Wente MN. Evaluation of the International Study Group of Pancreatic Surgery definition of delayed gastric emptying after pancreatoduodenectomy in a high-volume centre. *The British journal of surgery* 2010; **97**(7): 1043-50.

141. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007; **142**(5): 761-8.

142. Ohwada S, Satoh Y, Kawate S, et al. Low-dose erythromycin reduces delayed gastric emptying and improves gastric motility after Billroth I pylorus-preserving pancreaticoduodenectomy. *Annals of surgery* 2001; **234**(5): 668-74.

143. Imamura M, Kimura Y, Ito T, et al. Effects of antecolic versus retrocolic reconstruction for gastro/duodenojejunostomy on delayed gastric emptying after pancreatoduodenectomy: a systematic review and meta-analysis. *The Journal of surgical research* 2016; **200**(1): 147-57.

144. Qian D, Lu Z, Jackson R, et al. Effect of antecolic or retrocolic route of gastroenteric anastomosis on delayed gastric emptying after pancreaticoduodenectomy: A meta-analysis of randomized controlled trials. *Pancreatology : official journal of the International Association of Pancreatology* 2016; **16**(1): 142-50.
145. Riediger H, Makowiec F, Schareck WD, Hopt UT, Adam U. Delayed gastric emptying after pylorus-preserving pancreatoduodenectomy is strongly related to other postoperative complications. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2003; **7**(6): 758-65.
146. Wellner UF, Kulemann B, Lapshyn H, et al. Postpancreatectomy hemorrhage--incidence, treatment, and risk factors in over 1,000 pancreatic resections. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2014; **18**(3): 464-75.
147. Correa-Gallego C, Brennan MF, D'Angelica MI, et al. Contemporary experience with postpancreatectomy hemorrhage: results of 1,122 patients resected between 2006 and 2011. *Journal of the American College of Surgeons* 2012; **215**(5): 616-21.
148. Grutzmann R, Ruckert F, Hippe-Davies N, Distler M, Saeger HD. Evaluation of the International Study Group of Pancreatic Surgery definition of post-pancreatectomy hemorrhage in a high-volume center. *Surgery* 2012; **151**(4): 612-20.
149. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007; **142**(1): 20-5.
150. Welsch T, Eisele H, Zschabitz S, Hinz U, Buchler MW, Wente MN. Critical appraisal of the International Study Group of Pancreatic Surgery (ISGPS) consensus definition of postoperative hemorrhage after pancreatoduodenectomy. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2011; **396**(6): 783-91.
151. Roulin D, Cerantola Y, Demartines N, Schafer M. Systematic review of delayed postoperative hemorrhage after pancreatic resection. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2011; **15**(6): 1055-62.
152. Okano K, Hirao T, Unno M, et al. Postoperative infectious complications after pancreatic resection. *The British journal of surgery* 2015; **102**(12): 1551-60.
153. Gavazzi F, Ridolfi C, Capretti G, et al. Role of preoperative biliary stents, bile contamination and antibiotic prophylaxis in surgical site infections after pancreaticoduodenectomy. *BMC gastroenterology* 2016; **16**: 43.
154. Schmid SW, Uhl W, Friess H, Malfertheiner P, Buchler MW. The role of infection in acute pancreatitis. *Gut* 1999; **45**(2): 311-6.
155. Kawai M, Tani M, Terasawa H, et al. Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for 104 consecutive patients. *Annals of surgery* 2006; **244**(1): 1-7.
156. Adham M, Chopin-Laly X, Lepilliez V, Gincul R, Valette PJ, Ponchon T. Pancreatic resection: drain or no drain? *Surgery* 2013; **154**(5): 1069-77.
157. Conlon KC, Labow D, Leung D, et al. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. *Annals of surgery* 2001; **234**(4): 487-93; discussion 93-4.

158. Van Buren G, 2nd, Bloomston M, Hughes SJ, et al. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. *Annals of surgery* 2014; **259**(4): 605-12.

159. McMillan MT, Malleo G, Bassi C, et al. Multicenter, Prospective Trial of Selective Drain Management for Pancreatoduodenectomy Using Risk Stratification. *Annals of surgery* 2016.

160. Witzigmann H, Diener MK, Kienkotter S, et al. No Need for Routine Drainage After Pancreatic Head Resection: The Dual-Center, Randomized, Controlled PANDRA Trial (ISRCTN04937707). *Annals of surgery* 2016; **264**(3): 528-37.

161. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Annals of surgery* 2010; **252**(2): 207-14.

162. Karmazanovsky G, Fedorov V, Kubyshkin V, Kotchatkov A. Pancreatic head cancer: accuracy of CT in determination of resectability. *Abdominal imaging* 2005; **30**(4): 488-500.

163. Mayo SC, Austin DF, Sheppard BC, Mori M, Shipley DK, Billingsley KG. Evolving preoperative evaluation of patients with pancreatic cancer: does laparoscopy have a role in the current era? *Journal of the American College of Surgeons* 2009; **208**(1): 87-95.

164. Nieveen van Dijkum EJ, Romijn MG, Terwee CB, et al. Laparoscopic staging and subsequent palliation in patients with peripancreatic carcinoma. *Annals of surgery* 2003; **237**(1): 66-73.

165. Kneuertz PJ, Cunningham SC, Cameron JL, et al. Palliative surgical management of patients with unresectable pancreatic adenocarcinoma: trends and lessons learned from a large, single institution experience. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2011; **15**(11): 1917-27.

166. Stark A, Hines OJ. Endoscopic and operative palliation strategies for pancreatic ductal adenocarcinoma. *Semin Oncol* 2015; **42**(1): 163-76.

167. Watanapa P, Williamson RC. Surgical palliation for pancreatic cancer: developments during the past two decades. *The British journal of surgery* 1992; **79**(1): 8-20.

168. Singh SM, Longmire WP, Jr., Reber HA. Surgical palliation for pancreatic cancer. The UCLA experience. *Annals of surgery* 1990; **212**(2): 132-9.

169. Lillemoe KD, Cameron JL, Hardacre JM, et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. *Annals of surgery* 1999; **230**(3): 322-8; discussion 8-30.

170. Van Heek NT, De Castro SM, van Eijck CH, et al. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. *Annals of surgery* 2003; **238**(6): 894-902; discussion -5.

171. Gurusamy KS, Kumar S, Davidson BR. Prophylactic gastrojejunostomy for unresectable periampullary carcinoma. *The Cochrane database of systematic reviews* 2013; (2): CD008533.

172. Smith AC, Dowsett JF, Russell RC, Hatfield AR, Cotton PB. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. *Lancet* 1994; **344**(8938): 1655-60.

173. Heinicke JM, Buchler MW, Laffer UT. Bilio-digestive double bypass for nonresectable pancreatic cancer. *Digestive surgery* 2002; **19**(3): 165-7.

174. de Rooij PD, Rogatko A, Brennan MF. Evaluation of palliative surgical procedures in unresectable pancreatic cancer. *The British journal of surgery* 1991; **78**(9): 1053-8.

175. Lyons JM, Karkar A, Correa-Gallego CC, et al. Operative procedures for unresectable pancreatic cancer: does operative bypass decrease requirements for postoperative procedures and in-hospital days? *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2012; **14**(7): 469-75.

176. Spanheimer PM, Cyr AR, Liao J, et al. Complications and survival associated with operative procedures in patients with unresectable pancreatic head adenocarcinoma. *Journal of surgical oncology* 2014; **109**(7): 697-701.

177. Ausania F, Vallance AE, Manas DM, et al. Double bypass for inoperable pancreatic malignancy at laparotomy: postoperative complications and long-term outcome. *Annals of the Royal College of Surgeons of England* 2012; **94**(8): 563-8.

178. White R, Winston C, Gonen M, et al. Current utility of staging laparoscopy for pancreatic and peripancreatic neoplasms. *Journal of the American College of Surgeons* 2008; **206**(3): 445-50.

179. Conlon KC, Dougherty E, Klimstra DS, Coit DG, Turnbull AD, Brennan MF. The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. *Annals of surgery* 1996; **223**(2): 134-40.

180. Nieveen van Dijkum EJ, de Wit LT, van Delden OM, et al. Staging laparoscopy and laparoscopic ultrasonography in more than 400 patients with upper gastrointestinal carcinoma. *Journal of the American College of Surgeons* 1999; **189**(5): 459-65.

181. Allen VB, Gurusamy KS, Takwoingi Y, Kalia A, Davidson BR. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. *The Cochrane database of systematic reviews* 2016; **7**: CD009323.

182. Koninger J, Wente MN, Muller MW, Gutt CN, Friess H, Buchler MW. Surgical palliation in patients with pancreatic cancer. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2007; **392**(1): 13-21.

183. Artifon EL, Sakai P, Cunha JE, et al. Surgery or endoscopy for palliation of biliary obstruction due to metastatic pancreatic cancer. *The American journal of gastroenterology* 2006; **101**(9): 2031-7.

184. Espat NJ, Brennan MF, Conlon KC. Patients with laparoscopically staged unresectable pancreatic adenocarcinoma do not require subsequent surgical biliary or gastric bypass. *Journal of the American College of Surgeons* 1999; **188**(6): 649-55; discussion 55-7.

185. Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. *The Cochrane database of systematic reviews* 2006; (1): CD004200.

186. Weber A, Mittermeyer T, Wagenpfeil S, Schmid RM, Prinz C. Self-expanding metal stents versus polyethylene stents for palliative treatment in patients with advanced pancreatic cancer. *Pancreas* 2009; **38**(1): e7-e12.

187. Davids PH, Groen AK, Rauws EA, Tytgat GN, Huibregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992; **340**(8834-8835): 1488-92.

188. Moss AC, Morris E, Leyden J, MacMathuna P. Do the benefits of metal stents justify the costs? A systematic review and meta-analysis of trials comparing endoscopic stents for malignant biliary obstruction. *Eur J Gastroenterol Hepatol* 2007; **19**(12): 1119-24.

189. Martinez JM, Anene A, Bentley TG, et al. Cost Effectiveness of Metal Stents in Relieving Obstructive Jaundice in Patients with Pancreatic Cancer. *J Gastrointest Cancer* 2017; **48**(1): 58-65.

190. Speer AG, Cotton PB, Russell RC, et al. Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. *Lancet* 1987; **2**(8550): 57-62.

191. Pinol V, Castells A, Bordas JM, et al. Percutaneous self-expanding metal stents versus endoscopic polyethylene endoprostheses for treating malignant biliary obstruction: randomized clinical trial. *Radiology* 2002; **225**(1): 27-34.

192. Fiori E, Lamazza A, Volpino P, et al. Palliative management of malignant antro-pyloric strictures. Gastroenterostomy vs. endoscopic stenting. A randomized prospective trial. *Anticancer research* 2004; **24**(1): 269-71.

193. Roy A, Kim M, Christein J, Varadarajulu S. Stenting versus gastrojejunostomy for management of malignant gastric outlet obstruction: comparison of clinical outcomes and costs. *Surgical endoscopy* 2012; **26**(11): 3114-9.

194. Johnsson E, Thune A, Liedman B. Palliation of malignant gastroduodenal obstruction with open surgical bypass or endoscopic stenting: clinical outcome and health economic evaluation. *World journal of surgery* 2004; **28**(8): 812-7.

195. Jeurnink SM, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC gastroenterology* 2007; **7**: 18.

196. Cote GA, Sherman S. Endoscopic palliation of pancreatic cancer. *Cancer journal* 2012; **18**(6): 584-90.

197. Jeurnink SM, Steyerberg EW, van Hooft JE, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. *Gastrointestinal endoscopy* 2010; **71**(3): 490-9.

198. Maire F, Hammel P, Ponsot P, et al. Long-term outcome of biliary and duodenal stents in palliative treatment of patients with unresectable adenocarcinoma of the head of pancreas. *The American journal of gastroenterology* 2006; **101**(4): 735-42.

199. Chandrasegaram MD, Eslick GD, Mansfield CO, et al. Endoscopic stenting versus operative gastrojejunostomy for malignant gastric outlet obstruction. *Surgical endoscopy* 2012; **26**(2): 323-9.

200. Aosasa S, Ono S, Mochizuki H, et al. Activation of monocytes and endothelial cells depends on the severity of surgical stress. *World journal of surgery* 2000; **24**(1): 10-6.

201. Tsujimoto H, Ono S, Majima T, et al. Differential toll-like receptor expression after ex vivo lipopolysaccharide exposure in patients with sepsis and following surgical stress. *Clinical immunology* 2006; **119**(2): 180-7.

202. Haywood A, Good P, Khan S, et al. Corticosteroids for the management of cancer-related pain in adults. *The Cochrane database of systematic reviews* 2015; (4): CD010756.

203. Johnson CD, Berry DP, Harris S, et al. An open randomized comparison of clinical effectiveness of protocol-driven opioid analgesia, celiac plexus block or thoracoscopic splanchnicectomy for pain management in patients with pancreatic and other abdominal malignancies. *Pancreatology : official journal of the International Association of Pancreatology* 2009; **9**(6): 755-63.

204. Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GN, van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. *Gut* 1998; **42**(1): 92-6.

205. Davidson W, Ash S, Capra S, Bauer J, Cancer Cachexia Study G. Weight stabilisation is associated with improved survival duration and quality of life in unresectable pancreatic cancer. *Clin Nutr* 2004; **23**(2): 239-47.

206. Martin RC, 2nd, Kwon D, Chalikonda S, et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: safety and efficacy. *Annals of surgery* 2015; **262**(3): 486-94; discussion 92-4.

207. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *American journal of surgery* 2002; **183**(6): 630-41.

208. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *British journal of anaesthesia* 1997; **78**(5): 606-17.

209. Wilmore DW, Kehlet H. Management of patients in fast track surgery. *BMJ* 2001; **322**(7284): 473-6.

210. Desborough JP. The stress response to trauma and surgery. *British journal of anaesthesia* 2000; **85**(1): 109-17.

211. Ansari D, Gianotti L, Schroder J, Andersson R. Fast-track surgery: procedure-specific aspects and future direction. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2013; **398**(1): 29-37.

212. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS((R))) Society recommendations. *World journal of surgery* 2013; **37**(2): 259-84.

213. Smith I, Kranke P, Murat I, et al. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. *European journal of anaesthesiology* 2011; **28**(8): 556-69.

214. Ljungqvist O, Nygren J, Thorell A. Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. *Proc Nutr Soc* 2002; **61**(3): 329-36.

215. Smith MD, McCall J, Plank L, Herbison GP, Soop M, Nygren J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. *The Cochrane database of systematic reviews* 2014; (8): CD009161.

216. Guay J, Nishimori M, Kopp S. Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, vomiting and pain after abdominal surgery. *The Cochrane database of systematic reviews* 2016; **7**: CD001893.

217. Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting-a clinical review. *J Intensive Care* 2016; **4**: 27.

218. Bragg D, El-Sharkawy AM, Psaltis E, Maxwell-Armstrong CA, Lobo DN. Postoperative ileus: Recent developments in pathophysiology and management. *Clin Nutr* 2015; **34**(3): 367-76.

219. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Annals of surgery* 2008; **248**(2): 189-98.

220. Kehlet H. Fast-track surgery-an update on physiological care principles to enhance recovery. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2011; **396**(5): 585-90.

221. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. *The Cochrane database of systematic reviews* 2007; (3): CD004929.

222. Lassen K, Kjaeve J, Fetveit T, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. *Annals of surgery* 2008; **247**(5): 721-9.

223. Zaouter C, Kaneva P, Carli F. Less urinary tract infection by earlier removal of bladder catheter in surgical patients receiving thoracic epidural analgesia. *Reg Anesth Pain Med* 2009; **34**(6): 542-8.

224. Castelino T, Fiore JF, Jr., Niculiseanu P, Landry T, Augustin B, Feldman LS. The effect of early mobilization protocols on postoperative outcomes following abdominal and thoracic surgery: A systematic review. *Surgery* 2016; **159**(4): 991-1003.

225. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. *The Cochrane database of systematic reviews* 2011; (2): CD007635.

226. Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. *The British journal of surgery* 2014; **101**(3): 172-88.

227. Balzano G, Zerbi A, Braga M, Rocchetti S, Beneduce AA, Di Carlo V. Fast-track recovery programme after pancreatico- duodenectomy reduces delayed gastric emptying. *The British journal of surgery* 2008; **95**(11): 1387-93.

228. Pillai SA, Palaniappan R, Pichaimuthu A, Rajendran KK, Sathyanesan J, Govindhan M. Feasibility of implementing fast-track surgery in pancreaticoduodenectomy with pancreaticogastrostomy for reconstruction--a prospective cohort study with historical control. *International journal of surgery* 2014; **12**(9): 1005-9.

229. Zouros E, Liakakos T, Machairas A, Patapis P, Agalianos C, Dervenis C. Improvement of gastric emptying by enhanced recovery after pancreaticoduodenectomy. *Hepatobiliary Pancreat Dis Int* 2016; **15**(2): 198-208.

230. Coolsen MM, van Dam RM, van der Wilt AA, Slim K, Lassen K, Dejong CH. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. *World journal of surgery* 2013; **37**(8): 1909-18.

231. Robertson N, Gallacher PJ, Peel N, et al. Implementation of an enhanced recovery programme following pancreaticoduodenectomy. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2012; **14**(10): 700-8.

232. Walters DM, McGarey P, LaPar DJ, et al. A 6-day clinical pathway after a pancreaticoduodenectomy is feasible, safe and efficient. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2013; **15**(9): 668-73.

233. Kennedy EP, Rosato EL, Sauter PK, et al. Initiation of a critical pathway for pancreaticoduodenectomy at an academic institution--the first step in multidisciplinary team building. *Journal of the American College of Surgeons* 2007; **204**(5): 917-23; discussion 23-4.

234. di Sebastiano P, Festa L, De Bonis A, et al. A modified fast-track program for pancreatic surgery: a prospective single-center experience. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2011; **396**(3): 345-51.

235. Abu Hilal M, Di Fabio F, Badran A, et al. Implementation of enhanced recovery programme after pancreatoduodenectomy: a single-centre UK pilot study. *Pancreatology : official journal of the International Association of Pancreatology* 2013; **13**(1): 58-62.

236. Nikfarjam M, Weinberg L, Low N, et al. A fast track recovery program significantly reduces hospital length of stay following uncomplicated pancreaticoduodenectomy. *JOP : Journal of the pancreas* 2013; **14**(1): 63-70.

237. Braga M, Pecorelli N, Ariotti R, et al. Enhanced recovery after surgery pathway in patients undergoing pancreaticoduodenectomy. *World journal of surgery* 2014; **38**(11): 2960-6.

238. Coolsen MM, van Dam RM, Chigharoe A, Olde Damink SW, Dejong CH. Improving outcome after pancreaticoduodenectomy: experiences with implementing an enhanced recovery after surgery (ERAS) program. *Digestive surgery* 2014; **31**(3): 177-84.

239. Coolsen MM, Bakens M, van Dam RM, Olde Damink SW, Dejong CH. Implementing an enhanced recovery program after pancreaticoduodenectomy in elderly patients: is it feasible? *World journal of surgery* 2015; **39**(1): 251-8.

240. Partelli S, Crippa S, Castagnani R, et al. Evaluation of an enhanced recovery protocol after pancreaticoduodenectomy in elderly patients. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2016; **18**(2): 153-8.

241. Lassen K, Coolsen MM, Slim K, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. *World journal of surgery* 2013; **37**(2): 240-58.

242. Group EC. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. *Annals of surgery* 2015; **261**(6): 1153-9.

243. Gillissen F, Ament SM, Maessen JM, et al. Sustainability of an enhanced recovery after surgery program (ERAS) in colonic surgery. *World journal of surgery* 2015; **39**(2): 526-33.

244. Martin D, Roulin D, Addor V, Blanc C, Demartines N, Hubner M. Enhanced recovery implementation in colorectal surgery-temporary or persistent improvement?

*Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2016; **401**(8): 1163-9.

245. Wolk S, Distler M, Mussle B, Sothje S, Weitz J, Welsch T. Adherence to ERAS elements in major visceral surgery-an observational pilot study. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2016; **401**(3): 349-56.
246. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery* 2004; **240**(2): 205-13.
247. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Annals of surgery* 2013; **258**(1): 1-7.
248. Slankamenac K, Nederlof N, Pessaux P, et al. The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. *Annals of surgery* 2014; **260**(5): 757-62; discussion 62-3.
249. AssesSurgery. One single patient CCI®-Calculator. http://www.assessurgery.com/calculator_single/ (accessed 16 Nov 2016).
250. Gouma DJ, van Geenen RC, van Gulik TM, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Annals of surgery* 2000; **232**(6): 786-95.
251. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; **85**(5): 365-76.
252. Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. *European journal of cancer* 1999; **35**(6): 939-41.
253. Roberts KJ, Sutcliffe RP, Marudanayagam R, et al. Scoring System to Predict Pancreatic Fistula After Pancreaticoduodenectomy: A UK Multicenter Study. *Annals of surgery* 2015; **261**(6): 1191-7.
254. Venkat R, Puhan MA, Schulick RD, et al. Predicting the risk of perioperative mortality in patients undergoing pancreaticoduodenectomy: a novel scoring system. *Archives of surgery* 2011; **146**(11): 1277-84.
255. Xiong J, Szatmary P, Huang W, et al. Enhanced Recovery After Surgery Program in Patients Undergoing Pancreaticoduodenectomy: A PRISMA-Compliant Systematic Review and Meta-Analysis. *Medicine (Baltimore)* 2016; **95**(18): e3497.
256. Nussbaum DP, Penne K, Stinnett SS, et al. A standardized care plan is associated with shorter hospital length of stay in patients undergoing pancreaticoduodenectomy. *The Journal of surgical research* 2014.
257. Pearson SD, Kleefield SF, Soukop JR, Cook EF, Lee TH. Critical pathways intervention to reduce length of hospital stay. *The American journal of medicine* 2001; **110**(3): 175-80.

258. Dy SM, Garg PP, Nyberg D, et al. Are critical pathways effective for reducing postoperative length of stay? *Medical care* 2003; **41**(5): 637-48.

259. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg* 2017; **152**(3): 292-8.

260. Pecorelli N, Nobile S, Partelli S, et al. Enhanced recovery pathways in pancreatic surgery: State of the art. *World journal of gastroenterology : WJG* 2016; **22**(28): 6456-68.

261. Vanounou T, Pratt W, Fischer JE, Vollmer CM, Jr., Callery MP. Deviation-based cost modeling: a novel model to evaluate the clinical and economic impact of clinical pathways. *Journal of the American College of Surgeons* 2007; **204**(4): 570-9.

262. Stowers MD, Lemanu DP, Hill AG. Health economics in Enhanced Recovery After Surgery programs. *Can J Anaesth* 2015; **62**(2): 219-30.

263. Joliat GR, Labgaa I, Petermann D, et al. Cost-benefit analysis of an enhanced recovery protocol for pancreaticoduodenectomy. *The British journal of surgery* 2015; **102**(13): 1676-83.

264. King PM, Blazeby JM, Ewings P, et al. The influence of an enhanced recovery programme on clinical outcomes, costs and quality of life after surgery for colorectal cancer. *Colorectal Dis* 2006; **8**(6): 506-13.

265. Chan C, Franssen B, Dominguez I, Ramirez-Del Val A, Uscanga LF, Campuzano M. Impact on quality of life after pancreatoduodenectomy: a prospective study comparing preoperative and postoperative scores. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2012; **16**(7): 1341-6.

266. Wellner UF, Sick O, Olschewski M, Adam U, Hopt UT, Keck T. Randomized controlled single-center trial comparing pancreatogastrostomy versus pancreaticojejunostomy after partial pancreatoduodenectomy. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2012; **16**(9): 1686-95.

267. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. *BMJ* 2015; **351**: h4672.

268. Roulin D, Donadini A, Gander S, et al. Cost-effectiveness of the implementation of an enhanced recovery protocol for colorectal surgery. *The British journal of surgery* 2013; **100**(8): 1108-14.

269. Bakker N, Cakir H, Doodeman HJ, Houdijk AP. Eight years of experience with Enhanced Recovery After Surgery in patients with colon cancer: Impact of measures to improve adherence. *Surgery* 2015; **157**(6): 1130-6.

270. Berberat PO, Ingold H, Gulbinas A, et al. Fast track--different implications in pancreatic surgery. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2007; **11**(7): 880-7.

271. Insulander J, Sanjeevi S, Haghighi M, et al. Prognosis following surgical bypass compared with laparotomy alone in unresectable pancreatic adenocarcinoma. *The British journal of surgery* 2016; **103**(9): 1200-8.

272. Menges P, Klocker C, Diedrich S, et al. Surgical trauma leads to a shorter survival in a murine orthotopic pancreatic cancer model. *Eur Surg Res* 2015; **54**(1-2): 87-94.

273. Pomposelli JJ, Baxter JK, 3rd, Babineau TJ, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN J Parenter Enteral Nutr* 1998; **22**(2): 77-81.

# Paper I

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**ORIGINAL ARTICLE**

# Pancreaticoduodenectomy – the transition from a low- to a high-volume center

DANIEL ANSARI, CAROLINE WILLIAMSSON, BOBBY TINGSTEDT, BODIL ANDERSSON, GERT LINDELL & ROLAND ANDERSSON

*Department of Surgery, Clinical Sciences Lund, Lund University, Skåne University Hospital, Lund, Sweden*

**Abstract**

***Objective.*** Previous studies have identified a significant volume–outcome relationship for hospitals performing pancreaticoduodenectomy (PD). However, scant information exists concerning the effects of increased caseload of PD within the same hospital. Here, we describe the effects of becoming a high-volume provider of PD. ***Material and methods.*** The study group comprised 221 patients who underwent PD between 2000 and 2012. Hospital volume was allocated into three groups: low-volume (<10 PDs/year), years 2000–2004, $n = 25$; medium-volume (10–24 PDs/year), years 2005–2009, $n = 86$; and high-volume (≥25 PDs/year), years 2010–2012, $n = 110$. ***Results.*** The annual number of PDs increased from 5 in 2000 to 39 in 2012. The median operative duration decreased over the volume categories ($p < 0.001$). Intraoperative blood loss dropped ($p < 0.001$). The need for intraoperative blood transfusion was reduced ($p < 0.001$). Increasing hospital volume was associated with fewer reoperations ($p = 0.041$) and shorter postoperative length of stay ($p = 0.010$). There was a tendency toward reduced mortality: 4.0% for the low-volume period, 2.3% for the medium-volume period, and 0% for the high-volume period ($p = 0.066$). ***Conclusions.*** The transition from a low- to a high-volume center resulted in optimized outcomes for PD and 0% operative mortality, favoring the continued centralization of this high-risk operation.

**Key Words:** *centralization, mortality, outcome, pancreaticoduodenectomy, transition, volume*

## Introduction

The volume–outcome relationship for high-risk operations such as pancreaticoduodenectomy (PD) has been demonstrated by numerous studies. Already in 1979, Luft et al. [1] reported the empirical relationship between higher surgical volume and lower postoperative mortality. This concept has led to the centralization of high-risk operations to improve the outcome. The association between hospital volume and operative mortality for PD has been confirmed with reported mortality rates <5% in high-volume centers and >10% in low-volume centers [2,3]. In 2011, Finks et al. [4] showed that higher hospital volume explained 67% of the reduction in mortality for pancreatic resection, and a similar trend was seen for cystectomy and esophageal resection but not for other procedures.

Most data regarding centralization of PD are derived from multi-institutional comparisons, and there is a lack of studies describing the effects of increased caseload of PD within the same unit. Furthermore, less is known regarding the effects of centralization on quality measures of PD such as operative blood loss, individual complications, and the need for reoperation.

The process of centralization can be slow as demonstrated by a nationwide survey of PD in the United States [5]. In Sweden, gradual centralization of PD has occurred in the last 10 years. To date, no information is available regarding the volume–outcome association for PD in Sweden. The aim of this study was to explore the impact of centralization of PD on perioperative outcome in southern Sweden in the period 2000–2012, investigating the effects of turning

Correspondence: Roland Andersson, MD PhD, Department of Surgery, Clinical Sciences Lund, Lund University, Skåne University Hospital, Lund, SE-221 85 Lund, Sweden. Tel: +46 46 17 23 59. E-mail: roland.andersson@med.lu.se

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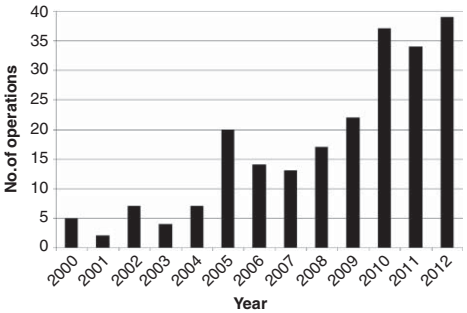


Figure 1. Pancreaticoduodenectomies performed between January 2000 and December 2012 at Skåne University Hospital, Lund, Sweden.

our surgical unit from a low- to a high-volume provider of PD.

## Methods

Patients undergoing PD from January 1, 2000, to December 31, 2012, at the Department of Surgery, Skåne University Hospital, Lund, Sweden were identified from the hospital records using a computerized search (surgical classification code JLC40). A total of 221 patients underwent PD during the study period. A retrospective chart review was conducted of patient demographics, surgical parameters, and postoperative course. The annual hospital volume was recorded. All complications were graded according to the Clavien–Dindo classification [6], where grades III–V were considered as major complications.

Pancreaticoduodenal resection was performed as a partial pancreatectomy with classic resection, including a limited distal gastrectomy. A pancreaticogastrostomy was achieved by anastomosing the pancreatic remnant to the posterior gastric wall midway between the lesser and greater curvature [7].

Hospital volume was categorized by the number of PDs performed annually into low-volume (<10 PDs/year), years 2000–2004, $n = 25$; medium-volume (10–24 PDs/year), years 2005–2009, $n = 86$; and high-volume (≥25 PDs/year), years 2010–2012, $n = 110$ based on established cut-off values [8]. Outcomes of interest were operative parameters, complications, reoperation, length of stay, and mortality.

### *Definitions*

Delayed gastric emptying (DGE) was defined according to the consensus definition proposed by the International Study Group of Pancreatic Surgery (ISGPS) [9]. DGE was classified as grades A, B, or C according to the clinical course and postoperative management. Postpancreatectomy hemorrhage was defined according to ISGPS based on the time of onset, site of bleeding, severity, and clinical impact [10]. Pancreatic fistula was defined according to the definition from the International Study Group on Pancreatic Fistula (ISGPF) [11]. On the basis of the need for therapeutic intervention, only grade B and C pancreatic fistulas were included in this study. Mortality was defined as death occurring in hospital or within 30 days of operation.

Table I. Indications for pancreaticoduodenectomy.

| Histopathological diagnosis | *n* (%) |
|---|---|
| Pancreatic ductal adenocarcinoma | 66 (29.9) |
| Cholangiocarcinoma | 42 (19.0) |
| Ampullary adenocarcinoma | 36 (16.3) |
| Duodenal adenocarcinoma | 22 (10.0) |
| Intraductal papillary mucinous neoplasm | 15 (6.8) |
| Neuroendocrine tumor | 10 (4.5) |
| Chronic pancreatitis | 10 (4.5) |
| Serous cystadenoma | 5 (2.3) |
| Mucinous cystadenoma | 3 (1.4) |
| Mucinous cystadenocarcinoma | 2 (0.9) |
| Solid pseudopapillary neoplasm | 2 (0.9) |
| Ampullary adenoma | 2 (0.9) |
| Duodenal adenoma | 1 (0.5) |
| Gastrointestinal stromal tumor | 1 (0.5) |
| Metastatic renal cell carcinoma | 1 (0.5) |
| Metastatic non-small cell carcinoma | 1 (0.5) |
| Benign bile stricture | 1 (0.5) |
| Duodenal ulcer | 1 (0.5) |

### *Statistical analysis*

Continuous variables are presented as median (range). Categorical variables are given as frequencies and percentages. Univariate analysis for continuous variables was conducted with the Kruskal–Wallis test. The Mantel–Haenszel $\chi^2$ test was used to assess trends in mortality and other categorical variables across volume groups [3,12]. Data were analyzed using SPSS version 20.0 (IBM, Armonk, New York, USA). The level of significance was set at $p < 0.05$.

## Results

The annual number of PDs increased from 5 in 2000 to 39 in 2012 (Figure 1). The most common indication for surgery was pancreatic ductal adenocarcinoma (Table I). Median age at the time of surgery ($p = 0.143$), percentage of female patients ($p = 0.218$), and preoperative comorbidity ($p = 0.225$) did not change during the study period (Table II).

The median operative duration decreased significantly over the volume categories ($p < 0.001$), ranging

Table II. Hospital volume and outcome for pancreaticoduodenectomy.

| | Low-volume <10 PDs/year 2000–2004 $n = 25$ | Medium-volume 10–24 PDs/year 2005–2009 $n = 86$ | High-volume ≥25 PDs/year 2010–2012 $n = 110$ | $p$-Value |
|---|---|---|---|---|
| Age | 63 (15–76) | 67 (17–83) | 67 (25–81) | 0.143 |
| Female gender | 14 (56.0) | 41 (47.7) | 47 (42.7) | 0.218 |
| ASA score | 2 (1–3) | 2 (1–3) | 2 (1–3) | 0.225 |
| Operative time (min) | 523 (300–758) | 534 (278–945) | 451 (235–820) | < 0.001 |
| Estimated blood loss (ml) | 1150 (200–3600) | 800 (100–2800) | 500 (100–4600) | < 0.001 |
| Blood transfusion | 13 (56.5) | 24 (31.6) | 10 (9.7) | < 0.001 |
| Delayed gastric emptying | 9 (37.5) | 29 (33.7) | 45 (40.9) | 0.588 |
| Grade A | 1 (4.2) | 6 (7.0) | 25 (22.7) | |
| Grade B | 2 (8.3) | 14 (16.3) | 12 (10.9) | |
| Grade C | 6 (25.0) | 9 (10.5) | 8 (7.3) | |
| Hemorrhage | 5 (20.8) | 14 (16.3) | 8 (7.3) | 0.022 |
| Grade A | 1 (4.2) | 4 (4.7) | 4 (3.6) | |
| Grade B | 2 (8.3) | 4 (4.7) | 2 (1.8) | |
| Grade C | 2 (8.3) | 6 (7.0) | 2 (1.8) | |
| Pancreatic fistula | 4 (16.7) | 13 (15.1) | 11 (10.0) | 0.238 |
| Grade B | 4 (16.7) | 5 (5.8) | 8 (7.3) | |
| Grade C | 0 (0.0) | 8 (9.3) | 3 (2.7) | |
| Wound infection | 6 (25.0) | 18 (20.9) | 25 (22.7) | 0.970 |
| Intra-abdominal infection | 2 (8.3) | 13 (15.1) | 10 (9.1) | 0.578 |
| Major morbidity (Clavien grade ≥III) | 5 (20.0) | 14 (16.3) | 19 (17.3) | 0.872 |
| Intensive care unit requirement | 3 (13.6) | 5 (5.8) | 8 (7.3) | 0.582 |
| Reoperation | 2 (8.3) | 3 (3.5) | 1 (0.9) | 0.041 |
| Postoperative length of stay (days) | 16 (9–89) | 15 (8–62) | 13 (6–78) | 0.010 |
| Mortality | 1 (4.0) | 2 (2.3) | 0 (0.0) | 0.066 |

Abbreviation: ASA = American Society of Anesthesiologists score.
Analysis is based on the available patient data.

from 523 min in the low-volume period to 451 min in the high-volume period. Intraoperative blood loss also dropped ($p < 0.001$). The need for blood transfusion decreased progressively with increasing hospital volume ($p < 0.001$).

The most common complication was DGE. There was no significant difference in the rate of DGE across volume groups. There was a reduced incidence of postoperative hemorrhage according to hospital volume ($p = 0.022$). Pancreatic fistula did not differ significantly between volume groups. Infectious complications were similar between groups. Additionally, major morbidity and intensive care unit requirement remained unaltered.

Reoperation was required in six patients, reasons being postoperative hemorrhage in five patients and ileus in one patient. The need for reoperation significantly decreased when comparing the volume categories ($p = 0.041$). Postoperative length of stay dropped significantly ($p = 0.010$), ranging from 16 days in the low-volume period to 13 days in the high-volume period. There were three postoperative deaths. Causes were sepsis-associated multiple organ failure in one patient, hemorrhage in one patient, and unknown in one patient. The mortality rates for the low-, medium-, and high-volume periods were 4.0%, 2.3%, and 0%, respectively ($p = 0.066$).

## Discussion

The relationship between hospital volume and mortality after PD has been known for many years. Previous studies have reported lower mortality rates at high-volume centers [2–4,8,13–19]. What separates our study is the analysis of outcomes from one individual center during transit from low- to high-volume. The core staff of senior pancreatic surgeons was stable over time with four senior pancreatic surgeons during the first period and six senior pancreatic surgeons during periods 2 and 3. One senior pancreatic surgeon was recruited during the first period, otherwise the increase in core staff was managed by internal training. Between 2000 and 2012, our hospital caseload of PD increased by eightfold. There was a tendency toward a decrease in mortality from 4% in the low-volume period to 0% in the high-volume period. Reduced need for reoperation and shorter length of stay in the high-volume period also suggest that centralization may be associated with less costs.

Two main theories have been put forth to explain the volume–outcome relationship in surgery [20]. The "practice makes perfect" concept suggests that repetition increases the ability of surgeons and hospitals to perform a given procedure, which may be especially relevant when it comes to complex and

high-risk operations. The underlying factors are multifactorial and include improved technical skill of the operating surgeon, more careful patient selection criteria, better postoperative and intensive care units, and improved multidisciplinary care. The "selective referral" concept suggests that centers that have good outcomes receive more referrals leading to higher volumes. However, this concept requires that referring doctors and their patients can choose hospital, but in Sweden, which has a mainly government-funded health care system, this is rarely the case.

The strength of this study is that volume groups were compared within the same surgical unit. This design eliminates several biased variables affecting interhospital comparisons. We also provided a detailed analysis of individual patient characteristics and clinical course, which most of the previous volume–outcome studies lack as they are based on administrative data and not medical records. It has been shown that other variables besides volume such as age, male gender, and comorbidity are positive predictors of complications and death following PD [21,22]. However, these factors were similar across volume groups in this study.

In conclusion, the results from this study demonstrate that the transition from a low- to a high-volume center optimizes the outcomes of PD. There was a tendency toward decreased mortality now reaching 0% in more than 100 PDs performed in the high-volume period. The results of this study support the beneficial effects of centralization in southern Sweden, and that patients should continue to be directed to regional centers.

***Declaration of interest:*** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

## References


[1] Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 1979;301:1364–9.

[2] Balzano G, Zerbi A, Capretti G, Rocchetti S, Capitanio V, Di Carlo V. Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. Br J Surg 2008;95:357–62.

[3] Birkmeyer JD, Finlayson SR, Tosteson AN, Sharp SM, Warshaw AL, Fisher ES. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. Surgery 1999;125:250–6.

[4] Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011;364:2128–37.

[5] Learn PA, Bach PB. A decade of mortality reductions in major oncologic surgery: the impact of centralization and quality improvement. Med Care 2010;48:1041–9.

[6] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.

[7] Topal B, Fieuws S, Aerts R, Weerts J, Feryn T, Roeyen G, et al. Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy for pancreatic or periampullary tumours: a multicentre randomised trial. Lancet Oncol 2013;14:655–62.

[8] Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232:786–95.

[9] Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007; 142:761–8.

[10] Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20–5.

[11] Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138:8–13.

[12] Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. J Am Stat Assoc 1963;58:690–700.

[13] Gordon TA, Bowman HM, Tielsch JM, Bass EB, Burleyson GP, Cameron JL. Statewide regionalization of pancreaticoduodenectomy and its effect on in-hospital mortality. Ann Surg 1998;228:71–8.

[14] Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–37.

[15] Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. Ann Surg 2003;237:509–14.

[16] Nordback L, Parviainen M, Raty S, Kuivanen H, Sand J. Resection of the head of the pancreas in Finland: effects of hospital and surgeon on short-term and long-term results. Scand J Gastroenterol 2002;37:1454–60.

[17] Topal B, Van de Sande S, Fieuws S, Penninckx F. Effect of centralization of pancreaticoduodenectomy on nationwide hospital mortality and length of stay. Br J Surg 2007;94: 1377–81.

[18] Urbach DR, Bell CM, Austin PC. Differences in operative mortality between high- and low-volume hospitals in Ontario for 5 major surgical procedures: estimating the number of lives potentially saved through regionalization. CMAJ 2003;168:1409–14.

[19] de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, Dejong CH, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg 2012;99:404–10.

[20] Lee CN, Daly JM. Provider volume and clinical outcomes in surgery: issues and implications. Bull Am Coll Surg 2002;87: 21–6.

[21] Eeson G, Chang N, McGahan CE, Khurshed F, Buczkowski AK, Scudamore CH, et al. Determination of factors predictive of outcome for patients undergoing a pancreaticoduodenectomy of pancreatic head ductal adenocarcinomas. HPB (Oxford) 2012;14:310–16.

[22] Venkat R, Puhan MA, Schulick RD, Cameron JL, Eckhauser FE, Choti MA, et al. Predicting the risk of perioperative mortality in patients undergoing pancreaticoduodenectomy: a novel scoring system. Arch Surg 2011;146:1277–84.

# Paper II

Original article

# Impact of a fast-track surgery programme for pancreaticoduodenectomy

**C. Williamsson, N. Karlsson, C. Sturesson, G. Lindell, R. Andersson and B. Tingstedt**

Department of Surgery, Skåne University Hospital at Lund, Lund, Sweden
*Correspondence to:* Associate Professor B. Tingstedt, Department of Surgery, Skåne University Hospital at Lund, Institution for Clinical Sciences, Lund University, Getingevägen 4, 221 85 Lund, Sweden (e-mail: bobby.tingstedt@med.lu.se)

**Background:** **Fast-track (FT) programmes are multimodal, evidence-based approaches to optimize patient outcome after surgery. The aim of this study was to evaluate the safety, clinical outcome and patients' experience of a FT programme after pancreaticoduodenectomy (PD) in a high-volume institution in Sweden.**

**Methods:** **Consecutive patients undergoing PD were studied before and after implementation of the FT programme. FT changes included earlier mobilization, standardized removal of the nasogastric tube and drain, and earlier start of oral intake. Patient experience was evaluated with European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ-PAN26 questionnaires 2 weeks before and 4 weeks after surgery.**

**Results:** **Between 2011 and 2014, 100 consecutive patients undergoing PD were studied, of whom 50 received standard care (controls), followed by 50 patients treated after implementation of the FT programme. The nasogastric tube was removed significantly earlier in the FT group, and these patients were able fully to tolerate fluids and solid food sooner after PD. Delayed gastric emptying was significantly reduced in the FT group (26 *versus* 48 per cent; $P = 0{\cdot}030$). Overall morbidity remained unchanged and there were no deaths in either group. Postoperative length of hospital stay was reduced from 14 to 10 days and hospital costs were decreased significantly. Health-related quality-of-life questionnaires showed similar patterns of change, with no significant difference between groups before or after surgery.**

**Conclusion:** **The FT programme after PD was safe. Delayed gastric emptying, hospital stay and hospital costs were all reduced significantly. Although patients were discharged 4 days earlier in the FT group, this did not influence health-related quality of life compared with standard care.**

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## Introduction

Fast-track (FT) or enhanced recovery after surgery (ERAS®) programmes are multimodal, evidence-based approaches to optimize patient outcomes. They aim to reduce the stress response to surgery in order to accelerate recovery and reduce morbidity. Such programmes have gained popularity in several surgical areas, although the implementation beyond colorectal surgery has been slow[1].

Pancreaticoduodenectomy (PD) is the surgical procedure of choice for periampullary malignancies and offers the only possibility of long-term survival. It is a complex operation, which historically has been accompanied by high rates of complications and long postoperative length of hospital stay (LOS). During the past decade, with centralization to high-volume centres, the mortality rate has decreased to below 2–3 per cent, but the morbidity rate remains high, at up to 69 per cent[2,3]. Postoperative complications are the main reason for a prolonged stay, although a general reduction in overall LOS reflects increased experience and higher caseloads at specialist centres[4].

Several studies have investigated the effects of a FT concept after PD. Although these studies were small or without a control group, they suggested that FT programmes reduce delayed gastric emptying (DGE)[5,6] and LOS without compromising patient safety[7–12]. Recently published cohort studies[13,14] involving 115 and 86 patients

in ERAS® programmes related to PD reported earlier recovery, mobilization and feeding, as well as shorter LOS in the ERAS® group. There is now also evidence that FT after PD is safe in the elderly[15].

Earlier studies failed, however, to assess patients' experience of FT programmes after PD. The aim of this study, therefore, was to evaluate safety, clinical outcome, costs and the impact on health-related quality of life (HRQoL) of a FT programme after PD using a before and after design to compare a historical control group receiving standard care with a group after implementation of an FT programme.

## Methods

Consecutive patients undergoing PD were followed at Skåne University Hospital, Lund, Sweden, from March 2011 until March 2014. The FT surgery programme was established in October 2012. Patients treated before adoption of the perioperative FT routine (control group) were compared with those treated after implementation of the programme. Information on the FT group was collected in a prospectively designed database and data for controls were collected retrospectively from patient records. Patients with both malignant and benign diseases were included, with no exclusions.

Operations were performed by eight surgeons using a standard technique involving a bilateral subcostal incision with classical PD, including resection of the pyloric region. Reconstruction was by pancreaticogastrostomy with retrocolic hepaticojejunostomy and gastrojejunostomy performed on the same loop. A nasogastric tube (NGT) was inserted and one intra-abdominal drain.

### Fast-track protocol

The protocol was established from the evening before surgery until discharge.

Defined criteria for removal of the NGT, intra-abdominal drain and urinary catheter, and stepwise introduction of oral intake were used. Anaesthesia and fluid administration were designed to achieve a perioperative near-zero fluid balance. Bodyweight was measured on a daily basis. Targets for mobilization and parenteral nutrition were established. A standard protocol for analgesia was designed (*Table 1*).

Postoperative pain control was achieved by initial thoracic (T7–T9) epidural analgesia, using a 50 per cent mixture of 2·5 mg/ml bupivacaine and 0·05 mg/ml morphine, monitored by a dedicated anaesthetic pain service team with stepwise reduction until cessation on postoperative day (POD) 4. Paracetamol was given intravenously from POD 0. Patients received oral analgesia (paracetamol and oxycodone) from POD 4.

All received low molecular weight heparin (LMWH) from the evening before surgery until discharge and oral antimicrobial prophylaxis (sulfamethoxazole–trimethoprim and metronidazole). The FT group received a second dose of sulfamethoxazole–trimethoprim if the operation exceeded 360 min. A proton pump inhibitor (PPI) was administered intravenously following surgery and converted to oral dosage once intake was tolerated. Octreotide was given subcutaneously every 8 h until POD 5. Laxatives (macrogol and picosulfate) were used from POD 2. An antiemetic cocktail (ondansetron, droperidol, betamethasone) was given at the end of surgery.

The NGT was removed on POD 1 or 2 if the drainage volume was below 300 ml/day, and at the latest by POD 3. Reinsertion followed persistent hiccups or emesis on two separate occasions. Oral intake began with 500 ml on the day of NGT withdrawal and increased stepwise with the goal of free fluids on POD 3 and solid food from POD 4. Patients were allowed to increase oral intake only if they had met the goal from the previous day. Parenteral nutrition (986 ml, 1100 kcal StructoKabiven®; Fresenius Kabi, Uppsala, Sweden) was given from POD 2 and stopped when oral intake exceeded 1200 kcal/day.

Drain amylase was analysed on POD 1 and 3, and every second day if the drain was still in place. The drain was removed after 3 days if the amylase level was below 480 units/l and drain output less than 200 ml/day.

Bedside assisted mobilization started 6 h after surgery with the aim of full mobilization on POD 4. Physiotherapists and ward nurses cooperated to mobilize patients according to the protocol.

Patients met with a dietician before discharge and a follow-up meeting was arranged after 4 weeks. The goal was hospital discharge from POD 8 or 9 if the criteria in *Table 1* had been fulfilled. On days 1, 3 and 5 after discharge, a staff nurse made telephone contact with the patient to answer any questions and address other concerns. A follow-up appointment with one of the surgeons was scheduled 4 weeks after operation.

### Routine for control patients

Patients received LMWH, a single dose of antimicrobial prophylaxis, PPI and octreotide routinely. Pain control was achieved by thoracic epidural or a patient-controlled pump device with intravenous opiates. Surgery was performed identically to that in the FT group, except with two intra-abdominal drains. Drains and the NGT were

**Table 1** Clinical pathway *versus* traditional care for pancreaticoduodenectomy

| | Clinical fast-track pathway | Traditional care |
|---|---|---|
| Before surgery | Written and oral information to patient about operation and perioperative care | Oral information about operation |
| Day of admission | Preoperative nutritional drink<br>Antithrombotic prophylaxis<br>Solid food until midnight | Antithrombotic prophylaxis<br>Fasting after midnight before procedure |
| Day of surgery, POD 0 | Drinks until 06.00 hours<br>Preoperative nutritional drink at 06·00 hours<br>Antimicrobial prophylaxis<br>Epidural analgesia<br>Secondary antimicrobial prophylaxis if duration of surgery > 6 h<br>Insertion of intra-abdominal drain, NGT and urinary catheter<br>Antiemetics at end of anaesthesia<br>Administration of PPI and pancreatic secretion inhibitor<br>Transfer to intermediate care unit; light mobilization and respiratory training<br>Sipping on clear fluids, 300 ml | Antimicrobial prophylaxis<br>EDA or patient-controlled analgesia<br>Insertion of two intra-abdominal drains, NGT and urinary catheter<br>PPI and pancreatic secretion inhibitor<br>Intermediate care unit |
| POD 1 | Transfer to ward<br>NGT removal if fluid output < 300 ml/day<br>Oral intake of fluids, 500 ml<br>Mobilization (sitting for 1 h at least twice daily, 1 walk in the ward)<br>Respiratory training<br>Sample of amylase from intra-abdominal drain<br>Blood glucose sampled 4 times daily, until discharge | Transfer to ward<br>Respiratory training<br>Sample of amylase from intra-abdominal drain<br>Sampling of blood glucose × 4 |
| POD 2 | Increased mobilization (sitting for 2 h twice daily, 2 walks around the ward)<br>Respiratory training<br>Oral intake of 1000 ml fluids and yoghurt | Mobilization according to patient's ability<br>Respiratory training |
| POD 3 | Increased mobilization (sitting for 2 h twice daily, 4 walks around the ward)<br>Respiratory training<br>Removal of NGT unless contraindicated<br>No limit on oral fluids, yoghurt and toast<br>Sample of amylase from intra-abdominal drain; removal if amylase < 480 units/l and fluids < 200 ml/day | Removal of NGT if accepted by operating surgeon<br>Oral intake 300 ml clear fluid<br>Sample of amylase from intra-abdominal drain on POD 3 and 5<br>Mobilization and respiratory training according to patient's ability |
| POD 4 | Full mobilization<br>Respiratory training<br>Normal diet<br>Termination of EDA, substitution with oral analgesics | Mobilization and respiratory training according to patient's ability<br>Stepwise increase of oral intake at discretion of consultant surgeon |
| POD 5 | Depending on previous day, removal of EDA and urinary catheter | Drain removal at discretion of consultant surgeon |
| POD 6–7 | Depending on previous day, continuous step up of oral intake and mobilization | Removal of EDA and urinary catheter |
| POD 8–9 | Discharge | |

Discharge criteria: absence of fever, no need for intravenous fluid, adequate pain control with oral analgesia, passage of first stool/flatus, full mobilization, patient agrees to discharge. EDA, epidural analgesia; POD, postoperative day; PPI, proton pump inhibitor; NGT, nasogastric tube.

removed at the discretion of the operating surgeon, at the earliest on POD 3, as was the decision to increase oral intake stepwise. Mobilization was based on the patient's ability, with support from physiotherapists and ward nurses, but not according to a specific programme.

## Patient outcome

Complications were assessed at 30 days after surgery or within the primary admission. Adherence to the protocol was analysed. After 10 and 25 patients had been included in the FT programme, an interim analysis of morbidity was carried out to assess safety.

## Costs

In-hospital costs were calculated retrospectively, and included cost of preoperative and postoperative consultations with a surgeon, operation, time spent in hospital, time in intensive care, all healthcare personnel, laboratory tests,

**Table 2** Patient characteristics

| | Control ($n = 50$) | Fast-track ($n = 50$) | $P$† |
|---|---|---|---|
| Age (years)* | 67 (25–81) | 69 (15–80) | 0·436‡ |
| Sex ratio (M : F) | 26 : 24 | 31 : 19 | 0·162§ |
| Body mass index (kg/m$^2$)* | 25·2 (16·3–33·4) | 24·3 (19·4–36·2) | 0·352‡ |
| Smoker | 7 (14) | 12 (24) | 0·307 |
| Diabetes mellitus | 13 (26) | 10 (20) | 0·635 |
| Preoperative jaundice | 40 (80) | 33 (66) | 0·176 |
| Preoperative biliary drainage | 38 (76) | 33 (66) | 0·378 |
| ASA fitness grade | | | 0·304§ |
| I | 6 (12) | 2 (4) | |
| II | 27 (54) | 28 (56) | |
| III | 17 (34) | 20 (40) | |
| Diagnosis | | | |
| Ductal adenocarcinoma | 15 (30) | 17 (34) | 0·830 |
| Cholangiocarcinoma | 13 (26) | 8 (16) | 0·326 |
| Ampullary adenocarcinoma | 7 (14) | 9 (18) | 0·786 |
| Duodenal adenocarcinoma | 4 (8) | 5 (10) | 1·000 |
| Neuroendocrine tumour | 2 (4) | 2 (4) | 1·000 |
| Premalignant tumour | 3 (6) | 6 (12) | 0·487 |
| Benign histopathology | 6 (12) | 3 (6) | 0·487 |
| R1 resection | 15 (30) | 13 (26) | 0·824 |
| Positive nodes (N1) | 27 (54) | 31 (62) | 0·544 |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Two-tailed Fisher's exact test, except ‡Mann–Whitney $U$ test and §$\chi^2$ test.

**Table 3** Postoperative parameters

| | Control ($n = 50$) | Fast-track ($n = 50$) | $P$† |
|---|---|---|---|
| Time to NGT removal (days)* | 3·5 (1–34) | 1·5 (1–24) | 0·001 |
| Time to full tolerance of free fluids (days)* | 6 (3–40) | 4 (2–24) | < 0·001 |
| Time to full tolerance of solid food (days)* | 8 (5–40) | 7 (4–25) | 0·024 |
| Required reinsertion of NGT | 4 | 7 | 0·524‡ |
| Time to drain removal (days)* | 7 (0–21) | 6 (0–32) | 0·061 |
| Postoperative length of stay (days)* | | | |
| All patients | 14 (9–42) | 10 (6–35) | 0·001 |
| Patients without complications | 11 (9–16) | 9 (6–12) | 0·032 |
| Radiology | | | |
| All examinations | 73 | 53 | 0·940 |
| Interventional radiology | 19 | 10 | 0·025 |
| Cost (€)* | 14 576 (8245–42 750) | 10 400 (6519–39 558) | < 0·001 |

*Values are median (range). NG T, nasogastric tube; †Mann–Whitney $U$ test, except ‡two-tailed Fisher's exact test.

nutrition and radiology (diagnostics and interventions). The internal price list for Skåne University Hospital at Lund was employed to translate resource use into costs (based on costs at 31 December 2014).

## Assessment of quality of life

HRQoL was assessed using validated general (European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30)[16] and pancreatic disease-related (EORTC QLQ-PAN26)[17] questionnaires 2 weeks before and 4 weeks after surgery. All patients were asked to complete the questionnaires themselves and return them at the outpatient clinic.

## Definitions

Complications were classified according to the Clavien–Dindo grading system[18], with Clavien I–II considered as minor and Clavien IIIa–V as major complications. Procedure-specific complications such as DGE, postpancreatectomy haemorrhage and postoperative pancreatic fistula (POPF) were classified according to definitions of the International Study Group of Pancreatic

**Table 4** Postoperative complications

| | Control ($n = 50$) | Fast-track ($n = 50$) | $P$* |
|---|---|---|---|
| Total morbidity rate | 34 (68) | 32 (64) | 0·156 |
| Minor complications | 29 (58) | 25 (50) | 0·545 |
| Clavien I | 11 (22) | 10 (20) | |
| Clavien II | 18 (36) | 15 (30) | |
| Major complications | 5 (10) | 7 (14) | 0·482 |
| Clavien IIIa | 3 (6) | 5 (10) | |
| Clavien IIIb | 1 (2) | 0 (0) | |
| Clavien IVa | 1 (2) | 2 (4) | |
| Clavien IVb | 0 (0) | 0 (0) | |
| Clavien V | 0 (0) | 0 (0) | |
| Wound infection | 11 (22) | 8 (16) | 0·611† |
| Deep infection | 2 (4) | 6 (12) | 0·155† |
| PD-specific complications | | | |
| Delayed gastric emptying | 24 (48) | 13 (26) | 0·030 |
| A | 16 | 6 | |
| B | 3 | 5 | |
| C | 5 | 2 | |
| Postoperative pancreatic fistula | 14 (28) | 11 (22) | 0·228 |
| A | 8 | 7 | |
| B | 6 | 4 | |
| C | 0 | 0 | |
| Postpancreatectomy haemorrhage | 2 (4) | 2 (4) | 1·000 |
| A | 1 | 0 | |
| B | 1 | 1 | |
| C | 0 | 1 | |

Values in parentheses are percentages. PD, pancreaticoduodenectomy. *$\chi^2$ test, except †two-tailed Fisher's exact test.

Surgery (ISGPS)[19–21]. Mortality was defined as in-hospital death or death within 30 days of surgery; deaths within 60 and 90 days were also noted. Postoperative LOS was calculated as the total number of days in hospital after PD, at both the specialized centre and community hospital, until the patient was self-caring and sent home. The day of surgery is referred to as POD 0. Full tolerance of fluids meant that the patient fulfilled the goal of no limit on oral intake of fluids, and full tolerance of food meant that the patient was eating without any nutritional support.

### Statistical analysis

Continuous data are presented as median (range), with analysis using the Mann–Whitney $U$ test. Comparisons of categorical variables were made using $\chi^2$ test and Fisher's exact test. $P < 0·050$ was considered statistically significant. Multivariable linear regression analysis was performed to assess whether any variables influenced LOS independently. Variables with $P < 0·050$ in the univariable analysis were included in the multivariable analysis. Statistical analysis was conducted using SPSS® version 22.0.0.0 (IBM, Armonk, New York, USA).

**Table 5** Adherence to fast-track protocol

| | Protocol criteria fulfilled (%) |
|---|---|
| Nasogastric tube removal | |
| POD 1 | 50 |
| POD 3 | 72 |
| Full tolerance of free fluids | |
| POD 3 | 48 |
| POD 5 | 56 |
| Full tolerance of normal diet | |
| POD 4 | 4 |
| POD 8 | 76 |
| Drain removal | |
| POD 3 | 22 |
| POD 5 | 44 |
| Discharge day | |
| POD 8 | 14 |
| POD 9 | 32 |
| POD 10 | 50 |
| POD 14 | 80 |

POD, postoperative day.

## Results

During the 36-month study interval, 100 consecutive patients underwent PD, 50 before and 50 after implementation of the FT programme. There was no statistically significant difference between the two groups with respect to demographics and co-morbidity (*Table 2*). All but one patient in the control group, who underwent reconstruction by pancreaticojejunostomy, had a standard PD.

There was a significant decrease in duration of surgery (422 *versus* 461 min; $P = 0·022$) and operative blood loss (375 *versus* 500 ml; $P = 0·016$) in favour of the FT group. Thirteen patients in each group (26 per cent) received blood transfusion.

Patients in the FT group had a significantly shorter time to removal of the NGT, full intake of free liquid and full tolerance of normal diet. There were no differences between the groups in drain amylase on POD 1 and 3. Postoperative LOS was significantly reduced in the FT group (10 *versus* 14 days; $P = 0·001$) (*Table 3*). The readmission rate within 60 days was 6 per cent (3 patients) in each group.

There were fewer radiological examinations and significantly fewer radiological interventions in patients treated within the FT programme. The cost per patient was significantly reduced (€10 400 *versus* €14 576; $P < 0·001$) in favour of FT management (*Table 3*).

There was no difference between the groups in overall morbidity. Most complications were minor (Clavien I–II). DGE was the most common complication in both groups, followed by POPF and wound infection. DGE was significantly less common in the FT group (26 *versus* 48 per cent;

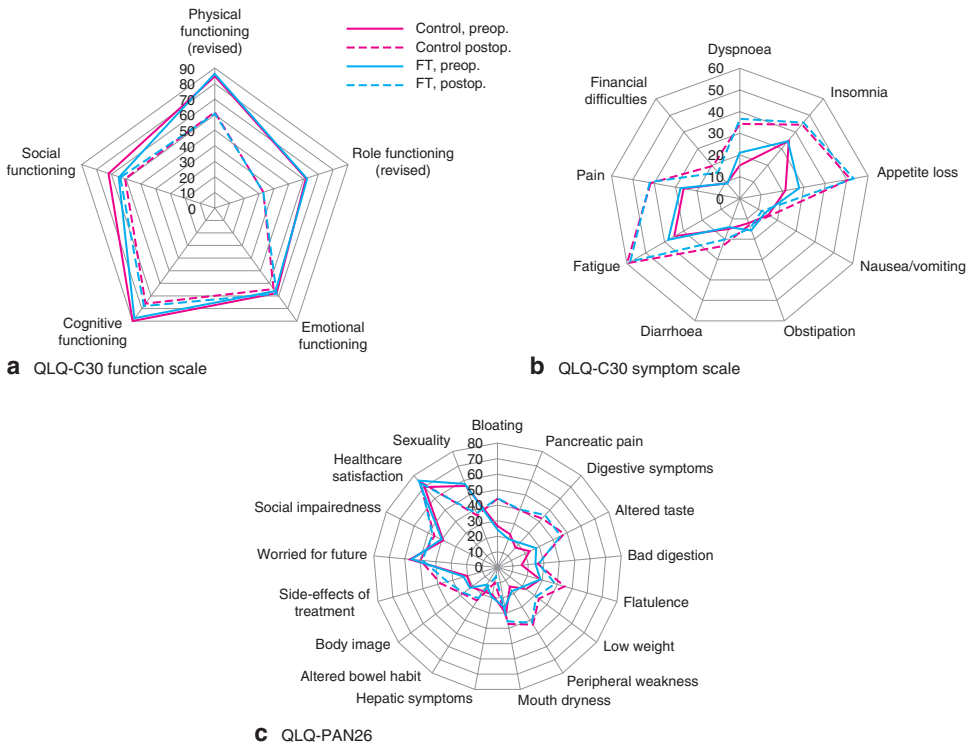


**Fig. 1** Quality of life before and after pancreaticoduodenectomy among control patients and those treated within the fast-track (FT) programme, assessed using the European Organization for Research and Treatment of Cancer **a** QLQ-C30 function scale (100 is the best outcome), **b** QLQ-C30 symptom scale (100 is the worst outcome) and **c** QLQ-PAN26 (100 is the worst outcome)

$P = 0{\cdot}030$) (*Table 4*). There were no differences in the need for intermediate or intensive care, and no deaths within 90 days.

Adherence to the FT protocol was analysed (*Table 5*). The goals of mobilization and respiratory training were met by all patients.

Factors included in the regression analysis were the FT programme itself, and variables that showed significant differences in univariable analysis (duration of surgery, blood loss, DGE, NGT removal, full tolerance of liquid, full tolerance of normal diet, interventional radiology). Age was included as a co-variable. Factors that independently influenced LOS were the FT programme ($P = 0{\cdot}049$), DGE ($P = 0{\cdot}012$) and full tolerance of normal diet ($P = 0{\cdot}002$).

Completed HRQoL questionnaires were returned by 70 per cent of the patients in both groups. Most aspects of quality of life deteriorated by 1 month after operation. However, health status and function scales showed similar patterns of change in the two groups, with no significance between them before or after surgery (*Fig. 1*). Fatigue and loss of appetite were the predominant symptoms following PD.

## Discussion

The protocol developed corresponds well with the guidelines for perioperative care for PD from the ERAS® Society[22] that were published while this study was under way. Since their initial development for patients

undergoing colorectal surgery[23], ERAS® protocols, clinical pathways or FT programmes have been implemented and gained popularity in several surgical specialties[1]. The aim is to accelerate recovery without compromising morbidity and mortality; this is achieved by reducing surgical stress through optimal control of pain, early reintroduction of oral diet and early mobilization[22,24].

Standard protocols for evidence-based patient management minimize unnecessary variation in care. The protocols also help healthcare providers to detect deviations, which can represent complications, and give an opportunity to study individual parameters.

FT management after PD has not gained widespread acceptance. The reluctance may be explained by fear of anastomotic leakage brought on by early feeding. The results of the present study indicate that care within a FT programme after PD reduces DGE, postoperative hospital stay and hospital costs without jeopardizing safety or worsening HRQoL.

Implementation of the FT programme was safe. Overall morbidity did not increase and the rate of severe PD-specific complications, such as bleeding and fistula, did not change. The slight reduction in wound infections might be a result of the introduction of secondary antimicrobial prophylaxis and shorter operating time, and not an effect of the FT programme itself[25,26]. The tendency towards an increase in deep infections has no obvious explanation, as there was no correlation with anastomotic leakage.

The most interesting finding was the distinct decrease in postoperative DGE. Balzano and colleagues[5] showed a similar decrease in DGE after implementation of a FT programme for PD, but this was not confirmed in a meta-analysis[27] of three case–control studies from 2013. A reduction in DGE is desirable because this is the most common complication following PD and constitutes one of the main reasons for prolonged hospital stay[8,28]. The assessment of DGE after PD can be difficult. The rate of DGE in the present study was twice that reported elsewhere[14]. In contrast to that study, the FT protocol here included use of a NGT, which might influence interpretation and analysis of DGE. In the control group, NGTs were left in place until POD 3. The ISGPS criteria[19] were used, and a patient was classified as having DGE A if they still had a NGT tube by POD 4–7 or were not tolerating normal food at POD 7, regardless of the reason for keeping the tube. Several studies[10,13,14,22] now support the omission of NGTs.

There is also the possible influence of the method of reconstruction. A recent meta-analysis[29] showed a lower frequency of postoperative fistula, but no difference in overall morbidity or DGE after pancreatogastrostomy *versus* pancreatojejunostomy. In addition to the present analysis, one other study[6] has also shown reduced DGE and LOS with use of pancreatogastrostomy in a FT setting.

FT was associated with an earlier return to intake of liquid and normal diet but, because resumption of oral intake does not adequately describe how well the patient managed, the term 'full tolerance of' was used for assessment. FT management challenges the traditional long fasting period after PD. The concern that early feeding could increase complication rates by stimulating pancreatic secretion or disrupting anastomosis was not proven. Early resumption of food did not have a negative impact on fistula frequency, in this or other[5,9,11,14] FT studies.

The present results showed a significant reduction in postoperative hospital stay, as reported elsewhere[5,9,11,14,30]. The earlier discharge was not associated with an increased readmission rate or reduced quality of life. Multiple factors can explain the reduction in hospital stay. An earlier study[12] revealed that the only factor independently associated with early discharge was the pathway itself. Multivariable regression analysis here showed that the FT programme, reduced rate of DGE and an early return to normal diet were all independently associated with reduced LOS. Patient information and expectations, as well as earlier mobilization, are possible components in the FT pathway that influence an early discharge. Furthermore, the impact of healthcare providers' expectations of earlier discharge in FT care probably also contribute to shorter LOS.

This study also demonstrated a significant reduction in costs per patient, mainly owing to the shorter hospital stay and diminished use of radiological examinations. Other studies have identified relationships between reduced costs and decreased LOS[9,31,32] and less frequent use of radiology, laboratory tests and nutrition[33].

Analysis of adherence to protocol showed that the majority of the patients did not meet the predetermined goals. Patients in whom the NGT was not removed on POD 1 had failed to meet the removal criteria and subsequently the resumption of oral intake was delayed. Greater adherence to dietary goals would probably be achieved if the criteria for removal of the NGT were widened. The main reason for not removing the abdominal drain on POD 3 was drainage volume exceeding 200 ml. Because high drainage volume was not associated with leakage of amylase or POPF in this study, there is an ongoing discussion within the authors' unit about increasing the acceptable volume. As shown by Walters and colleagues[8], increased adherence to the protocol is most likely when the healthcare staff become more familiar and comfortable with the FT protocol.

Analysis of the questionnaires did not reveal any differences in quality of life between the groups. A decline in HRQoL 1 month after PD is expected and has been described previously[34]. There are no studies evaluating quality of life after implementation of FT PD, but a comparison of FT *versus* traditional management of patients undergoing colorectal surgery showed no difference in EORTC QLQ-C30 scores[35]. The present results indicate that a FT programme with earlier discharge does not worsen HRQoL compared with a more conservative traditional approach.

Some authors have questioned the value of FT programmes. It has been argued that reduced LOS may simply reflect existing trends within healthcare systems towards shorter hospital stays, owing to improved healthcare quality and economic pressures as well as selection bias towards healthier patients[36,37]. Falling morbidity rates and reduced hospital stay had already been identified at this institution in the past decade[38], but a distinct decrease in LOS after implementation of the FT pathway was clearly apparent in the present study. The similarity in demographics and histopathology in the two cohorts, and their consecutive inclusion in the study argue against selection bias. Randomized clinical studies[39,40] showing reduced LOS and complications after FT care in different fields of surgery, and well designed cohort studies[13,14] supporting positive effects of FT protocols in pancreatic surgery, all suggest that objections to a FT programme for PD are weak.

The main limitation of this study is its design, as there was no prospective database for the control group. This gives a risk of bias in outcome analysis. The main problem is likely to be underestimation of complications in the control group. Even if this were small, it would only increase the difference in favour of the FT programme. As argued by others[14,27], it would seem impossible to conduct a prospective randomized study within the same unit.

## Disclosure

The authors declare no conflict of interest.

## References


1 Ansari D, Gianotti L, Schroder J, Andersson R. Fast-track surgery: procedure-specific aspects and future direction. *Langenbecks Arch Surg* 2013; **398**: 29–37.

2 Ansorge C, Lindström P, Strömmer L, Blomberg J, Lundell L, Andrén-Sandberg A *et al.* Assessing surgical quality: comparison of general and procedure-specific morbidity estimation models for the risk adjustment of pancreaticoduodenectomy outcomes. *World J Surg* 2014; **38**: 2412–2421.

3 Enestvedt CK, Diggs BS, Cassera MA, Hammill C, Hansen PD, Wolf RF. Complications nearly double the cost of care after pancreaticoduodenectomy. *Am J Surg* 2012; **204**: 332–338.

4 Topal B, Van de Sande S, Fieuws S, Penninckx F. Effect of centralization of pancreaticoduodenectomy on nationwide hospital mortality and length of stay. *Br J Surg* 2007; **94**: 1377–1381.

5 Balzano G, Zerbi A, Braga M, Rocchetti S, Beneduce AA, Di Carlo V. Fast-track recovery programme after pancreaticoduodenectomy reduces delayed gastric emptying. *Br J Surg* 2008; **95**: 1387–1393.

6 Pillai SA, Palaniappan R, Pichaimuthu A, Rajendran KK, Sathyanesan J, Govindhan M. Feasibility of implementing fast-track surgery in pancreaticoduodenectomy with pancreaticogastrostomy for reconstruction – a prospective cohort study with historical control. *Int J Surg* 2014; **12**: 1005–1009.

7 Robertson N, Gallacher PJ, Peel N, Garden OJ, Duxbury M, Lassen K *et al.* Implementation of an enhanced recovery programme following pancreaticoduodenectomy. *HPB (Oxford)* 2012; **14**: 700–708.

8 Walters DM, McGarey P, LaPar DJ, Strong A, Good E, Adams RB *et al.* A 6-day clinical pathway after a pancreaticoduodenectomy is feasible, safe and efficient. *HPB (Oxford)* 2013; **15**: 668–673.

9 Kennedy EP, Rosato EL, Sauter PK, Rosenberg LM, Doria C, Marino IR *et al.* Initiation of a critical pathway for pancreaticoduodenectomy at an academic institution – the first step in multidisciplinary team building. *J Am Coll Surg* 2007; **204**: 917–923.

10 di Sebastiano P, Festa L, De Bonis A, Ciuffreda A, Valvano MR, Andriulli A *et al.* A modified fast-track program for pancreatic surgery: a prospective single-center experience. *Langenbecks Arch Surg* 2011; **396**: 345–351.

11 Abu Hilal M, Di Fabio F, Badran A, Alsaati H, Clarke H, Fecher I *et al.* Implementation of enhanced recovery programme after pancreatoduodenectomy: a single-centre UK pilot study. *Pancreatology* 2013; **13**: 58–62.

12 Nikfarjam M, Weinberg L, Low N, Fink MA, Muralidharan V, Houli N *et al.* A fast track recovery program significantly reduces hospital length of stay following uncomplicated pancreaticoduodenectomy. *JOP* 2013; **14**: 63–70.

13 Braga M, Pecorelli N, Ariotti R, Capretti G, Greco M, Balzano G *et al.* Enhanced recovery after surgery pathway in patients undergoing pancreaticoduodenectomy. *World J Surg* 2014; **38**: 2960–2966.

14 Coolsen MM, van Dam RM, Chigharoe A, Olde Damink SW, Dejong CH. Improving outcome after pancreaticoduodenectomy: experiences with implementing an enhanced recovery after surgery (ERAS) program. *Dig Surg* 2014; **31**: 177–184.

15 Coolsen MM, Bakens M, van Dam RM, Olde Damink SW, Dejong CH. Implementing an enhanced recovery program after pancreaticoduodenectomy in elderly patients: is it feasible? *World J Surg* 2015; **39**: 251–258.

16 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365–376.

17 Fitzsimmons D, Johnson CD, George S, Payne S, Sandberg AA, Bassi C *et al.* Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. *Eur J Cancer* 1999; **35**: 939–941.

18 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.

19 Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR *et al.* Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007; **142**: 761–768.

20 Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ *et al.* Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007; **142**: 20–25.

21 Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al.* Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**: 8–13.

22 Lassen K, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schäfer M *et al.* Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *World J Surg* 2013; **37**: 240–258.

23 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–617.

24 Kehlet H. Future perspectives and research initiatives in fast-track surgery. *Langenbecks Arch Surg* 2006; **391**: 495–498.

25 Pessaux P, Msika S, Atalla D, Hay JM, Flamant Y; French Association for Surgical Research. Risk factors for postoperative infectious complications in noncolorectal abdominal surgery: a multivariate analysis based on a prospective multicenter study of 4718 patients. *Arch Surg* 2003; **138**: 314–324.

26 Fujita S, Saito N, Yamada T, Takii Y, Kondo K, Ohue M *et al.* Randomized, multicenter trial of antibiotic prophylaxis in elective colorectal surgery: single dose *vs* 3 doses of a second-generation cephalosporin without metronidazole and oral antibiotics. *Arch Surg* 2007; **142**: 657–661.

27 Coolsen MM, van Dam RM, van der Wilt AA, Slim K, Lassen K, Dejong CH. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. *World J Surg* 2013; **37**: 1909–1918.

28 Lermite E, Pessaux P, Brehant O, Teyssedou C, Pelletier I, Etienne S *et al.* Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. *J Am Coll Surg* 2007; **204**: 588–596.

29 Xiong JJ, Tan CL, Szatmary P, Huang W, Ke NW, Hu WM *et al.* Meta-analysis of pancreaticogastrostomy *versus* pancreaticojejunostomy after pancreaticoduodenectomy. *Br J Surg* 2014; **101**: 1196–1208.

30 Nussbaum DP, Penne K, Stinnett SS, Speicher PJ, Cocieru A, Blazer DG III *et al.* A standardized care plan is associated with shorter hospital length of stay in patients undergoing pancreaticoduodenectomy. *J Surg Res* 2015; **193**: 237–245.

31 Kennedy EP, Grenda TR, Sauter PK, Rosato EL, Chojnacki KA, Rosato FE Jr *et al.* Implementation of a critical pathway for distal pancreatectomy at an academic institution. *J Gastrointest Surg* 2009; **13**: 938–944.

32 Vanounou T, Pratt W, Fischer JE, Vollmer CM Jr, Callery MP. Deviation-based cost modeling: a novel model to evaluate the clinical and economic impact of clinical pathways. *J Am Coll Surg* 2007; **204**: 570–579.

33 Porter GA, Pisters PW, Mansyur C, Bisanz A, Reyna K, Stanford P *et al.* Cost and utilization impact of a clinical pathway for patients undergoing pancreaticoduodenectomy. *Ann Surg Oncol* 2000; **7**: 484–489.

34 Chan C, Franssen B, Dominguez I, Ramirez-Del Val A, Uscanga LF, Campuzano M. Impact on quality of life after pancreatoduodenectomy: a prospective study comparing preoperative and postoperative scores. *J Gastrointest Surg* 2012; **16**: 1341–1346.

35 King PM, Blazeby JM, Ewings P, Longman RJ, Kipling RM, Franks PJ *et al.* The influence of an enhanced recovery programme on clinical outcomes, costs and quality of life after surgery for colorectal cancer. *Colorectal Dis* 2006; **8**: 506–513.

36 Pearson SD, Kleefield SF, Soukop JR, Cook EF, Lee TH. Critical pathways intervention to reduce length of hospital stay. *Am J Med* 2001; **110**: 175–180.

37 Dy SM, Garg PP, Nyberg D, Dawson PB, Pronovost PJ, Morlock L *et al.* Are critical pathways effective for reducing postoperative length of stay? *Med Care* 2003; **41**: 637–648.

38 Ansari D, Williamsson C, Tingstedt B, Andersson B, Lindell G, Andersson R. Pancreaticoduodenectomy – the transition from a low- to a high-volume center. *Scand J Gastroenterol* 2014; **49**: 481–484.

39 Wang G, Jiang ZW, Xu J, Gong JF, Bao Y, Xie LF *et al.* Fast-track rehabilitation program *vs* conventional care after colorectal resection: a randomized clinical trial. *World J Gastroenterol* 2011; **17**: 671–676.

40 Ni CY, Yang Y, Chang YQ, Cai H, Xu B, Yang F *et al.* Fast-track surgery improves postoperative recovery in patients undergoing partial hepatectomy for primary liver cancer: a prospective randomized controlled trial. *Eur J Surg Oncol* 2013; **39**: 542–547.

# Paper III

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ORIGINAL ARTICLE

# A wait-and-see strategy with subsequent self-expanding metal stent on demand is superior to prophylactic bypass surgery for unresectable periampullary cancer

Caroline Williamsson[1], Johanna Wennerblom[2], Bobby Tingstedt[1] & Claes Jönsson[2]

[1]Department of Surgery, Skåne University Hospital at Lund and Lund University, and [2]Department of Surgery, Sahlgrenska University Hospital, Gothenburg and Gothenburg University, Sweden

## Abstract

**Background:** A patient with unresectable periampullary malignancy found at laparotomy has traditionally received a prophylactic double bypass (biliary and duodenal), associated with considerable morbidity. With modern endoscopic treatments, surgical bypass has become questionable. This study aims to compare the two strategies. Sahlgrenska University Hospital (SU) performs a double bypass (DoB) routinely, and Skåne University Hospital Lund (SUL) secures biliary drainage endoscopically and treats only symptomatic duodenal obstruction (Wait and See, WaS).

**Method:** Between 2004 and 2013, 73 patients from SU and 70 from SUL were retrospectively identified. Demographics, tumour-related factors and postoperative outcomes during the remaining lifetime were noted.

**Results:** The DoB group had significantly more complications (67% vs. 31%, p = 0.00002) and longer hospital stay (14 vs. 8 days, p = 0.001) than the WaS-group. The two groups had similar proportion of patients in need of readmission. The DoB patients and the WaS patients with metallic biliary stents were comparable regarding their need of re-interventions and hospitalisation due to biliary obstruction. Surgical duodenal bypass did not prevent future duodenal obstructions.

**Conclusion:** 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.

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## Correspondence

Claes Jönsson, Department of Surgery, Sahlgrenska University Hospital, Per Dubbsgatan 15, 413 45 Göteborg, Sweden. Tel: +46 31 342 10 00. Fax: +46 31 821811. E-mail: claes.jonsson@vgregion.se

## Introduction

Pancreatic cancer is the fourth leading cause of cancer death and the tenth most common cancer diagnosed in the United States.[1] The overall five-year survival rate is less than 7%.[1] The only cure for pancreatic cancer is still surgery and at presentation only 15–20% are resectable.[2,3] Among the remaining patients, locally advanced or disseminated disease is found during the preoperative workup or finally at surgery, that was intended as a curative resection.

In patients with periampullary malignancies, 8–20% of the patients planned for radical resections are found to have unresectable disease during surgery.[4,5] The majority of these patients already have a biliary drainage procedure performed. Whether to perform prophylactic double bypass (hepaticojejunostomy and gastrojejunostomy) or wait until signs of GOO develop at the discovery of unresectable periampullary cancer is still debated.[6] Proponents of prophylactic surgical bypass quote that 75% will develop biliary obstruction[7] and up to 25% will develop GOO[7,8] when the disease progresses. Critics claim that 98% of patients without prophylactic bypass can be managed without surgery.[9]

The result of this paper was presented at the 22nd UEG Week in Vienna, Oct 18–22 2014.

 

Until now, recommendations have been to perform a double bypass at the time of surgery in patients with a life expectancy of more than 6–8 months since studies have shown that the surgical trauma does not lead to increased mortality or morbidity and diminishes episodes of cholangitis, icterus and GOO.[10,11]

The studies referred to are, however, more than ten years old and compare two groups that both underwent major surgery. No other prospective randomized studies have been produced. More recently, different bypass procedures have retrospectively been compared with laparotomy alone, indicating that the proportion of patients requiring re-intervention and total number of in-hospital days prior to death was similar regardless of the initial procedure.[12] Furthermore, there have been substantial developments in the field of self-expanding metallic stents (SEMS) and in the practice of using stents in patients with malignant obstruction. So the question is still, or once again, valid.

A Swedish prospective randomized multicentre study started in 2010 to determine whether to perform a prophylactic double bypass or await symptoms and conduct endoscopic treatment in patients with unresectable periampullary cancer. Due to difficulties related to the inclusion of patients, mainly due to problems with informed consent, this study was stopped in 2013.[13] Therefore, the present study was designed, based on power calculations of the halted RCT, to try to answer this clinically important question.

At Sahlgrenska University Hospital the approach to the perioperative finding of unresectable cancer has been to perform a double bypass, hepaticojejunostomy and gastrojejunostomy, over the last decade. At Skåne University Hospital Lund, on the other hand, the approach has been to treat only patients with symptoms of dysfunctioning biliary stent and/or GOO at the time of laparotomy and to wait until symptoms of GOO or biliary dysfunction develop in the remaining patients before performing endoscopic drainage and/or bypass procedures.

The aim of this study was to retrospectively analyse the postoperative complications and long-term follow-up for patients managed by the two different strategies to perioperative unresectable periampullary cancer at the two aforementioned tertiary referral centres.

## Method

A retrospective search in the lists of planned pancreaticoduodenectomies, between January 2004 and December 2013, in the Surgery Planning Software was conducted. All included patients had surgery with the intent of performing a pancreaticoduodenectomy but had perioperative findings of locally advanced or metastasized tumours. Only patients with periampullary cancer were included. Endocrine cancers and benign findings were excluded. Patients who, after responding to oncologic treatment, were subjected to a second operation with curative intent were also excluded.

Metastatic disease was defined as histological proven liver or peritoneal metastases. Locally advanced disease was defined as the presence of lymph node metastasis above the celiac trunk or in the region below the left renal vein and aorta. Furthermore, invasion or encasement of celiac axis, hepatic artery, superior mesenteric artery or more than 2 cm of the portal vein were also defined as locally advanced disease. Involvement of locoregional lymph nodes and/or less involvement of the portal vein were not contraindications for resection.

Palliative procedures performed included biliary-enteric bypass (usually hepaticojejunostomy) and/or gastrojejunostomy.

Information about these patients was obtained from medical records including medical charts, operation records, pathology records and radiology records. Demographic data were collected as well as information regarding tumour size, TNM-grading, histopathological grading and oncological treatment given. Perioperative parameters were noted for all patients including reason of unresectability.

Postoperatively, data on complications, time to functioning oral food intake and length of primary hospital stay were obtained. All complications were classified according to the Clavien–Dindo classification.[14] Delayed gastric emptying (DGE) was graded according to the standards depicted by ISGPS.[15]

During follow-up, all readmissions due to obstructed biliary drainage or GOO syndrome were noted, including procedures and radiology performed as well as length of stay (LoS). Cholangitis was defined as a febrile episode treated with at least antibiotics, where the biliary tree was defined as the locus of infection or no other locus was defined. Readmissions for reasons other than biliary and/or duodenal obstruction were excluded. The type and length of palliative chemotherapy was noted.

This study was approved by the Regional Medical Ethics Committee in Gothenburg (005-14) with the participation of the Surgical Clinics of Skåne University Hospital at Lund and affiliated hospitals in the southern and west health care regions in Sweden.

Continuous data are presented as numbers and percentages, median and range as appropriate. Differences between groups were evaluated by the Chi square analysis, Fisher exact test, Mann–Whitney U-test and Kruskal–Wallis test. Survival analysis was performed using the Kaplan–Meier method. A p-value of $<0.05$ was considered significant. All analyses were performed using the SPSS statistical package (v22.0, SPSS Inc.®, Chicago, Ill).

## Results

Between 2004 and 2013, 73 (51%) patients at Sahlgrenska University Hospital and 70 (49%) patients at Skåne University Hospital at Lund were found to be unresectable at the time of laparotomy. Demographics, histopathology and reason for unresectability are shown in Table 1. Palliative chemotherapy was

**Table 1** Demographics, histopathology and reason for unresectability

| Variable (n, % or median (range)) | WaS, n = 70 | DoB, n = 73 | p-value |
|---|---|---|---|
| Age | 70 (42–81) | 66 (39–81) | ***0.013*** |
| Gender, (male) | 46 (66%) | 43 (59%) | 0.490 |
| Preoperative biliary drainage | 54 (77%) | 62 (84%) | 0.287 |
| ASA score | | | ***0.049*** |
| 1 | 7 (10%) | 8 (11%) | |
| 2 | 34 (49%) | 53 (73%) | |
| 3 | 29 (41%) | 12 (16%) | |
| Histopathology | | | |
| Pancreatic adenocarcinoma | 50 (71%) | 50 (68%) | 0.501 |
| Distal bile duct | 11 (16%) | 16 (22%) | |
| Ampullary | 2 (3%) | 1 (1%) | |
| Duodenum | 4 (6%) | 3 (4%) | |
| Unspecified cancer | 3 (4%) | 3 (4%) | |
| Tumour size (cm) | 3.0 (1.0–7.0) | 3.2 (1.3–9.0) | 0.379 |
| Stage | | | 0.195 |
| 1 | 1 (1%) | 3 (4%) | |
| 2a | 14 (20%) | 9 (12%) | |
| 2b | 8 (11%) | 3 (4%) | |
| 3 | 17 (24%) | 23 (32%) | |
| 4 | 30 (43%) | 35 (48%) | |
| Reason for unresectability | | | 0.453 |
| Locally advanced | 41 (58%) | 41 (56%) | |
| Peritoneal carcinomatosis | 4 (6%) | 4 (6%) | |
| Distant metastases | 25 (36%) | 28 (38%) | |

Italicized bold values indicates statistically significant changes.

**Table 2** Initial procedure and postoperative complications by strategy

| Procedure or outcome | WaS n = 70 | DoB n = 73 | p-value |
|---|---|---|---|
| Operative procedure | | | |
| Wait and see | 48 (69%) | 0 | |
| Double bypass | 12 (17%) | 59 (81%) | |
| Gastroenterostomy | 10 (14%) | 2 (3%) | |
| Hepaticojejunostomy | 0 | 12 (16%) | |
| Patients with complications | **22 (31%)** | **48 (67%)** | ***<0.001*** |
| Complications, (Clavien–Dindo) | | | ***0.017*** |
| 1 | 2 | 6 | |
| 2 | 17 | 25 | |
| 3a | 1 | 8 | |
| 3b | 1 | 6 | |
| 4a | 0 | 2 | |
| 4b | 0 | 0 | |
| 5 | 1 | 1 | |
| Delayed gastric emptying | **12 (17%)** | **26 (36%)** | ***0.017*** |
| A | 5 (7%) | 12 (16%) | |
| B | 5 (7%) | 12 (16%) | |
| C | 2 (3%) | 2 (3%) | |
| Reoperation | **1 (2%)** | **4 (5%)** | 0.366 |
| Primary LoS | **8 (2–36)** | **14 (6–71)** | ***0.001*** |

Italicized bold values indicates statistically significant changes.
NG, nasogastric tube; LoS, Length of stay. Delayed gastric emptying according to ISPGS classification.[15]
Numbers presented as median (range) or n (%).

administered to 42 (60%) of the patients in the WaS group as compared to 47 (64%) in the DoB group.

All patients in the DoB group underwent a prophylactic bypass procedure, most often a double bypass, while all asymptomatic patients in the WaS group (69%) were closed without a surgical bypass. The procedures performed are listed in Table 2. The operative time was longer for the DoB group (208 min [114–719] vs. 177 min [65–420], p = 0.107) than the WaS group, but not significant. The DoB group suffered from significantly higher blood loss (600 ml [100–5000] vs. 200 ml [0–900], p < 0.001) and a higher need of transfusion (32% vs. 14%, p = 0.017) than the WaS group.

Postoperative outcomes are shown in Table 2. Patients in the WaS group had their nasogastric tube removed significantly earlier (0 days [0–22] vs. 2 days [0–17], p < 0.001) and returned to a normal diet significantly faster (2 days [1–31] vs. 7 days [3–19], p < 0.001) than the DoB group.

The two groups have similar numbers of patients in need of readmission for biliary or gastric outlet symptoms during their remaining lifetime, 43 patients (61%) in the WaS group and 49 patients (67%) in the DoB group, p = 0.491. In total, counting both the length of primary hospital stay and that of readmissions, the WaS group still has significantly shorter total LoS with 18 days (3–74) compared with the DoB group with 24 days (8–53), p = 0.001.

Long-term outcomes by type of biliary drainage are shown in Table 3. The WaS group was further analysed by initial stent type (plastic vs. metal). Long-term outcomes for both groups with regard to delayed GOO syndrome are shown in Table 4.

There was no significant difference in overall survival between the two groups (WaS group median survival 330 days [15–1005] vs. 248 days [23–833] for the DoB group, p = 0.117).

## Discussion

When patients are found to be unresectable at laparotomy, it is of major importance to provide the best quality of life during their short remaining lifetime. Non-therapeutic laparotomy has been

**Table 3** Outcome regarding hospital stay and re-interventions for bile duct problems. The WaS patients who were only treated with stents are divided in two groups, depending on if the patients received plastic or metallic stents (SEMS) in the perioperative time

| | WaS plastic n = 25 | WaS SEMS n = 23 | DoB, n = 73 | p-value |
|---|---|---|---|---|
| Primary hospital stay | 7 (3–39) | 7 (3–27) | 14 (6–71) | <**0.001** |
| Total LoS# | 18 (3–74) | 15 (5–73) | 24 (8–53) | **0.001** |
| Patients readmitted due to cholangitis/ cholestasis | 17 | 6 | 11 (15%) | **0.001** |
| Hospital days due to biliary related problems | 10 (0–36) | 4 (0–27) | 4 (0–42) | **0.001** |
| ERC/PTC, post initial intervention | 37 | 13 | 10 | **0.001** |

Italicized bold values indicates statistically significant changes.
Numbers presented as total numbers and median (range).
# Total LoS, includes primary LoS and total LoS of readmissions.
ERC, endoscopic retrograde cholangiography; PTC, percutaneous transhepatic cholangiography.

**Table 4** Outcome regarding gastric outlet obstruction (GOO)

| | WaS, n = 70 | DoB, n = 73 | p-value |
|---|---|---|---|
| Gastric outlet obstruction | 13 (18%) | 9 (12%) | 0.35 |
| Endoscopic stent | 7 (10%) | 5 (7%) | 0.55 |
| Surgical bypass | 6 (8%) | 1 (1%) | 0.06 |
| Hospital stay due to GOO | 15 (8–46) | 17 (7–92) | 0.473 |

Number of patients and days in median and range.

shown to be associated with significant morbidity, potential mortality, a decreased likelihood of receiving systemic treatment and decreased quality of life.[7,16]

When less invasive methods are available, routine bypass must be challenged. Palliation by non-surgical techniques is standardised practice when unresectable cancer is found during workup.[6] The double bypass procedure has a morbidity and mortality rate of 31–56% and 0–5% respectively.[10–12,17–19] Considering that not all patients will develop biliary or gastric obstruction, surgical bypass might even be unnecessary.

The results of the present study show that patients in the WaS group returned to normal diet significantly faster (2 vs. 7 days) and had a significantly shorter hospital stay (8 vs. 14 days) than patients in the DoB group. Furthermore, the patients in the DoB group suffered from significantly more complications postoperatively (67% vs. 31%). Similar results were recently shown by Spanheimer *et al.*, who also showed an overall survival that was significantly shorter in the bypass group.[17] Moreover, others have shown that postoperative complications have a significant impact on long-term survival.[18,20] In accordance with Lyons *et al.*, the two groups in this study have similar numbers of patients in need of readmission during their remaining lifetimes, 61% in WaS vs. 67% in DoB,[12] indicating that a prophylactic double bypass does not prevent future need for hospitalisation.

Most patients present with obstructive jaundice and receive biliary drainage during workup, plastic endoprosthesis in the majority. During the observed period there was a tendency in the WaS group to change all plastic stents to metallic stents in the perioperative time.

A Cochrane meta-analysis comparing surgical hepaticojejunostomy with plastic biliary stents showed no differences in technical or therapeutic success but a significantly higher risk of re-intervention due to recurrent biliary obstruction in the plastic stent group.[21] Additionally, metallic stents are shown to be superior to plastic stents regarding patency and reduced risk of recurrent biliary obstruction.[22–24] Artifon *et al.* demonstrated that the overall cost of care is lower and that the patients' quality of life score is better with metallic stents compared to surgical bypass.[25]

The current study shows that patients in the WaS group with metallic stent had a slightly higher proportion of readmissions due to biliary obstruction but a similar need of re-interventions and total hospital length of stay due to bile-related problems than the DoB patients. These results suggest that a metallic biliary stent has comparable benefits with surgical biliary bypass in the long run, with the benefit of faster recovery and a shorter hospital stay after initial laparotomy. A wait-and-see strategy is preferable if the biliary drainage is secured by a metallic stent.

A prophylactic gastrojejunostomy does not prevent or diminish future GOO according to this study, as also shown by Spanheimer *et al.*[17] All 70 patients in the WaS group are included in the analysis, since it is a part of the WaS strategy to supply symptomatic patients with a gastrojejunostomy at initial laparotomy. The patients in the two groups had similar proportions of late GOO and interventions to restore the ability to eat.

Duodenal SEMS is a safe and effective alternative to surgery.[26] Trials comparing SEMS and surgical bypass for patients with symptomatic GOO have shown significantly shorter LoS, lower costs,[27–30] faster relief of symptoms[26] and symptomatic relief to a higher extent[28,29] in favour of endoscopy. Published data has not shown any difference in the rates of technical success, delayed complications[26,27,29] or quality of life between the two treatments.[31] Recurrent GOO is more common after stent placement, as is the need of re-interventions accordingly.[29] However, it is also shown that for 75% of the endoscopically treated patients a single stent was both effective and sufficient during the remaining lifetime.[32]

Besides the obvious limitations of a retrospective study, data were recruited from two different hospitals. However, data from the Swedish National Quality Registry for pancreatic cancer show no differences in complications, LoS or overall management between the two hospitals.[33] Furthermore, the subdivision of the WaS group by plastic or metallic stent, gives two relatively small groups, although the outcome in the two groups are clearly significant.

This study shows that surgical biliary bypass and the use of metallic biliary stent have similar outcomes regarding the need for postoperative interventions due to biliary obstruction. Moreover, the data show that a surgical duodenal bypass does not prevent future gastric outlet obstruction. Considering the higher morbidity and longer postoperative stay after surgical bypass, the result of this study supports a wait-and-see strategy.

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**Conflicts of interest**

None declared.

**References**

1. Society ACSAAC. (2015). *Cancer facts & figures 2015*. Available from: http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf.
2. Michelassi, F., Erroi, F., Dawson, P. J., Pietrabissa, A., Noda, S., Handcock, M., et al. (1989). Experience with 647 consecutive tumors of the duodenum, ampulla, head of the pancreas, and distal common bile duct. *Ann Surg, 210*, 544–554. discussion 54–6.
3. Shaib, Y., Davila, J., Naumann, C., & El-Serag, H. (2007). The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. Population-based study. *Am J Gastroenterol, 102*, 1377–1382.
4. Karmazanovsky, G., Fedorov, V., Kubyshkin, V., & Kotchatkov, A. (2005). Pancreatic head cancer: accuracy of CT in determination of resectability. *Abdom Imaging, 30*, 488–500.
5. Mayo, S. C., Austin, D. F., Sheppard, B. C., Mori, M., Shipley, D. K., & Billingsley, K. G. (2009). Evolving preoperative evaluation of patients with pancreatic cancer: does laparoscopy have a role in the current era? *J Am Coll Surg, 208*, 87–95.
6. Koninger, J., Wente, M. N., Muller, M. W., Gutt, C. N., Friess, H., & Buchler, M. W. (2007). Surgical palliation in patients with pancreatic cancer. *Langenbeck's archives Surg/Dtsch Gesellschaft fur Chir, 392*, 13–21.
7. Watanapa, P., & Williamson, R. C. (1992). Surgical palliation for pancreatic cancer: developments during the past two decades. *Br J Surg, 79*, 8–20.
8. Singh, S. M., Longmire, W. P., Jr., & Reber, H. A. (1990). Surgical palliation for pancreatic cancer. The UCLA experience. *Ann Surg, 212*, 132–139.
9. Espat, N. J., Brennan, M. F., & Conlon, K. C. (1999). Patients with laparoscopically staged unresectable pancreatic adenocarcinoma do not require subsequent surgical biliary or gastric bypass. *J Am Coll Surg, 188*, 649–655. discussion 55–7.
10. Lillemoe, K. D., Cameron, J. L., Hardacre, J. M., Sohn, T. A., Sauter, P. K., Coleman, J., et al. (1999). Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. *Ann Surg, 230*, 322–328. discussion 8–30.
11. Van Heek, N. T., De Castro, S. M., van Eijck, C. H., van Geenen, R. C., Hesselink, E. J., Breslau, P. J., et al. (2003). The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. *Ann of Surg, 238*, 894–902. discussion -5.
12. Lyons, J. M., Karkar, A., Correa-Gallego, C. C., D'Angelica, M. I., DeMatteo, R. P., Fong, Y., et al. (2012). Operative procedures for unresectable pancreatic cancer: does operative bypass decrease requirements for postoperative procedures and in-hospital days? *HPB: Off J Int Hepato Pancreato Biliary Assoc, 14*, 469–475.
13. Double bypass versus stent-treatment in irresectable pancreatic cancer [Internet]. U.S. National Institutes of Health; 2012 [cited 2015 April 10]. NCT01569282]. Available from: https://clinicaltrials.gov/ct2/show/NCT01569282?term=double+bypass+vs+stent&rank=1.
14. Dindo, D., Demartines, N., & Clavien, P. A. (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg, 240*, 205–213.
15. Wente, M. N., Bassi, C., Dervenis, C., Fingerhut, A., Gouma, D. J., Izbicki, J. R., et al. (2007). Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery, 142*, 761–768.
16. de Rooij, P. D., Rogatko, A., & Brennan, M. F. (1991). Evaluation of palliative surgical procedures in unresectable pancreatic cancer. *Br J Surg, 78*, 1053–1058.
17. Spanheimer, P. M., Cyr, A. R., Liao, J., Johlin, F. C., Hoshi, H., Howe, J. R., et al. (2014). Complications and survival associated with operative procedures in patients with unresectable pancreatic head adenocarcinoma. *J Surg Oncol, 109*, 697–701.
18. Ausania, F., Vallance, A. E., Manas, D. M., Prentis, J. M., Snowden, C. P., White, S. A., et al. (2012). Double bypass for inoperable pancreatic malignancy at laparotomy: postoperative complications and long-term outcome. *Ann R Coll Surg Engl, 94*, 563–568.
19. Kneuertz, P. J., Cunningham, S. C., Cameron, J. L., Torrez, S., Tapazoglou, N., Herman, J. M., et al. (2011). Palliative surgical management of patients with unresectable pancreatic adenocarcinoma: trends and lessons learned from a large, single institution experience. *J Gastrointest Surg Off J Soc Surg Aliment Tract, 15*, 1917–1927.
20. Kamphues, C., Bova, R., Schricke, D., Hippler-Benscheidt, M., Klauschen, F., Stenzinger, A., et al. (2012). Postoperative complications deteriorate long-term outcome in pancreatic cancer patients. *Ann Surg Oncol, 19*, 856–863.
21. Moss, A. C., Morris, E., & Mac Mathuna, P. (2006). Palliative biliary stents for obstructing pancreatic carcinoma. *Cochrane Database Syst Rev, 1*. CD004200.
22. Garcea, G., Ong, S. L., Dennison, A. R., Berry, D. P., & Maddern, G. J. (2009). Palliation of malignant obstructive jaundice. *Dig Dis Sci, 54*, 1184–1198.
23. Weber, A., Mittermeyer, T., Wagenpfeil, S., Schmid, R. M., & Prinz, C. (2009). Self-expanding metal stents versus polyethylene stents for palliative treatment in patients with advanced pancreatic cancer. *Pancreas, 38*, e7–e12.
24. Davids, P. H., Groen, A. K., Rauws, E. A., Tytgat, G. N., & Huibregtse, K. (1992). Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet, 340*, 1488–1492.
25. Artifon, E. L., Sakai, P., Cunha, J. E., Dupont, A., Filho, F. M., Hondo, F. Y., et al. (2006). Surgery or endoscopy for palliation of biliary obstruction due to metastatic pancreatic cancer. *Am J Gastroenterol, 101*, 2031–2037.
26. Fiori, E., Lamazza, A., Volpino, P., Burza, A., Paparelli, C., Cavallaro, G., et al. (2004). Palliative management of malignant antro-pyloric

 

strictures. Gastroenterostomy vs. endoscopic stenting. A randomized prospective trial. *Anticancer Res, 24*, 269–271.

**27.** Roy, A., Kim, M., Christein, J., & Varadarajulu, S. (2012). Stenting versus gastrojejunostomy for management of malignant gastric outlet obstruction: comparison of clinical outcomes and costs. *Surg Endosc, 26*, 3114–3119.

**28.** Johnsson, E., Thune, A., & Liedman, B. (2004). Palliation of malignant gastroduodenal obstruction with open surgical bypass or endoscopic stenting: clinical outcome and health economic evaluation. *World J Surg, 28*, 812–817.

**29.** Jeurnink, S. M., van Eijck, C. H., Steyerberg, E. W., Kuipers, E. J., & Siersema, P. D. (2007). Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC Gastroenterol, 7*, 18.

**30.** Cote, G. A., & Sherman, S. (2012). Endoscopic palliation of pancreatic cancer. *Cancer J, 18*, 584–590.

**31.** Jeurnink, S. M., Steyerberg, E. W., van Hooft, J. E., van Eijck, C. H., Schwartz, M. P., Vleggaar, F. P., et al. (2010). Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. *Gastrointest Endosc, 71*, 490–499.

**32.** Maire, F., Hammel, P., Ponsot, P., Aubert, A., O'Toole, D., Hentic, O., et al. (2006). Long-term outcome of biliary and duodenal stents in palliative treatment of patients with unresectable adenocarcinoma of the head of pancreas. *Am J Gastroenterol, 101*, 735–742.

**33.** Linköping Rcsi. (2013). *Kvalitetsregister för tumörer i pankreas och periampullärt*. Årsrapport 2013 [Internet] [cited 2015 10 Apr]. Available from: http://www.cancercentrum.se/PageFiles/571/Pankreascancer%C3%85rsrapport2013_(20140930)2.pdf.

# Paper IV

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ORIGINAL ARTICLE

# Postoperative pancreatic fistula-impact on outcome, hospital cost and effects of centralization

Caroline Williamsson, Daniel Ansari, Roland Andersson & Bobby Tingstedt

Department of Surgery, Skåne University Hospital at Lund and Clinical Sciences, Lund University, Sweden

## Abstract

**Background:** One of the most serious complications after pancreaticoduodenectomy (PD) is postoperative pancreatic fistula (POPF). This study investigated the incidence of POPF before and after centralization of pancreatic surgery in Southern Sweden and its impact on outcome and health care costs.

**Methods:** The local registry comprising all pancreatic resections at Skåne University Hospital, Lund, Sweden, was searched for PDs from 2005 to 2015. The patients were analysed in three groups: low-volume, high-volume and after introduction of an enhanced recovery program. Only the clinically relevant POPF grades B and C (CR-POPF) were investigated.

**Results:** 322 consecutive patients were identified. The annual operation volume increased almost threefold and the postoperative length of stay and total hospital cost decreased concurrently. The incidence of CR-POPF did not decrease over time. The group with CR-POPF had more complications and prolonged length of stay. The cost was 1.5 times higher for patients with CR-POPF and the cost did not decline despite the increase of hospital volume.

**Conclusion:** Centralization of pancreatic surgery did not decrease the rate of CR-POPF nor its subsequent impact on LOS and costs. Further efforts must be made to reduce the incidence of CR-POPF.

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## Correspondence

Bobby Tingstedt, Department of Surgery, Skåne University Hospital at Lund, Getingevägen 4, 221 85 Lund, Sweden. E-mail: bobby.tingstedt@med.lu.se

## Introduction

Pancreaticoduodenectomy (PD) is one of the most complex abdominal operations with a significant impact on patient health and physical function. Postoperative pancreatic fistula (POPF) is regarded as the major cause of morbidity after PD. Prior reports have described risk factors for POPF, but comparisons have been hampered by heterogeneous definitions.[1] In 2005, the International Study Group of Pancreatic Fistula (ISGPF), established a universal definition for POPF,[2] which has been validated[3] and is the currently most used classification.[4] With standardized definition, accurate comparisons on fistula rates between institutions can be made.

This paper was presented at the 12th World Congress of IHPBA, April 20–23 2016, Sao Paulo, Brazil.

While recent improvements in surgical technique and perioperative management have reduced mortality, overall morbidity after PD appears to remain at a constant high level.[5] The centralization to high volume units has decreased mortality and improved outcome.[6–9]

It is unclear whether the process of centralization has generated any improvements on POPF rates. The aim of this study was therefore to elucidate the incidence of clinically relevant postoperative fistulas (CR-POPF) during the transition from a low volume to a high volume pancreatic centre and delineate their management, impact on patient outcomes and health care costs.

## Methods

### Patients

This was a retrospective study of consecutive patients who underwent pancreaticoduodenectomy (PD) at the Department of





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Surgery, Skåne University Hospital, Lund, Sweden from January 2005 to December 2015. Pancreatic surgery was previously performed in seven hospitals in the region and during the last decade it has gradually been transferred to Skåne University Hospital due to policy changes. Patients were identified from a local database comprising all pancreatic resections at this unit. Only patients with complete data to evaluate CR-POPF and other morbidity were included. Patients with both benign and malignant disease were included. Necrosectomy, enucleations and distal pancreatectomy were excluded from this study.

Demographic data, operative parameters and postoperative course were collected and evaluated. Surgical outcomes were sorted and analysed by hospital volume, categorized by the annual number of PDs based on established cut-off values and a previous report from this institution.[9,10] The categories were low-volume, years 2005–2009 (LV, <25 PDs/year), high-volume, years 2010–2012 (HV, ≥25 PDs/year) and after introduction of an Enhanced Recovery Program, years 2013–2015 (ERP). ERP was introduced October 2012 and seven patients from late 2012 were analysed together with patients from years 2013–2015. The study protocol was approved by the human ethics committee at Lund University (2015/833).

All complications were classified according to the Clavien–Dindo grading system at 30 days or in-hospital.[11] Clavien IIIa-V were considered as major complications based on their need for intervention. Complications specific to pancreatic surgery, such as delayed gastric emptying (DGE), postpancreatectomy haemorrhage (PPH) and postoperative pancreatic fistula (POPF), were classified according to the standards depicted by the International Study Group of Pancreatic Surgery (ISGPS) and ISGPF.[2,12,13] POPF were graded as A, B or C fistulas, where Grade A is a biochemical fistula with no impact on clinical course. Grades B and C severely impacts patient's health and requires changes in management. If an invasive procedure was needed, together with sepsis or organ dysfunction, the POPF is graded as C. When analysing outcome, patients without POPF were unitized with POPF grade A, furthermore, POPF grades B and C were unitized and compared based on their clinical effect and need for therapeutic interventions. POPF grades B and C constitute the CR-POPFs.

CR-POPF, deep abscesses and anastomotic leakages were also merged and analysed since they frequently overlap.[14] Following the same line of reasoning as with POPF, the clinically relevant PPH grades B and C and DGE grades B and C are presented. Mortality was defined as in-hospital or within 30 days. The procedure specific complications and reoperations within 90 days were recorded. The pancreatic fistula risk score described by Roberts was calculated from derived from body mass index (BMI) and pancreatic duct width.[15,16]

### Patient management

Pancreaticoduodenectomy was performed using a standard technique including resection of the pyloric region, after access through a bilateral subcostal incision. Reconstruction was made by pancreaticogastrostomy. Two layers of interrupted sutures were used, first the pancreatic capsule at the resection margin to posterior gastric wall and thereafter, the pancreatic remnant was finally invaginated with a second layer into the posterior gastric wall. The reconstruction of the gastrointestinal tract was performed on a single jejunal limb. The divided end of jejunum was pulled through retrocolically. A side to side gastrojejunal anastomosis was created and, distally to this on the same limb, an end-to-side hepatojejunostomy. No duct stents, sealants or patches were used. PD was performed without extended lymphadenectomy. Over the period, the pancreatic surgeons have been consistent in their surgical technique and management of complications. A nasogastric tube (NGT) was inserted and one or two passive intra-abdominal drains placed. Prophylactic octreotide was used routinely for all patients. ERP was introduced October 2012 and details of the protocol have been reported previously.[17]

### Costs

In-hospital costs included cost of operation, time spent in hospital, time in intensive care, all healthcare personnel, laboratory tests, nutrition and radiology (diagnostics and interventions). The internal price list for Skåne University Hospital at Lund was employed to translate resource use into costs (based on costs at 1 January 2016). Health care in Sweden is publically financed by the government with little differences in reimbursement over the country.

### Statistics

Descriptive data are presented as numbers and percentages, median and range as appropriate. Differences between groups were evaluated by the Fisher's Exact Test or the Chi-square analysis for categorical variables and Mann–Whitney U-test or Kruskal–Wallis test for continuous variables. A p-value of <0.050 was considered significant. Statistical analysis was conducted using SPSS® version 23.0 (SPSS Inc.®, Chicago, IL, USA).

## Results

### Outcomes of the overall cohort

From 1st January 2005 until 31st December 2015, 325 PDs were performed but complete data were not available for three patients. Patient demographics, pathology and postoperative data are presented in Table 1 for the three groups. The annual operation volume was 17 PDs/year over the low volume period, 2005–2009 and increased to 34/year up to 2012 and 45/year thereafter. Operative time, estimated blood loss, need for blood transfusion, length of stay and cost decreased significantly during the same era. Pancreatic fistula risk score for each group was (median and range) LV = 14.5 (0–57), HV = 11 (0–60), ERP = 10 (0–45), p = 0.036.

### Outcomes for CR-POPF patients

The incidence of CR-POPF did not change between the groups (Fig. 1), neither did the proportion of patients suffering from




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**Table 1** Patient demographics and postoperative parameters for all PD patients 2000–2015 in the different volume groups

| | Low-volume 2005–2009 n = 85 | High-volume 2010–2012 n = 102 | ERP 2013–2015 n = 135 | p-Value |
|---|---|---|---|---|
| Age (years) | 67 (17–83) | 66 (25–81) | 68 (15–83) | **0.070** |
| Body mass index (kg/m$^2$) | 23.8 (17.8–36.5) | 24.8 (16.3–41.2) | 25.1 (17.1–40.9) | 0.370 |
| Diabetes mellitus | 21 (25) | 25 (25) | 33 (24) | 0.995 |
| Smoker | 27 (32) | 24 (24) | 55 (41) | **0.022** |
| Pathology | | | | **0.011** |
| Adenocarcinoma[a] | 64 (75) | 87 (85) | 107 (79) | |
| Neuroendocrine tumour | 2 (2) | 4 (4) | 5 (4) | |
| Premalignant tumour[b] | 1 (1) | 2 (2) | 10 (7) | |
| Benign histopathology | 12 (14) | 9 (9) | 11 (8) | |
| Other | 6 (7) | 0 | 2 (1) | |
| Postoperative length of stay (days) | 15 (8–62) | 13 (6–78) | 12 (6–97) | **0.001** |
| Cost (€) | 28 112 (17 278–152 066) | 23 160 (16 068–94944) | 22 292 (13 405–140 852) | **<0.001** |

Bold text indicates significant differences.
Data presented as median (range) and n (%).
[a] Pancreatic, biliary, ampullary and duodenal adenocarcinoma.
[b] Includes IPMN, mucinous cystadenoma and ampullary adenoma.

CR-POPF, deep abscess or anastomotic leakage (LV n = 23, HV n = 18, ERP n = 28, p = 0.286.) They did not return to oral intake earlier over time and there was a similar frequency of interventional radiology requirement and reoperation. There was no significant decrease in intensive care stay, overall postoperative length of stay (LOS) or associated costs in these patients with complications (Table 2).

In total, 39 patients (12%) developed a CR-POPF over the 11 years. These patients had a significantly higher BMI (median 27.9 vs. 24.3, p < 0.001) and greater proportion of underlying benign histopathology (9/39 [23%] vs. 23/283 [8%], p = 0.008) than those without a pancreatic fistula, but there were no significant differences regarding age, gender, smokers, diabetes mellitus or distribution of ASA score. Operative time did not differ but patients who developed CR-POPF had significantly higher blood loss (650 ml vs. 500 ml p = 0.030). Only one patient with chronic pancreatitis who developed CR-POPF. Except for medical complications, patients with CR-POPF had significantly higher incidence of all complications and therapeutic interventions. The subsequent cost was approximately 50% higher for patients that developed CR-POPF (Table 3).

## Discussion

Despite advancements in surgical technique and perioperative care, the incidence of postoperative pancreatic fistulas is

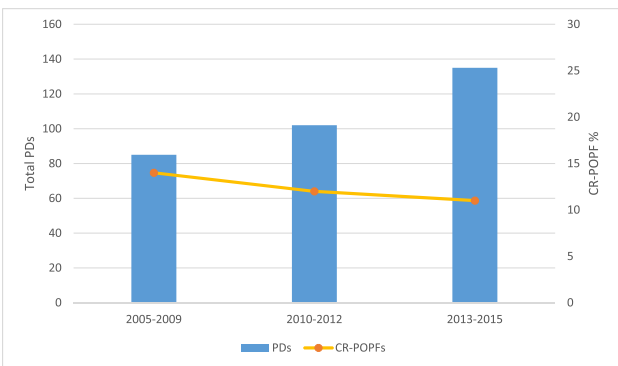


**Figure 1** Evolution of total PDs and CR-POPFs in the different volume groups. The rate of CR-POPF remained unaltered (p = 0.926) over the period




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**Table 2** Postoperative parameters and pancreatic fistula score for PD patients with CR-POPF

| B C fistlar/abscess/läckage | Low-volume 2005–2009 n = 12 | High-volume 2010–2012 n = 12 | ERP 2013–2015 n = 15 | p-Value |
|---|---|---|---|---|
| Postoperative length of stay (days) | 30 (17–62) | 27 (8–78) | 24 (8–97) | 0.684 |
| Removal of drain (days) | 16 (2–48) | 10 (5–36) | 7 (2–74) | 0.239 |
| Removal of NGT (days) | 9 (5–27) | 7 (2–39) | 5 (1–78) | 0.632 |
| Deep infection | 4 | 6 | 11 | 0.111 |
| Intensive care unit (days) | 22 (1.8) | 20 (1.8) | 20 (1.3) | 0.293 |
| Interventional radiology | 4 | 5 | 9 | 0.382 |
| Reoperation | 2 | 0 | 2 | 0.357 |
| Cost (€) | 42 887 (30 572–80 263) | 30 810 (23 000–81 948) | 29 355 (20 112–141 246) | 0.075 |
| Clavien | | | | 0.232 |
| 1 | 0 | 0 | 0 | |
| 2 | 4 | 7 | 4 | |
| 3a | 1 | 2 | 5 | |
| 3b | 1 | 0 | 3 | |
| 4a | 4 | 3 | 2 | |
| 4b | 0 | 0 | 1 | |
| 5 | 2 | 0 | 0 | |
| Pancreatic fistula score | 24 (7–57) | 22 (11–60) | 17 (4–40) | 0.142 |

Data presented as median (range) or n, except intensive care unit which is total days (mean).
NGT, nasogastric tube.

**Table 3** Pathology and outcome presented for patients with no or a grade A fistula compared to the CR-POPF patients

| | POPF 0/A n = 283 | CR-POPF n = 39 | p-Value |
|---|---|---|---|
| Pathology | | | **0.047** |
| Adenocarcinoma[a] | 233 | 25 | |
| Neuroendocrine tumour | 9 | 2 | |
| Premalignant tumour[b] | 11 | 2 | |
| Benign histopathology | 23 | 9 | |
| Other | 7 | 1 | |
| Pancreatic fistula score | 10 (0–51) | 21 (4–60) | **<0.001** |
| Outcome | | | |
| Clavien ≥3 | 30 | 23 | **<0.001** |
| Medical complications | 75 | 12 | 0.570 |
| Intensive care unit | 21 | 14 | **<0.001** |
| PPH B/C | 11 | 16 | **<0.001** |
| DGE B/C | 42 | 24 | **<0.001** |
| Interventional radiology | 34 | 18 | **<0.001** |
| Reoperation | 4 | 4 | **0.009** |
| Length of stay | 12 (6–77) | 27 (8–97) | **<0.001** |
| Cost (€) | 22 181 (12 943–146 418) | 34 061 (19 365–135 999) | **<0.001** |

Bold text indicates significant differences.
Data presented as median (range) and n.
PPH, postoperative pancreatic haemorrhage; DGE, delayed gastric emptying.
[a] Pancreatic, biliary, ampullary and duodenal adenocarcinoma.
[b] Includes IPMN, mucinous cystadenoma and ampullary adenoma.




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unaltered. This study shows that the incidence of CR-POPF and their related resource utilization have not decreased during a regional centralization process of pancreatic surgery to a single site. Furthermore, the patients with CR-POPFs are not managed within a shorter postoperative length of stay or with diminished costs for their care.

The annual rate of PDs made an almost threefold increase during the study time. As previously shown for all PDs, operative outcome improved as a result of increased surgical experience following growth of volume.[10] This institution has also demonstrated the evolution in the perioperative care, with earlier removal of nasogastric tubes and drains, which result in faster mobilisation and shorter LOS.[10,17] The current study additionally presents the decreased costs for all patients in the different volume groups. During this time seven senior surgeons performed or supervised all operations, and except for two senior surgeons, all training was done in-house.

The introduction of ERP, enhanced recovery after surgery (ERAS®) or fast track programs has recently gained popularity for PDs. There are reports on decreased delayed gastric emptying,[18] earlier feeding and recovery as well as shorter LOS[17,19,20] and decreased costs without jeopardizing patients' safety or worsening health related quality of life.[17]

The CR-POPF incidence of 12% in the overall cohort in this study corresponds well with figures reported in international literature. A recent analysis showed that the current incidence of overall POPF following PD was 22–26% and approximately 12% for CR-POPF.[4] To incorporate POPF grade A with patients without POPF is not controversial, as they have been shown to have no adverse clinical or economic impact on patient recovery.[3] The proportion of CR-POPF did not change in the different volume groups, implying that the rate of CR-POPF is not affected by the increased experience among surgeons and health care staff. The result is congruent with reports on cohorts prior to the adoption of the ISGPF's definition; Lin and Schmidt did not see a significant decline in pancreaticocutaneous fistulas despite an increase in surgical volume during the 1980's until the early 2000's.[21,22] Earlier comparisons were difficult due to the variability of the definition of pancreatic fistula, shown e.g. by Bassi and colleagues 2004; where the rate of pancreatic fistulas varied from 10 to 29% according to four different definitions.[1] The POPF classification by ISGPF is now allowing a uniform assessment and reporting.

Patients with fistulas are more likely to have bile leak, deep abscesses and wound infections[21] and abscesses are furthermore most frequently associated with fistulas.[23] To make an accurate distinction between these complications can be difficult, as they commonly overlap. Due to their similar clinical presentation and management, they have previously been presented as a group.[14] In the present study, the proportion of CR-POPF together with deep abscesses and leakages were unaltered in the different volume groups and the total incidence of 21% corresponds with the previous report.[14]

Prior studies have identified a diversity of, and sometimes contradictive, patient, tumour and operative factors associated with an increased risk of CR-POPF. Factors include obesity,[24] increased operative time,[21,22,25] blood loss,[26] intraoperative transfusions,[21] soft pancreatic parenchyma and a gracile main pancreatic duct.[21,26–28] Additionally, high risk disease pathology, specifically the ampullary, duodenal and biliary tumours in addition to the cystic cases, have been shown to correlate with a higher occurrence of pancreatic fistulas compared with pancreatic adenocarcinoma and chronic pancreatitis.[25,26,29] The results from this study supports the correlation of BMI and CR-POPF. Moreover, pancreatic adenocarcinoma was less common and benign histopathology was more frequent among patients with CR-POPF.

As shown by many before, patients with CR-POPF have longer LOS, more septic complications and a higher rate of reoperations.[3,21,22] As expected, a greater proportion of patients with CR-POPF in this current study were in need of ICU care, interventional radiology and reoperations compared to patients without CR-POPF. The two mortalities in this cohort were patients suffering from complications of CR-POPF.

There has been a shift in literature from operative to non-operative management of postoperative complications after PD, where interventional radiology has gained a significant role.[30] Most patients can be managed with percutaneous drainages without need for reoperation.[22,31,32] This shift in management over time was not demonstrated by our data, but the utilization of ICU decreased and interventional radiology increased.

There is a clear decline in health care cost for the care of PD patients overall. The cost for CR-POPF is naturally higher than for patients without fistulas, but the gradual decrease over time is not significant for this group. Enestvedt *et al.* have shown that clinically relevant pancreatic fistula was an independent predictor for increased cost and patients with CR-POPF had 1.3 times the cost than those without CR-POPF.[5] Patients with CR-POPF in this present study were discharged in median on POD 27 (8–97) compared with POD 12 (6–77) for no CR-POPF, which is the major expense item. This implies, that even though the multidisciplinary team are more familiar with the care of these complex surgical patients, and recognize rising complications at an early stage, we might not have improved our management of fistulas.

Many aspects of pancreatic surgery and its perioperative care have been favourably affected by the organisation in high volume units, but not the incidence of CR-POPF. Positive effects might be outweighed by patients with more risk factors predisposing them to CR-POPF, such as conditions associated with a soft pancreatic texture. Improved experience and outcome may encourage units to accept frail patients or more high risk cases. This is though not supported by this study. The frequency of premalignant cases or pancreatic risk score for fistulas has not increased.




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The technical aspect of the reconstruction has not changed during the transition to a high volume centre. The lack of change in anastomotic technique might be the reason to the unchanged rate of CR-POPFs. There have been several reports on different anastomotic techniques with or without artificial resources, and none, so far, seems to be distinctly superior.[33,34] Further improvements in CR-POPFs might possibly occur by evolution of technique.

Limitations of this study include its retrospective design. When comparing different volume groups at one single institution, it consequently implies comparing different eras. This has not been adjusted for in these analyses. Missing data were occasionally encountered. Parenchymal texture was not possible to evaluate, since it has not been routinely collected within our database.

## Conclusions

Centralization of pancreatic surgery did not decrease the rate of CR-POPF nor its subsequent impact on LOS and costs. Since the frequency of CR-POPF is unaltered despite an increase in volume, further efforts must be made on earlier detection and management to minimize morbidity and total health care costs.

### Conflicts of interest

None declared.

### References


1. Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, Falconi M *et al*. (2004) Pancreatic fistula rate after pancreatic resection. The importance of definitions. *Dig Surg* 21:54–59.
2. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al*. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 138:8–13.
3. Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, Vollmer, CM, Jr.. (2007) Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. *Ann Surg* 245:443–451.
4. Harnoss JC, Ulrich AB, Harnoss JM, Diener MK, Buchler MW, Welsch T. (2014) Use and results of consensus definitions in pancreatic surgery: a systematic review. *Surgery* 155:47–57.
5. Enestvedt CK, Diggs BS, Cassera MA, Hammill C, Hansen PD, Wolf RF. (2012) Complications nearly double the cost of care after pancreaticoduodenectomy. *Am J Surg* 204:332–338.
6. de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, Dejong CH *et al*. (2012) Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *Br J Surg* 99: 404–410.
7. Balzano G, Zerbi A, Capretti G, Rocchetti S, Capitanio V, Di Carlo V. (2008) Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. *Br J Surg* 95:357–362.
8. Gooiker GA, Lemmens VE, Besselink MG, Busch OR, Bonsing BA, Molenaar IQ *et al*. (2014) Impact of centralization of pancreatic cancer surgery on resection rates and survival. *Br J Surg* 101:1000–1005.
9. Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR *et al*. (2000) Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Ann Surg* 232:786–795.
10. Ansari D, Williamsson C, Tingstedt B, Andersson B, Lindell G, Andersson R. (2014) Pancreaticoduodenectomy–the transition from a low- to a high-volume center. *Scand J Gastroenterol* 49:481–484.
11. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 240:205–213.
12. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR *et al*. (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 142:761–768.
13. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ *et al*. (2007) Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 142: 20–25.
14. Vin Y, Sima CS, Getrajdman GI, Brown KT, Covey A, Brennan MF *et al*. (2008) Management and outcomes of postpancreatectomy fistula, leak, and abscess: results of 908 patients resected at a single institution between 2000 and 2005. *J Am Coll Surg* 207:490–498.
15. Roberts KJ, Hodson J, Mehrzad H, Marudanayagam R, Sutcliffe RP, Muiesan P *et al*. (2014) A preoperative predictive score of pancreatic fistula following pancreatoduodenectomy. *HPB* 16:620–628.
16. Roberts KJ, Sutcliffe RP, Marudanayagam R, Hodson J, Isaac J, Muiesan P *et al*. (2015) Scoring system to predict pancreatic fistula after pancreaticoduodenectomy: a UK multicenter study. *Ann Surg* 261: 1191–1197.
17. Williamsson C, Karlsson N, Sturesson C, Lindell G, Andersson R, Tingstedt B. (2015) Impact of a fast-track surgery programme for pancreaticoduodenectomy. *Br J Surg* 102:1133–1141.
18. Balzano G, Zerbi A, Braga M, Rocchetti S, Beneduce AA, Di Carlo V. (2008) Fast-track recovery programme after pancreaticoduodenectomy reduces delayed gastric emptying. *Br J Surg* 95: 1387–1393.
19. Braga M, Pecorelli N, Ariotti R, Capretti G, Greco M, Balzano G *et al*. (2014) Enhanced recovery after surgery pathway in patients undergoing pancreaticoduodenectomy. *World J Surg* 38:2960–2966.
20. Coolsen MM, van Dam RM, Chigharoe A, Olde Damink SW, Dejong CH. (2014) Improving outcome after pancreaticoduodenectomy: experiences with implementing an enhanced recovery after surgery (ERAS) program. *Dig Surg* 31:177–184.
21. Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. (2004) Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. *J Gastrointest Surg* 8:951–959.
22. Schmidt CM, Choi J, Powell ES, Yiannoutsos CT, Zyromski NJ, Nakeeb A *et al*. (2009) Pancreatic fistula following pancreaticoduodenectomy: clinical predictors and patient outcomes. *HPB Surg* 2009:404520.
23. Schulick RD. (2008) Complications after pancreaticoduodenectomy: intraabdominal abscess. *J Hepatobiliary Pancreat Surg* 15:252–256.
24. Fang CH, Chen QS, Yang J, Xiang F, Fang ZS, Zhu W. (2016) Body mass index and stump morphology predict an increased incidence of pancreatic fistula after pancreaticoduodenectomy. *World J Surg* 40:1467–1476.
25. de Castro SM, Busch OR, van Gulik TM, Obertop H, Gouma DJ. (2005) Incidence and management of pancreatic leakage after pancreatoduodenectomy. *Br J Surg* 92:1117–1123.





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**26.** Pratt WB, Callery MP, Vollmer, CM, Jr.. (2008) Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. *World J Surg* 32:419–428.

**27.** McMillan MT, Vollmer, CM, Jr.. (2014) Predictive factors for pancreatic fistula following pancreatectomy. *Langenbecks Arch Surg Deutsche Gesellschaft Chir* 399:811–824.

**28.** Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer, CM, Jr.. (2013) A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg* 216:1–14.

**29.** Bartoli FG, Arnone GB, Ravera G, Bachi V. (1991) Pancreatic fistula and relative mortality in malignant disease after pancreaticoduodenectomy. Review and statistical meta-analysis regarding 15 years of literature. *Anticancer Res* 11:1831–1848.

**30.** Malleo G, Pulvirenti A, Marchegiani G, Butturini G, Salvia R, Bassi C. (2014) Diagnosis and management of postoperative pancreatic fistula. *Langenbecks Arch Surg Deutsche Gesellschaft Chir* 399:801–810.

**31.** Sanjay P, Kellner M, Tait IS. (2012) The role of interventional radiology in the management of surgical complications after pancreatoduodenectomy. *HPB* 14:812–817.

**32.** Lermite E, Sommacale D, Piardi T, Arnaud JP, Sauvanet A, Dejong CH *et al*. (2013) Complications after pancreatic resection: diagnosis, prevention and management. *Clin Res Hepatol Gastroenterol* 37:230–239.

**33.** Shrikhande SV, Sivasanker M, Vollmer CM, Friess H, Besselink MG, Fingerhut A *et al*. (2016) Pancreatic anastomosis after pancreatoduodenectomy: a position statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. http://dx.doi.org/10.1016/j.surg.2016.11.021 [Epub ahead of print].

**34.** Crippa S, Cirocchi R, Randolph J, Partelli S, Belfiori G, Piccioli A *et al*. (2016) Pancreaticojejunostomy is comparable to pancreaticogastrostomy after pancreaticoduodenectomy: an updated meta-analysis of randomized controlled trials. *Langenbecks Arch Surg Deutsche Gesellschaft Chir* 401:427–437.





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Caroline Williamsson is a surgeon at the Hepato-Pancreato-Biliary unit at Skåne University Hospital in Lund. Here, in company by her former colleague dr. Per-Jonas Blind.

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