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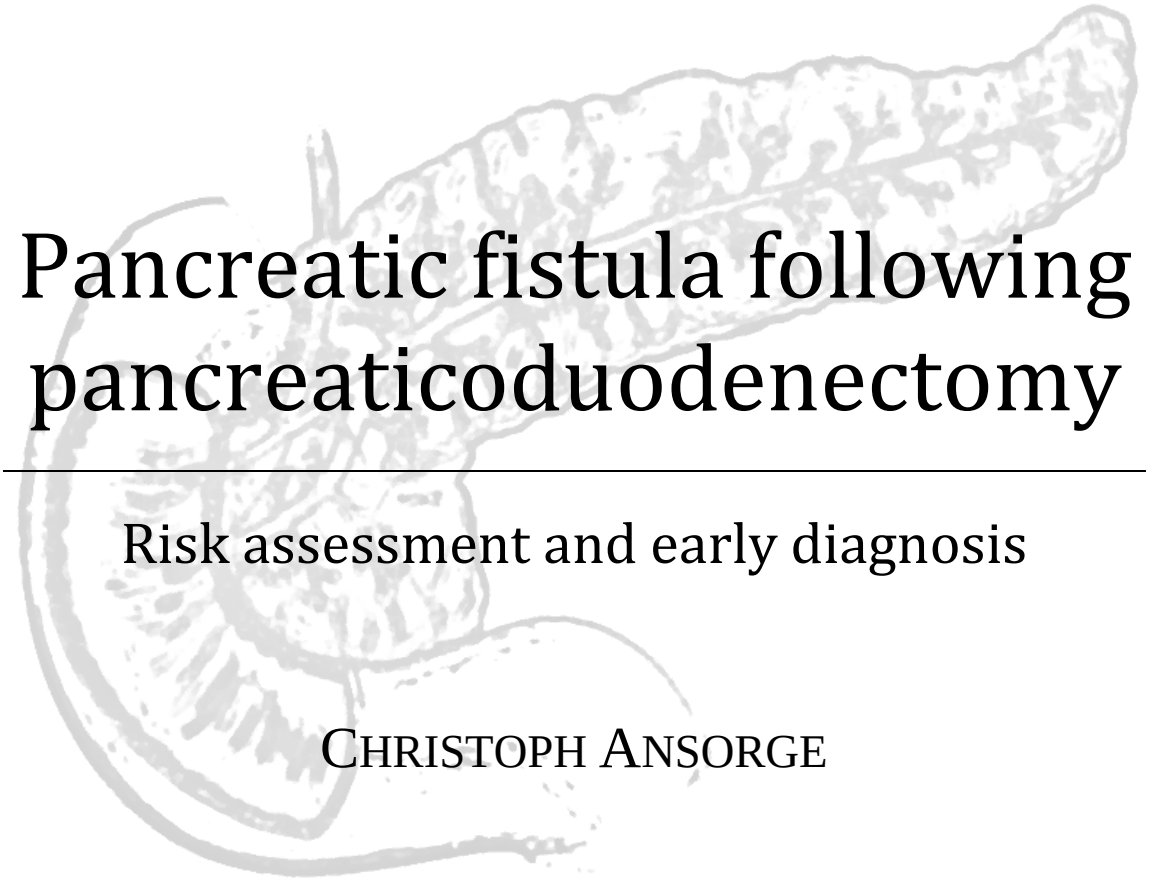

Pancreatic fistula following pancreaticoduodenectomy

Risk assessment and early diagnosis

CHRISTOPH ANSORGE

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“Richtiges Auffassen einer Sache und

Missverstehen der gleichen Sache schliessen einander nicht aus.“

FRANZ KAFKA

”Desperate to control, unable to forgive, and we are sinking deeper.”

TOOL

EMILY, MARIE, JULIE AND KJERSTI

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Br J Surg. 2012 Jan;99(1):104-11. doi: 10.1002/bjs.7730.
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II Ansorge C, Strömmer L, Andrén-Sandberg Å, Lundell L, Herrington MK, Segersvärd R.
Structured intraoperative assessment of pancreatic gland characteristics in predicting complications after pancreaticoduodenectomy.
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III Ansorge C, Lindström P, Strömmer L, Blomberg J, Lundell L, del Chiaro M, Segersvärd R.
Assessing surgical quality: Comparison of general and procedure-specific morbidity estimation models for the risk adjustment of pancreatico-duodenectomy outcomes.
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IV Ansorge C, Nordin JZ, Lundell L, Strömmer L, Andrén-Sandberg Å, Segersvärd R.
The analysis of amylase levels in drain output as an early diagnostic marker for pancreatic fistula formation following pancreatico-duodenectomy.
Submitted.

Summary of the thesis

Pancreaticoduodenectomy (PD), a complex surgical procedure for resecting tumors of the pancreatic head, distal bile duct or periampullary region, is associated with a considerable morbidity. Postoperative pancreatic fistula (POPF), the main contributor, is caused by leakage from the pancreatico-enteric anastomosis and ranges from 15 to 26%. If not controlled promptly, POPF may lead to a complex postoperative course with septic or hemorrhagic complications, organ failure and increased mortality. Although multiple approaches to decrease POPF rates have been reported, an effective preventive strategy has not been found. The aims of this thesis were to study the contributing factors and early diagnostic markers of clinically relevant POPF, and to formulate predictive models that may facilitate clinical management of patients undergoing PD.

In study I, a prospective observational cohort study on 48 non-consecutive PD patients 2007-10, local metabolite changes and protease activation in the proximity of the pancreaticojejunostomy (PJ) were measured by microdialysis to investigate the pathophysiology of POPF. In patients subsequently developing POPF, high glycerol and lactate/pyruvate (LP) ratio levels, low glucose concentrations and presence of trypsinogen activation peptides were observed before any POPF symptoms appeared. The fact that glycerol level peaks preceded the elevations in LP ratios suggested that the early glycerol release in POPF patients was not initiated by local ischemia.

In study II, a prospective observational cohort study on 110 non-consecutive PD patients 2008-10, the predictive impact of a standardized intraoperative assessment of pancreatic consistency (PC) and pancreatic duct diameter (PDD) on the development of POPF was investigated. Combining both characteristics in a composite classification, the risk for POPF or fluid collections could be stratified as ‘high’ (softer PC and smaller PDD, incidence of associated morbidity 51%), ‘intermediate’ (softer PC or smaller PDD, 26%) or ‘low’ (no risk factors, 2%). Only patients with smaller PDD developed severe POPF.

In study III, a prospective observational cohort study on 195 consecutive PD patients 2008-10, the importance of POPF for PD-associated morbidity was evaluated by comparing the predictive impact of an intraoperative pancreatic risk assessment (IPRA) with the generally applicable “Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity” (POSSUM). Although the POSSUM-estimated risk corresponded with observed morbidity for the entire cohort, individual and grouped POSSUM risk estimates did not reveal any association with the incidence or severity of overall morbidity. However, the IPRA model identified patients with high POPF-risk and was even significantly associated with the incidence and severity of overall morbidity.

In study IV, a prospective observational cohort study on 315 consecutive PD patients 2008-12, the analysis of pancreatic amylase from intraabdominal drainage (DPA) as an early diagnostic marker of POPF following PD was evaluated. DPA at selected cut-off levels was proven to be superior to that of plasma pancreatic amylase in predicting clinically relevant POPF. A model combining DPA and C-reactive protein (CRP) had the highest POPF-predictive impact. Persistently raised CRP levels on POD 3 proved to be an independent indicator for subsequent POPF development.

In summary, standardized intraoperative pancreatic risk assessment (IPRA) constitutes a central tool for surgical decision making in the risk management of patients undergoing PD. It had a stronger predictive impact on the incidence and severity of overall postoperative morbidity than an established generally applicable risk adjustment model (POSSUM). Analyses of local metabolite concentrations or pancreatic amylase levels from intraabdominal fluids in the proximity of the PJ could serve as diagnostic markers for subsequent POPF development at an early subclinical stage.

Abbreviations

ANCR	Association of Nordic Cancer Registries
AUC	Area under the curve
CAPAP	Carboxypeptidase B activation peptide
CBD	Common bile duct
CCK	Cholecystokinin
CDC	Clavién-Dindo Classification of surgical complications
CEP	Cut edge of the pancreas
DA	Drain amylase
DGE	Delayed gastric emptying
DPA	Drain pancreatic amylase
ERQ	Equal risk quintile
GDA	Gastroduodenal artery
IPRA	Intraoperative pancreatic risk assessment
ISGPF	International Study Group of Pancreatic Fistula
ISGPS	International Study Group of Pancreatic Surgery
LHA	Left hepatic artery
L/P	Lactate / pyruvate
OCS	Observational cohort study
OR	Odds ratio
PBD	Preoperative biliary drainage
PC	Pancreatic consistency
PD	Pancreaticoduodenectomy
PDAC	Pancreatic ductal adenocarcinoma
PDD	Pancreatic duct diameter
PDO	Pancreatic duct occlusion
PDS	Polydioxanone sutures
PG	Pancreaticogastrostomy
PITR	Pancreatic Intention-To-Resect Register
PJ	Pancreaticojejunostomy
PJAM	Pancreaticojejunostomy-associated morbidity
POD	Postoperative day
POPF	Postoperative pancreatic fistula
POSSUM	Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity
PPP	Pancreatic polypeptide
PPA	Plasma pancreatic amylase
P-POSSUM	Portsmouth POSSUM
PPPD	Pylorus-preserving pancreaticoduodenectomy
PV	Portal vein
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
SC	Split cohort
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein
SPPC	Symptomatic peripancreatic collections
TAP	Trypsinogen activation peptide

I INTRODUCTION

Pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC), one of the most lethal human cancers, remains an unsolved major health problem (Vincent *et al.*, 2011). 3600 new cases occurred in the Nordic Countries between 2006 and 2010 (1752 in males, 1848 in females), while 4014 deaths were registered (1893 males and 2121 females, incidence 7.5 and 6.2, mortality 7.9 and 6.5 per 100.000, respectively). The fact that mortality rates are higher than incidence rates reflects the underreporting of new pancreatic cancer cases in individuals older than 70 years (Lambe *et al.*, 2011). In Sweden, pancreatic cancer is the 14th most common cancer form with 825 new cases (1.8% of all new cancer cases) but the 5th most common cancer mortality behind prostate, lung, breast and colorectal cancer with 1575 deaths, representing 7.1% of all cancer deaths per year (NORDCAN; ANCR).

Despite huge efforts, clinicians and researchers have not been able to improve PDAC survival rates. Surgery as the cornerstone of treatment with curative intent can be offered to only 15-20% of patients at the time of diagnosis (Li *et al.*, 2004). Even with complete local surgical tumor clearance, the relapse rate remains high with poor outcomes at 5 years (Sohn *et al.*, 2000; Yeo *et al.*, 1997a; Neoptolemos *et al.*, 2012). Cancer detection at earlier stages might give more patients access to surgery; however, most critical to improving the outcomes of resected PDAC is the development of effective systemic therapies. Future development of curative intent therapy in randomized clinical trials (RCT) is limited to those patients with non-disseminated disease, and undergoing a strictly assessed R0 resection (Crane *et al.*, 2010).

Besides achieving complete tumor clearance, a major objective in the research field of pancreatic surgery is to control the high post-pancreatectomy morbidity, which is predominated by two major complications; delayed gastric emptying (DGE) and post-operative pancreatic fistula (POPF). The latter is still challenging; if not controlled immediately, POPF may lead to severe secondary morbidity and significantly increased mortality (Hackert *et al.*, 2011a). Patients with other cancer forms than PDAC and the associated better survival rates have the highest risk of developing POPF (Pratt *et al.*, 2008a).

The intensive research on understanding pathways of cancer development, early detection strategies for PDAC, identification of cancer precursors, and the management of patients in high-volume centers with surgical and oncologic expertise may show promise to improve outcomes (Li *et al.*, 2004; Saif, 2011). However, the extension of surgical indications, shifting from curative-intent towards cancer-preventive surgery, might even implicate a change of the patient profile. Pancreatic surgeons will have to respond to an increasing demand for preventive surgery in younger, apparently healthier, more hesitant patients, with a greater need of information about the legitimacy of surgery in their individual cases. A lesser acceptance of possible severe postoperative complications will necessitate radical improvements to control surgical complications. Theoretically, the ability to control POPF could change the public picture of pancreatic resections and contribute to rationalizing more aggressive preventive surgical strategies in the fight against pancreatic cancer.

Anatomical aspects

The pancreatic gland is a retroperitoneal organ centrally located in the upper abdomen and ventral to the mesenteric vessels, extending from the pancreatic head in the C-loop of the duodenum to the pancreatic tail in the splenic hilum. In an adult, the pancreas is 15-20 cm long and weighs 75-100 g. The fact that even a minor surgical trauma to the pancreas can result in the release of pancreatic enzymes and cause pancreatitis, illustrates the importance of anatomic knowledge of the pancreatic gland and its surrounding structures for surgeons (Fisher W.E., 2010).

The pancreatic gland develops in the fourth week of fetal life by a fusion of the dorsal and ventral pancreatic bud from the caudal part of the foregut. With gut rotation, the ventral bud rotates around the posterior side of the duodenum to fuse with the dorsal bud. In the adult pancreas, both the caudal head portion and the uncinate process are derived from the ventral bud, whereas the cranial head portion, body and tail are derived from the dorsal bud. The ducts of the dorsal and ventral pancreas join to form the main pancreatic duct (duct of Wirsung); a smaller part of the dorsal duct persists in the pancreatic head as an accessory duct (duct of Santorini). In 5–15% of the population, the ventral and dorsal ducts fail to fuse resulting in a pancreas divisum and pancreatic drainage mainly through the duct of Santorini and through the minor papilla into the duodenum (Doherty, 2010).

The pancreatic regions and their blood supply

Pathological lesions in the pancreas are typically described in relation to four pancreatic regions (head, neck, body, and tail). The pancreatic head with the uncinate process lies within the C-loop of the duodenum and is associated medially to the mesentery of the transverse colon. The retroperitoneum behind the head of the pancreas contains the caval vein with the left renal vein and the aorta with the right renal artery.

The neck of the pancreas lies over the mesenteric root, where the splenic vein and superior mesenteric vein (SMV) join to continue in the hepatoduodenal ligament as the portal vein (PV). At the inferior border, the inferior mesenteric vein (IMV) joins the splenic vein near its junction with the SMV, or the SMV directly. The superior mesenteric artery (SMA) leaves the aorta above the crossing of the left renal vein and continues in the root of the mesentery to the left of the SMV. The inferior pancreaticoduodenal artery branches from the SMA and divides into the anterior and posterior inferior pancreaticoduodenal arteries which form the arterial pancreatic arcade giving off numerous branches to the duodenum and pancreatic head.

The pancreatic head contains the most distal part of the common bile duct (CBD). The intra-pancreatic CBD joins the main pancreatic duct at the ampulla of Vater. The uncinate process and the head of the pancreas wrap around the right side of the SMV/PV. Venous branches draining the pancreatic head and uncinate process enter along the right lateral and posterior sides of the SMV/PV (Fisher W.E., 2010). As there are usually no anterior venous

tributaries, a dissection plane can be developed between the neck of the pancreas and the SMV/PV. The gastroduodenal artery (GDA) leaves from the common hepatic artery and continues as the superior pancreaticoduodenal artery behind the first portion of the duodenum. It branches into the anterior and posterior superior pancreaticoduodenal arteries. It is not possible to resect the pancreatic head without devascularizing the duodenum, unless a rim containing the pancreaticoduodenal vascular arcade is preserved (Fisher W.E., 2010). Variations in the anatomy of the right hepatic artery, common hepatic artery, or GDA occur in 20% of patients (Michels, 1962), and the preoperative knowledge of the individual anatomy regarding the arterial liver supply is important for surgical and oncological reasons.

Table 1. Regional abdominal lymph nodes.

1	Right paracardial
2	Left paracardial
3	Lesser curvature
4sa	Short gastric vessels
4sb	Left gastroepiploic vessels
4d	Right gastroepiploic vessels
5	Suprapyloric
6	Infrapyloric
7	Left gastric artery
8a	Common hepatic artery anterosuperior
8p	Common hepatic artery posterior
9	Celiac artery
10	Splenic hilum
11p	Proximal splenic artery
11d	Distal splenic artery
12a	Hepatoduodenal ligament (LHA)
12b	Hepatoduodenal ligament (CBD)
12p	Hepatoduodenal ligament (PV)
13	Pancreatic head posterior surface
14v	Superior mesenteric vein
14a	Superior mesenteric artery
15	Middle colic vessels
16a1	Aortic hiatus
16a2	Abdominal aorta CT to LRV
16b1	Abdominal aorta LRV to IMV
16b2	Abdominal aorta IMV to AB
17	Pancreatic head anterior surface
18	Pancreas inferior margin
19	Infradiaphragmatic
20	Diaphragm esophageal hiatus
110	Lower thorax Paraesophagea
111	Supradiaphragmatic
112	Posterior mediastinal

Map of lymph node stations (Kawarada, 1998).

Once the gastrocolic omentum is divided and the omental bursa is opened, the body and tail of the pancreas is visible posterior to the stomach, and anterior to the splenic artery and vein. Multiple small venous branches from the pancreatic body and tail drain to the splenic vein running in a groove on the posterior aspect. The splenic artery branches from the celiac trunk and continues superior to the vein along the posterior superior edge of the pancreatic body and tail. The body of the pancreas is situated ventral to the aorta at the origin of the SMA and the neck of the pancreas ventral to the vertebral body of L1 and L2. Blunt anteroposterior trauma can compress the neck of the pancreas against the spine and cause a pancreatic "fracture" with parenchymal and/or ductal injury (Rekhi *et al.*, 2010). The pancreatic tail contains the portion from anterior to the left kidney to the hilum of the spleen (Fisher W.E., 2010). The body and tail of the pancreas are supplied by multiple branches of the splenic artery. The inferior pancreatic artery, ordinarily branching from the SMA, runs along the inferior border of the body and tail of the pancreas, parallel to the splenic artery, forming arcades within the body and tail of the pancreas, and accounting for

the rich blood supply of the organ. The venous drainage of the pancreas follows a similar pattern (Fisher W.E., 2010).

Lymphatic drainage and innervation

The widespread and diffuse lymphatic drainage from the pancreas contributes to early lymphatic invasion and dissemination in pancreatic cancer. The profuse network of lymph node stations has been mapped systematically (Kawarada, 1998). The pancreatic lymphatic system communicates with lymph nodes in the mesentery of the transverse colon and the proximal jejunum. In the pancreatic parenchyma, the acinar cells responsible for exocrine secretion and the islet cells responsible for endocrine secretion are stimulated by parasympathetic and inhibited by sympathetic nerves. In several studies about pancreatic nociception, the rich supply of afferent sensory fibers in the pancreatic parenchyma has been made responsible for the intense pain associated with advanced pancreatic cancer, as well as acute and chronic pancreatitis (Fisher W.E., 2010; Bradley & Bem, 2003).

Physiological aspects

The endocrine (2% of the cells in the pancreatic gland) and exocrine (85%) functions of the pancreatic gland are not functionally separated but components of a single complex regulatory feedback system for digestive enzyme and hormone secretion. Although it is possible to live without the pancreas if insulin and digestive enzymes are substituted, the loss of the pancreatic regulation after a total pancreatectomy leads to severe impairments in digestive function. Although only 20% of the normal pancreatic parenchyma is required to prevent functional insufficiency (Leahy *et al.*, 1984), many patients undergoing pancreatic resection have pancreatic remnants with impaired endocrine and exocrine function, and 5-11% develop pancreatic fibrosis and atrophy due to malfunction of the pancreatico-enteric anastomosis (Morgan *et al.*, 2010; Reid-Lombardo *et al.*, 2007a) or insufficient pancreatic stimulation.

Exocrine function

The external secretion of the pancreas is stimulated by the hormones secretin and cholecystokinin (CCK) and by parasympathetic vagal discharge. Pancreatic juice is an alkaline (pH 7.0–8.3) and isosmotic solution of 1–2 liters per day containing the secretions of acinar and duct cells. The acinar cells secrete amylase, proteases and lipases, enzymes responsible for the digestion of carbohydrate, protein, and fat, respectively. Unlike the endocrine islet cells that specialize in the secretion of one hormone type, individual acinar cells are capable of secreting all enzyme types. Due to a sequential regulation of secretion, the ratio of different enzymes secreted can be adjusted to the mix of food being digested. Pancreatic juice helps to neutralize gastric acid in the duodenum and adjusts luminal pH to a level that provides optimal conditions for the catalytic activity of the enzymes. Lipase and amylase are stored and secreted in active forms. Pancreatic amylase completes the digestive process that was started by salivary amylase. Phospholipase A and the proteases are secreted as an inactive proenzyme and activated in the duodenum (Davenport, 1982).

Proteolysis and lipolysis

The conversion of trypsinogen into active trypsin and the inactive cleavage product trypsinogen activation peptide (TAP) occurs at the intestinal brush border, catalyzed by enterokinase, an enzyme which is produced by the duodenal mucosal cells (Rinderknecht, 1993a). Trypsin, in turn, activates other proteolytic enzymes. The separate storage of proteases from other cell proteins, the secretion of proenzymes that require activation, and the presence of proteolytic enzyme inhibitors in the pancreatic juice and in the pancreatic parenchyma prevent the pancreas from autodigestion. A failure to express the pancreatic secretory trypsin inhibitor (PSTI), also known as serine protease inhibitor Kazal-type 1 (SPINK1) or tumor-associated trypsin inhibitor (TATI), is one of the causes of hereditary pancreatitis (Chen *et al.*, 2000). Trypsinogen is expressed in several isoforms. Trypsinogen-1, also known as cationic trypsinogen, is the main isoform of trypsinogen and encoded by the PRSS1 gene. Mutations on the cationic trypsinogen gene can result in the premature

intrapancreatic activation of trypsinogen, which accounts for about two thirds of cases of hereditary pancreatitis (Mitchell *et al.*, 2003). Trypsin activates chymotrypsin, elastase, carboxypeptidase A and B, and phospholipase, which together with other pancreatic lipases (pancreatic triglyceride lipase, carboxylester lipase) hydrolyze phospholipids and triglycerides into the end products glycerols and free fatty acids. Trypsin, chymotrypsin, and elastase cleave bonds between amino acids within a target peptide chain, and carboxypeptidase A and B cleave amino acids at the end of peptide chains. The individual amino acids and small dipeptides are then actively transported into the intestinal epithelial cells. Pancreatic lipase hydrolyzes triglycerides to 2-monoglyceride and fatty acid and phospholipase A2 hydrolyzes phospholipids. All lipases require bile salts to be active and are enhanced by co-lipase. Fat is hydrolyzed by carboxylic ester hydrolase and cholesterol esterase and packaged into micelles for transport into the intestinal epithelial cells, where the fatty acids are reassembled and packaged inside chylomicrons for transport through the lymphatic system into the blood (Doherty, 2010).

Table 2. Exocrine Pancreatic Enzymes.

Elastase	Cleaves carboxyl side of peptide bonds after small amino acid residues (alanine, glycine, serine) to produce oligopeptides
Trypsinogen/ Trypsin	Cleaves internal bonds at lysine or arginine residues to produce oligopeptides, activates other pancreatic proenzymes
Chymotrypsinogen/ Chymotrypsin	Cleaves carboxyl side of peptide bonds at aliphatic amino acid residues to produce oligopeptides
Pancreatic carboxypeptidase (A1, A2, and B)	Removes aromatic amino acids from carboxyl terminal end of protein or peptide chains, produces Arginine and Lysine
Pancreatic lipase	Cleaves triacylglycerol "fat" molecules into glycerol, two free fatty acids, and monoglycerides
Pancreatic amylase	Cleaves starches
Phospholipase A2	Cleaves phospholipid molecules at the second glycerol carbon
Lysophospholipase	Cleaves 2-lysophosphatidylcholine to produce glycerophosphocholine (a precursor of acetylcholine)
Cholesterol esterase	Cleaves fatty acid

Acinar secretion

An acinus consists of about 40 acinar cells. The duct cells, located near the center of the acinus (centroacinar cells), are responsible for the secretion of fluid and electrolyte in the pancreatic juice and contain carbonic anhydrase, an enzyme needed for bicarbonate secretion. Secretin-stimulated bicarbonate secretion buffers the acidic fluid entering the duodenum from the stomach. Chloride secretion varies inversely with the bicarbonate secretion. Sodium and potassium levels in the pancreatic secretion are constant and independent of the secretory rate. CCK stimulates bicarbonate secretion to a much lesser extent than secretin but potentiates secretin-stimulated bicarbonate secretion and augments the secretion of insulin. Somatostatin, pancreatic polypeptide (PPP), and glucagon of the endocrine pancreas inhibit exocrine secretion (Harris, 1994). The acinar cells release pancreatic enzymes into the lumen of the acinus, where they join with the fluid and bicarbonate secretions of the centroacinar cells. The pancreatic juice drains into small intercalated ducts and interlobular ducts, where fluid is added and electrolytes are adjusted, and into side branches that empty into the main pancreatic duct. Recurrent inflammation, trauma or manipulation, contributes to destruction of the branching structure, and together

with acinar or mesenchymal cell damage to the development of inter-, intralobular fibrosis and exocrine pancreatic insufficiency (Bro-Rasmussen *et al.*, 1956; Kloppel *et al.*, 2004).

Endocrine function

There are at least one million islets of Langerhans in the normal adult pancreas. Larger islets are located in proximity to the major arterioles and smaller islets are embedded in the pancreatic parenchyma. Most islets contain 3000 to 4000 cells of five major types: alpha cells that secrete glucagon, beta cells that secrete insulin, delta cells that secrete somatostatin, epsilon cells that secrete ghrelin, and PP cells that secrete PPP.

Insulin

Stored insulin can be released rapidly during a first secretion phase. The second phase is a sustained release due to ongoing production of new insulin. Insulin synthesis is regulated by plasma glucose levels, neural signals, and the paracrine influence of other islet cells. Glycogenolysis, fatty acid breakdown, ketone formation and hepatic glucose production is inhibited by Insulin, whereas protein synthesis is stimulated and glucose transport into cells facilitated (Ebert, 1987).There is a considerable amount of functional reserve in insulin secretory capacity. If the remaining portion of the pancreas is healthy, about 80% of the pancreas can be resected without the patient becoming diabetic; however, in chronic pancreatitis or other disease conditions, even smaller pancreatic resections can result in diabetes (Leahy *et al.*, 1984). Insulin deficiency (type I diabetes) results in an up-regulation of insulin receptors, leading to an enhanced insulin sensitivity. Type II diabetes is associated with insulin resistance, down-regulation of insulin receptors and relative hyperinsulinemia (Doherty, 2010).

Glucagon, somatostatin and pancreatic polypeptide

Glucagon is a peptide that promotes hepatic glycogenolysis and gluconeogenesis and counteracts the effects of insulin. Insulin and somatostatin inhibit glucagon secretion in a paracrine fashion within the islets. The same neural impulses that regulate insulin secretion also regulate glucagon secretion, so that the two hormones work together in a balance of actions to maintain glucose levels (Brunicardi *et al.*, 1987). Somatostatin is a peptide with a wide anatomic distribution and is important in many regulatory processes throughout the body. Endocrine release of somatostatin occurs during a meal by intraluminal fat and the acidification of the gastric and duodenal mucosa. Acetylcholine from the cholinergic neurons inhibits somatostatin release (Brunicardi *et al.*, 1994). Pancreatic polypeptides (PPP), discovered during the process of insulin purification (Kimmel *et al.*, 1968), are known to inhibit bile secretion, gallbladder contraction, and secretion by the exocrine pancreas. A number of studies suggest that PPP control glucose levels through the regulation of hepatic insulin sensitivity at the transcriptional level (Saltiel, 2001; Asakawa *et al.*, 2003). Deficiencies in PPP secretion due to proximal pancreatectomy or severe chronic pancreatitis are associated with diminished hepatic insulin sensitivity due to a reduced number of hepatic insulin receptors (Seymour *et al.*, 1998).

Historical aspects

The first anatomical descriptions of the pancreas have been attributed to Herophilus of Chalcedon in the third century BC (McClusky *et al.*, 2002; Busnardo *et al.*, 1983) . The observation that it did not consist of cartilage or bone prompted Ruphos of Ephesus to name the organ “pancreas” (Greek “pan” means “all”; Greek “kreas” means “flesh”) two hundred years later (Howard, 2003).

Pancreatic research

In the 16th century, in the fifth book of his opus “De humani corporis fabrica” (Fabric of the Human Body), Vesalius referred to the pancreas as a “glandulous organ” postulating that it exerted a protective effect on the stomach by serving as a cushion (Busnardo *et al.*, 1983). The main pancreatic duct was described by Wirsung in 1642, not understanding its function, and the accessory pancreatic duct by Santorini in 1775 (Stern, 1986). In 1720, Vater described the duodenal ampulla, and in 1887, Oddi the papillary sphincter (Howard *et al.*, 1998).

The first discoveries in pancreatic physiology were made in the late 17th century. In 1671, Sylvius de le Boe proposed in his work “Praxeos medicae idea nova”, that digestion was a multistep process including a fermentation through saliva in mouth and stomach, in a second phase involving the pancreas, followed by the passage of chyle into the lymphatic and the venous system, and eventually, into the right side of the heart (Kidd, 1999). In contrast, Brunner proposed some years later that specialized duodenal glands were the major source of digestive juice secretion, and that the pancreas was not a vital organ. In 1682, Peyer concluded that the lymphatic nodules in the walls of the ileum and Brunner’s glands were main adjuncts to digestion, and the pancreas was a minor contributor (Busnardo *et al.*, 1983). This reductionist modification of Silvius’ innovative theories delayed the progress of pancreatic research for years (Pannala *et al.*, 2009). In 1815, Marcet discovered lipase, and in 1876, Kuhne discovered trypsin and its role in the digestion of proteins. In 1843, Eberle showed that pancreatic juice emulsified fat, and one year later, Valentin demonstrated its activity on starch (Kidd, 1999). In 1848, Bernard proposed that gastric digestion was "only a preparation act" and that pancreatic juice emulsified fatty foods. In addition, he revealed the pancreatic contribution to converting starch into sugar, and its solvent action on the "proteides that have not been cleaved in the stomach" (Kidd, 1999). The regulative concept of pancreatic secretion was initially addressed by Pavlov in “The Work of the Digestive Glands” in 1897, suggesting that the vagal nerve was a predominant neurological regulator (Pavlov, 1953). In 1869, Langerhans had published his “Contribution to the Microscopic Anatomy of the Pancreas”, he was the first to describe the structure of the islet tissue, which Laguesse in 1893 named the islands of Langerhans (Busnardo *et al.*, 1983). In 1902, Bayliss and Starling demonstrated that pancreatic secretion was controlled by chemical messengers, which led to the introduction of “hormones” (derived from the Greek “hormonos” meaning ‘I arouse to excitement’) and the putative agent "secretin" (Bayliss, 1902). In 1922, Insulin was discovered and isolated

(Banting *et al.*, 1922). The discovery of the serum amylase test by Elman in 1927 was a great contribution to the differential diagnosis of acute pancreatitis (Busnardo *et al.*, 1983; Elman, 1937). Further developments included the discovery of CCK by Ivy and Oldberg in 1928 (Mutt, 1994) and their understanding that pancreatic secretion was regulated by a complex chemical messenger system (Pannala *et al.*, 2009).

Surgical pioneers

Most of the early pancreatic surgeons resected only portions of the duodenum and pancreas. Allen Oldfather Whipple was the first surgeon to perform a complete resection of the duodenum and head of the pancreas; in 1935 in a two-stage, and in 1940 in a one-stage procedure (Busnardo *et al.*, 1983).

The first pancreatic head resection with transection of the pancreatic duct was performed by Biondi in 1894, resecting a pancreatic fibroadenoma and re-approximating the duodenum and the pancreatic remnant. The postoperative course was complicated by biliary and pancreatic fistula which eventually resolved. In 1898, Codivilla performed the first reported pancreaticoduodenectomy (PD) on a 46 year old male with a locally advanced cancer, removing parts of the pancreas, duodenum, distal stomach and distal bile duct. Continuity was restored using a Roux-en-Y gastrojejunostomy and a cholecystojejunostomy excluding the pancreatic stump. The patient died at 18 days from steatorrhea-induced cachexia (Schnelldorfer *et al.*, 2008). In 1898, Halsted performed the first successful resection for ampullary cancer by resecting portions of the duodenum and pancreas in a 60 year old female with painless jaundice. The operation included a CBD exploration, transduodenal papillectomy and reanastomosis of the pancreatic and bile duct (Are *et al.*, 2011).

In 1905, Garre re-approximated the capsule of a traumatically cleaved pancreatic gland with silk sutures. The duct was not sutured and the result was a pancreatic fistula which resolved after two months. A similar technique was used in the first successful partial PD performed by Erhardt in 1907 (Howard, 2003). In 1909, Kausch applied Kocher's maneuver in a resection of the duodenum en bloc with a portion of the pancreas, establishing continuity by a pancreaticoduodenostomy. The patient recovered initially from a pancreatic fistula, but died nine months later due to cholangitis (Whipple, 1946). In 1912, Hirschel performed a one-stage resection removing parts of the duodenum, ampulla, head of pancreas and the lower part of the CBD. Continuity was established by re-implanting the pancreatic duct into the duodenum, a posterior gastroenterostomy and bridging of the common bile duct to the duodenum by a rubber tube. The patients jaundice was relieved and he lived for one year. The cause of death or fate of the rubber tube was unknown as an autopsy was never performed (Whipple, 1946). In 1922, Tenani performed a successful two-stage resection for ampullary carcinoma in a 43-year-old male by a posterior gastroenterostomy and choledochoduodenostomy to the lower duodenum in a first stage, and excising portions of the duodenum, and pancreatic head in a second stage, establishing continuity by a pancreaticoduodenostomy. The patient recovered after a severe post-operative course and lived for 3 years (Whipple, 1963).

Allen Oldfather Whipple

The first complete duodenectomy and pancreatic head resection was reported in 1935 by Whipple, Parsons and Mullins from Columbia Presbyterian Hospital in New York who had operated three patients for ampullary cancer in a two-stage procedure including a radical resection of the duodenum and head of the pancreas for ampullary cancer. The third patient underwent a total duodenectomy and excision of a large portion of the head of the pancreas. The first patient died shortly after the operation due to consequences of anastomotic breakdown, the others lived for 9 and 24 months and died of cholangitis and liver metastasis, respectively (Whipple, 1946; Whipple *et al.*, 1935). In 1937, Brunschwig performed the first radical anatomic pylorus-preserving PD with complete transection of the pancreatic head to the right of the SMV due to pancreatic carcinoma in two stages (Brunschwig, 1974). With the use of vitamin K to control hemorrhage in the presence of jaundice, and due to difficulties in dealing with adhesions at the time of the second stage operation, it became evident that one-stage operations for radical PD would have definite advantages (Busnardo *et al.*, 1983).

In 1940 at New York's Presbyterian Hospital, Whipple performed a distal gastrectomy on a non-jaundiced patient thought to have a gastric carcinoma. A group of visiting European surgeons watched the operation. At laparotomy, palpation confirmed the presence of a tumor and the stomach was transected in its mid-portion. When the tumor was recognized as pancreatic tumor and having to make decisions on the spot, Whipple proceeded with a one-stage resection of the head of the pancreas, including distal gastrectomy and resection of the entire duodenum. The transected pancreatic duct was ligated. The tumor proved to be a malignant glucagonoma, and the patient survived for 9 years (Howard, 2003). This procedure known to be the "Whipple operation" was reported five years later, and regarding the pancreatico-enteric reconstruction, Whipple recommended his then-current practice of duct re-implantation (Whipple, 1946; Whipple, 1963; Whipple, 1945). Unaware of the Whipple's procedure, Trimble performed a similar resection a few weeks after, adding a distal gastrectomy to avoid blow out of the duodenal stump (Stafford *et al.*, 1954). In the same year, Hunt added a pancreaticojejunostomy (PJ) to avoid leakage of the pancreatic stump (Hunt, 1941).

In 1946, Whipple published his 10-year PD experience. In this report he proposed several modifications to the original procedure and advocated a one-stage procedure; oozing and hemorrhage could be controlled by preoperative vitamin K therapy, and a single procedure with continuous anesthesia and blood transfusion was safer than two major procedures (Whipple, 1946).

Table 3. Some important contributions to the development of pancreatic surgery.

Gastrojejunostomy	C. Roux. De la gastroenterostomie Rev Gynecol Chir Abdom, 1, 1897 (Roux, 1897)
First pancreatic head resection	B. Dal Monte (1899). Rendiconto statistico della sezione chirurgica dell' Ospedale d'Imola, anno 1898. Galeati, 1899 (Dal Monte, 1899)
Partial pancreatic head resection	W.S. Halsted. Contribution to the surgery of the bile passages, especially of the common bile duct. Boston Med Surg J 141, 1899 (Halsted, 1899)
Pancreatic head resection (two-stage)	A.O. Whipple, W.B. Parsons, and C.R. Mullins. Treatment of Carcinoma of the Ampulla of Vater. Ann Surg 102, 1935 (Whipple et al., 1935)
Pancreatic head resection (one-stage)	A.O. Whipple. Pancreaticoduodenectomy for Islet Carcinoma : A Five-Year Follow-Up. Ann Surg 121, 1945 (Whipple, 1945)
Pancreaticogastrostomy	M. Waugh, and O.T. Clagett. Resection of the duodenum and head of the pancreas for carcinoma; an analysis of thirty cases. Surgery 20, 1946 (Waugh & Clagett, 1946)
Pancreaticojejunostomy	R.B. Cattell. A technic for pancreatoduodenal resection. Surg Clin North Am 28, 1948 (Cattell, 1948)
Total pancreatectomy	L.S. Fallis, and D.E. Szilagyi. Observations on some metabolic changes after total pancreatoduodenectomy. Ann Surg 128, 1948 (Fallis & Szilagyi, 1948)
Mesenteric superior vein resection	G.E. Moore, Y. Sako et al. Radical pancreatoduodenectomy with resection and re-anastomosis of the superior mesenteric vein. Surgery 30, 1951 (Moore et al., 1951)
Central liver artery resection	L.H. Appleby. The coeliac axis in the expansion of the operation for gastric carcinoma. Cancer 6, 1953 (Appleby, 1953)
First larger series without mortality	J.M. Howard. Pancreaticoduodenectomy: forty-one consecutive Whipple resections without an operative mortality. Ann Surg 168, 1968 (Howard, 1968)
Pylorus preserving resection	L.W. Traverso, and W.P. Longmire, Jr. Preservation of the pylorus in pancreaticoduodenectomy a follow-up evaluation. Ann Surg 192, 1980. (Traverso & Longmire, 1980)
Extended resections	J.G. Fortner. Surgical principles for pancreatic cancer: regional total and subtotal pancreatectomy. Cancer 47, 1981 (Fortner, 1981)
Mortality 2%	D.W. Crist, J.V. Sitzmann, and J.L. Cameron. Improved hospital morbidity, mortality, and survival after the Whipple procedure. Ann Surg 206,1987 (Crist et al., 1987)
Centralization	J.D. Birkmeyer, S.R. Finlayson, A.N. Tosteson, S.M. Sharp, A.L. Warshaw, and E.S. Fisher. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. Surgery 125, 1999 (Birkmeyer et al., 1999)

Modern pancreaticoduodenectomy

Although modified multiple times, the principles of Whipple's operation have never changed. The gastric resection, originally the result of an error in diagnosis, remained as a part of the procedure until the pylorus preserving PD (PPPD) was described (Traverso & Longmire, 1980). In 1948, Cattell proposed an end-to-side PJ in order to reduce the incidence of POPF, which later became an established reconstruction technique (Cattell, 1948).

Centralization of pancreatic surgery

In 1968, a series of 41 consecutive Whipple resections was reported, performed by one surgeon during a 13-year period without perioperative mortality and a fistula rate of 10% (Howard, 1968). In the publication, the importance of a dedicated clinical pancreatic team for successful patient management was emphasized. Despite these encouraging results, the Whipple's procedure gradually fell into disrepute due to excessive postoperative mortality and morbidity, procedure-dependent technical difficulties, and dismal long-term survival (Busnardo *et al.*, 1983). The fact that comparisons of radical resections and bypass procedures of the obstructed bile duct did not reveal differences in long-term survival led some surgeons to conclude that resection for pancreatic cancers should be abandoned (Crile, 1970). However, the postoperative mortality after total pancreatectomy (TP) was reported even higher than in Whipple's procedure in several series, although the pancreaticojejunal anastomosis was avoided (Tarazi *et al.*, 1986).

In 1981, a series of 146 patients from Mayo clinic reported for the first time a postoperative mortality below 5%, advocating for the continued use of the Whipple procedure (van Heerden *et al.*, 1981). The publication was the prelude to a decade of centralization and systematic constitution of high-volume pancreatic centers resulting in larger series with similar mortality rates (Trede *et al.*, 1990; Cameron *et al.*, 1993). The reduction of mortality rates was regarded as a result of the concentration of operative experience and the improvement of supportive perioperative care (Howard, 2007). Regarding the remaining high morbidity rates, DGE accounted for half of the complications whereas the incidence of POPF varied from 0% to 30% (Ramacciato *et al.*, 2011a). Complications following PD had also an impact on long-term outcome (Reddy *et al.*, 2009). Some authors concluded that mortality rates below 5% and morbidity rates below 40% should constitute preconditions for experienced centers to perform PD (Orr, 2010).

Extended resections

Numerous efforts have been made to improve survival rates of resected PDAC by extending the PD resection. Although the first total pancreatectomy (Rockey, 1943), and the report of a successful total pancreatectomy for PDAC (Fallis & Szilagyi, 1948) was received with enthusiasm, the subsequent evaluation revealed disappointing short-term and

long-term results (Dresler *et al.*, 1991). In 1951, Moore performed the first SMV resection, restoring continuity by re-anastomosis (Moore *et al.*, 1951). In 1977, Fortner introduced the surgical concept of “regional pancreatectomy” in patients with advanced diseases (Fortner, 1981), which included total or subtotal pancreatectomy and resection of adjacent arteries and veins. The operative mortality rate was high, and the procedure was not generally adopted. The report that up to one third of PD patients had metastases in lymph nodes not usually removed with standard operation (Cubilla *et al.*, 1978) resulted in an increased interest in the role of lymphadenectomy. In a retrospective study, an improved 5-year survival rate after extended lymphadenectomy was reported (Ishikawa *et al.*, 1988). A subsequent randomized trial could not confirm these results, although patients with lymph node metastases had improved survival in the extended resection group (Pedrazzoli *et al.*, 1998). The study emphasized the need for defining the modern standard Whipple resection, including the extent of lymphadenectomy. A classification was proposed by a European Consensus Conference in 1998 (Pedrazzoli *et al.*, 1999a).

An extensive review of 340 studies revealed that only one out of 30 patients who underwent resection had a survival of five years or longer. A cumulative cost per ‘‘successful’’ resection was calculated (~$4.5M), and it was concluded that ‘‘pancreatic resections are wasteful of resources’’, emphasizing the need for procedure standardization and reporting (Gudjonsson, 1995). Also other authors considered the definition of standard techniques as crucial for outcome comparisons between institutions and for prospective RCTs comparing different procedure modifications (Jones *et al.*, 1999).

Indications

Today, PD represents the standard of surgical care for patients with tumors originating from the pancreatic head, neck, uncinate process, duodenum or distal bile duct (Pedrazzoli *et al.*, 1999b). Apart from malignancy, the procedure is commonly performed for a wide array of indications ranging from benign conditions such as chronic pancreatitis, to pre-malignant lesions like intraductal papillary mucinous neoplasms, IPMNs (Balcom *et al.*, 2001). PD is performed with the goal of achieving a complete tumor clearance with tumor-negative resection margins (R0). Referral to high-volume centers and surgeons is encouraged (Birkmeyer *et al.*, 2006; de Wilde *et al.*, 2012). Both the classic Whipple and PPPD are accepted techniques with similar outcomes (Diener *et al.*, 2007; Iqbal *et al.*, 2009). Extended lymphadenectomy has so far not shown improved survival (Michalski *et al.*, 2007). Portal vein resection has increased the number of patients amenable to resection, with equivalent survival rates compared with those of standard resections, and portal vein involvement is no longer considered a contraindication (Christians, 2009; Evans *et al.*, 2010). Resection and reconstruction of involved arteries have been too rarely performed to give evidence about possible surgical benefits in those selected patients (Matsuoka *et al.*, 2012; Mollberg *et al.*, 2011). The pancreatico-enteric reconstruction has been the target for numerous RCTs and observational cohort studies (OCS); standards remain PJ and the pancreaticogastrostomy (PG).

Risk adjustment and outcome measurement

Through its history, PD has been associated with a high morbidity. POPF was noted and documented in the first patients undergoing pancreatic surgery at the end of the 19th century (Whipple, 1946). Since then, prevention of POPF has been one of the main objectives in the research field of pancreatic surgery. Procedure centralization, one of the first successful measures to reduce morbidity, turned uncommon complex procedures into standard procedures. The idea of accumulating procedure volume in order to catalyze the development of knowledge and experience for uncommon procedures was not new, and its implementation had been documented early to result in improved outcomes (Howard, 1968; van Heerden *et al.*, 1981; Donabedian, 1966; Mizumoto & Kawarada, 1980).

Volume/outcome

During the past decades, numerous studies have reported a strong volume/outcome relationship for pancreatic surgery, particularly for PD (Gooiker *et al.*, 2011). In prevalence studies high-volume centers had lower in-hospital mortality rates (Birkmeyer *et al.*, 1999; Gooiker *et al.*, 2011; Teh *et al.*, 2009; Eppsteiner *et al.*, 2009; Birkmeyer *et al.*, 2007), shorter hospital stay (Topal *et al.*, 2007a) and improved long-term survival rates (Gooiker *et al.*, 2011; Birkmeyer *et al.*, 2007) compared to general surgical units. Longitudinal studies have showed that centralization of pancreatic surgery resulted not only in increased resection rates (Lemmens *et al.*, 2011) and a reduction of postoperative mortality (de Wilde *et al.*, 2012; McPhee *et al.*, 2007; Gordon *et al.*, 1998), but also in improved long-term survival (Lemmens *et al.*, 2011). In contrast to the documented reduction of mortality, PD-associated morbidity remains 20-50% (Ramacciato *et al.*, 2011a), and the relationship between procedure volume and morbidity is not equally well documented (Dimick *et al.*, 2003). The lower mortality rates of high-volume centers could not be attributed to lower morbidity rates (Dimick *et al.*, 2003; Allareddy *et al.*, 2010). In fact, high-volume centers had morbidity rates similar to those of general units (Ghaferi *et al.*, 2009), suggesting that more effective complication management or lower failure-to-rescue rates could explain the difference (Silber *et al.*, 1997; Ghaferi *et al.*, 2011). In the US, the increased focus on variations in surgical outcomes (Birkmeyer & Dimick, 2004; Birkmeyer & Birkmeyer, 2006) has resulted in use of strategy models like selective referral, process compliance or outcome measurement in order to improve the quality of care (Birkmeyer & Dimick, 2009).

Outcome measurement

Outcome measurement has always been important in pancreatic surgery, not in the least to demonstrate the benefits of centralization (Birkmeyer *et al.*, 1999), but only recently, more systematic standardizations of outcome parameters allowed meaningful comparisons between different surgical institutions (Dindo *et al.*, 2004). Mortality is probably the oldest parameter used to evaluate surgical outcomes, and the term “in-hospital mortality” has been used for over 60 years (Ramberg, 1947). Subsequently, 30-days mortality had been

established as an alternative to in-hospital mortality. To capture the complete figure, several studies, mostly from the field of cardiac and thoracic surgery, have merged both parameters into "30 days or in-hospital mortality" (Shiraishi *et al.*, 2006; Daebritz *et al.*, 2000; Fremes *et al.*, 1995; Handa *et al.*, 2001). In pancreatic surgery, the great need for definitions in postoperative morbidity is illustrated by the numerous citations of available consensus definitions.

Table 4. Examples of widely used classifications.

Surgical complications	D. Dindo et al. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery 240. (Dindo et al., 2004)
Postoperative pancreatic fistula	C. Bassi et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 138 (Bassi et al., 2005a)
Delayed Gastric Emptying	M.N. Wente et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 142 (Wente et al., 2007a)
Postpancreatectomy hemorrhage	M.N. Wente et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 142 (Wente et al., 2007b)
SIRS	R.C. Bone et al. Definitions for sepsis and organ failure, guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101 (Bone et al., 1992)

One of the most widely accepted definitions of postoperative complications in surgery is the Clavién-Dindo Classification of surgical complications (CDC), which elegantly defines the severity of procedure-associated complications, i.e. procedure outcome, by the efforts made in order to control the complications (Dindo *et al.*, 2004). The classification has during recent years been widely used in surgical reports (Clavien *et al.*, 2009).

Table 5. Clavién-Dindo Classification of surgical complications (Dindo *et al.*, 2004).

Grade I		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
Grade II		Requiring pharmacological treatment, blood transfusions or total parenteral nutrition
Grade III		Requiring surgical, endoscopic or radiological intervention
	IIIa	Not under general anesthesia
	IIIb	Under general anesthesia
Grade IV		Life-threatening complication requiring IC/ICU management
	IVa	Single organ dysfunction
	IVb	Multiorgan dysfunction
Grade V		Death of a patient

Postoperative pancreatic fistula

The dismal survival rates of resected PDAC are above all the consequence of unsolved disease-related and tumor-biological issues. They illustrate not only the surgical challenge of achieving R0 resections, but also the failure to develop methods of early cancer detection and effective adjuvant treatment. However, the poor short-term outcomes and high postoperative morbidity rates are mainly associated with insufficiencies in the surgical procedure.

A postoperative pancreatic fistula is an abnormal communication from the pancreas to an epithelialized surface (Bassi *et al.*, 2005a). POPF, typically caused by leakage from the pancreatico-enteric anastomosis (Butturini *et al.*, 2006), constitutes the predominant cause of high PD-associated morbidity together with DGE (Ramacciato *et al.*, 2011a; Tewari *et al.*, 2010a). DGE is a common complication more accompanying rather than modifying the postoperative course. It may delay diet reinstitution and hospital discharge, and lead to persisting nutritional problems and impaired quality of life (Tani *et al.*, 2006). In contrast, POPF is a dynamic complication that interferes with the postoperative course. It has the potential to induce severe secondary morbidity with sepsis and organ failure or lethal hemorrhage, high frequency of re-operations and increased associated mortality (Denbo *et al.*, 2012; Fuks *et al.*, 2009; Pessaux *et al.*, 2011a; Yekebas *et al.*, 2007; Shrikhande *et al.*, 2005). Even when controlled and successfully treated, POPF results in higher rates of readmission (Ahmad *et al.*, 2012). Moreover, POPF has major social and economic impacts (Gudjonsson, 1995; Topal *et al.*, 2007b; Enestvedt *et al.*, 2012).

Table 6. Stages of clinically relevant POPF and associated mortality. Accumulating mortality with increasing severity and deterioration of patients with uncontrolled POPF (Ansorge, 2010).

	Mortality
Pancreaticoduodenectomy	3.5%
↓ 24%	
Postoperative pancreatic fistula (POPF A/B/C)	13%
↓ 79%	
Requiring additional drainage (POPF B/C)	17%
↓ 41%	
Requiring re-operation (POPF C)	33%
↓ 60%	
Requiring ICU and additional intervention	40%

The pancreatico-enteric anastomosis has been labeled the "Achilles heel" of the procedure (Swope *et al.*, 1994). Reported POPF incidences range from 0 to 33% (Tewari *et al.*, 2010b; Ramacciato *et al.*, 2011b), reflecting different POPF definitions as much as any real difference (Ramacciato *et al.*, 2011b; Bassi *et al.*, 2004). Even studies using current standard definitions have reported POPF rates of between 15 and 26% (Reid-Lombardo *et al.*, 2007b). Different terms have been used to identify POPF; fistula, leak, leakage, anastomotic failure, or anastomotic insufficiency. In a review of available literature from 1991 to 2000, 26 different definitions of pancreatic leakage were identified (Bassi *et al.*, 2004). Applying the different definitions to a cohort of 242 patients, it was demonstrated that the incidence of POPF varied from 10 to 29% depending on the

definition. As shown in table 1, the majority of reports investigating causes and risk factors of POPF use drain discharge (associated with amylase content), clinical signs, radiological parameters, and intraoperative findings as criteria to define POPF (Bassi *et al.*, 2004).

Table 7. Some established definitions of POPF in recent literature.

Drain output > 50 mL/day of amylase-rich fluid (> three times the serum amylase activity) on or after POD 7	(Parviainen *et al.*, 1996)
Drain output > 50 mL/day of amylase-rich fluid (> three times the serum amylase activity) on or after POD 10 or radiological demonstration of pancreatic anastomosis disruption	(Yeo *et al.*, 1997b)
Amylase level >1000 U/L in the drainage fluid collected from the peripancreatic drains and/or anastomotic disruption demonstrated radiographically.	(Sato *et al.*, 1998a)
Drain output > 30 mL/day of amylase-rich fluid (> 5000 U) for more than 10 days	(Buchler *et al.*, 2000)
Drain output >f 30 mL/day of amylase-rich fluid or at least 7 days beyond POD 4; confirmed by fistulography	(Bassi *et al.*, 2001)
Drain output > 30 mL/day of amylase-rich fluid (> five times the serum amylase activity) on or after POD 5	(Sarr, 2003)
Drain output of any volume of amylase-rich fluid (> three times upper serum amylase) on or after POD 3	(Bassi *et al.*, 2005a)

ISGPF definition and "clinically relevant fistula"

The POPF definition that was provided by the International Study Group of Pancreatic Fistula (ISGPF) in 2005 is today widely accepted. The ISGPF defines POPF as a healing or sealing failure of the pancreatico-enteric anastomosis or a parenchymal leak, which is characterized by an amylase concentration greater than three times the upper normal serum value in drain fluids on or after postoperative day three (Bassi *et al.*, 2005a). Cases matching these criteria are classified into subclinical (grade A), clinical (grade B) or severe fistulas (grade C). The ISGPF fistula definition is not a tool for clinical decision making (Gebauer *et al.*, 2012) but a retrospective reporting instrument facilitating inter-institutional comparison and standardization of outcomes in clinical translational research. The concept of clinically significant pancreatic leaks has been introduced in 1997 (Lowy *et al.*, 1997); transferred to the ISGPF definition, multiple studies have merged the POPF-B and -C grades into a group of "clinically-relevant" fistulas (Reid-Lombardo *et al.*, 2007b; Ansorge *et al.*, 2012a; Facy *et al.*, 2012; Moskovic *et al.*,

Table 8. Definition of Postoperative Pancreatic Fistula according to ISGPF.

Clinical Criteria	No fistula	Grade A	Grade B	Grade C
Drain amylase	< 3 x	> 3 x normal S-amylase		
Persistent drainage	no		yes	
Signs of infection	no		yes	
Readmission	no		yes / no	
Clinical condition	well		often well	bad
Specific treatment	no		yes / no	yes
US/CT	no		yes / no	yes
Sepsis	no			yes
Reoperation	no			yes
Death	no			yes

2010; Noji *et al.*, 2012; Malleo *et al.*, 2012). Aside from few experimental studies on the pathological mechanisms in the manifestation of POPF, the two main objectives within POPF research have been to identify risk factors for POPF (often in form of OCS) or to improve short-term outcome in preventive approaches (often in the form of randomized RCTs).

POPF risk factors

Multiple risk factors for POPF following PD have been reported. In this thesis unalterable factors that have been observed to have an impact on POPF have been considered as risk factors, whereas procedure alterations with the intention to reduce POPF rates have been considered as POPF-preventive approaches (Machado, 2012). Factors with a reported impact on POPF can be divided into three categories: patient-related factors, disease-related (pancreatic) factors and treatment-related (surgeon-related or operative) factors (Lin *et al.*, 2004).

Patient related risk factors

Age and gender

The reviewed literature is inconclusive regarding age or gender as risk factors for POPF. The majority of studies report statistically significant higher morbidity and mortality rates following PD in older patients when compared to younger patients, others show no differences (Ramacciato *et al.*, 2011a). A retrospective review of 1891 PDs found that male gender correlated with POPF rate on univariate but not multivariate analysis (Lin *et al.*, 2004), while other reports did not confirm these findings (Cheng *et al.*, 2007; DeOliveira *et al.*, 2006).

Obesity

Obesity has been evaluated as a risk factor for morbidity following abdominal surgery (Mullen *et al.*, 2008), and the impact of the body mass index (BMI) on PD-associated POPF rates has been investigated. A retrospective study of 92 standardized PDs showed a significant difference in POPF rates between obese (37%) and non-obese patients (15%), but no differences in other complications (Noun *et al.*, 2008). The results of a series of 356 PDs did not reveal significant correlations between BMI and POPF; however, the degree of visceral fat visualized on preoperative cross-sectional computer tomography imaging was significantly associated with higher rates of POPF and other complications (House *et al.*, 2008). A recent retrospective analysis of 240 PDs showed that obese patients undergoing PD had substantially increased blood loss and longer operative duration, whereas length of hospital stay or the rate of serious complications was not increased, the authors advocated not to preclude obese individuals from undergoing pancreatic surgery (Williams *et al.*, 2009).

Cardiovascular disease

Cardiovascular disease was correlated with increased POPF incidence in a study on 633 consecutive PDs (DeOliveira *et al.*, 2006), whereas coronary artery disease was found to be a significant risk factor for POPF in a prospective series of 131 patients (Lermite *et al.*, 2007). This was indirectly confirmed in a review of 1891 PDs demonstrating that patients with a history of coronary artery disease had a significantly increased likelihood of developing POPF (Lin *et al.*, 2004). The authors explained the association by a decreased

visceral perfusion that resulted in anastomotic ischemia; alternatively that medications such as aspirin, β-blockers, etc. might compromise the anastomotic healing processes (Lin *et al.*, 2004). In contrast, arterial hypertension was found to be a protective factor for POPF (POPF incidence 14% in patients with high blood pressure and 44% in patients with normal blood pressure); according to the authors, arterial hypertension might help anastomotic healing by allowing improved visceral perfusion (Lermite *et al.*, 2007).

Diabetes Mellitus

In the reviewed literature, studies have reported diabetes as both a risk and protective factor. In two prospective studies of 295 and 120 PDs, respectively, diabetes mellitus increased the probability of developing abdominal complications by a factor of seven (Cheng *et al.*, 2007) and was associated with an increased POPF rate (Satoi *et al.*, 2006); however, in a large retrospective study, preoperative diabetes mellitus was associated with a significantly lower POPF incidence (Lin *et al.*, 2004).

Disease related risk factors

Histopathology

The association between histological diagnosis and POPF development has been investigated by several studies. A retrospective study of 581 patients reported a POPF incidence of 27% for ampullary carcinoma compared to 5% for PDAC (Veillette *et al.*, 2008). The findings were confirmed in a series of 459 patients, reporting a POPF incidence of 13% for ampullary carcinoma compared to 5% for PDAC (de Castro *et al.*, 2005a) and re-confirmed one year later (Satoi *et al.*, 2006). In a sub-analysis of 303 patients of their large retrospective review, Lin et al. reported that CBD cancer was a significant predictive factor for POPF development (Lin *et al.*, 2004). In a series of 233 patients ampullary, duodenal, cystic, or islet cell pathologies were suggested as independent risk factors for clinically relevant POPF (Pratt *et al.*, 2008a). Other studies have confirmed an association between the histological diagnosis and POPF development (Kazanjian *et al.*, 2005; Liang *et al.*, 2007; Yeo *et al.*, 1995).

Pancreatic characteristics

The most validated risk factors for POPF, soft parenchyma consistency (PC) or texture, and a non-dilated pancreatic duct are characteristics of a normal, unaffected pancreatic gland, as described in study II. In the current thesis, the terms “pancreatic consistency” and “pancreatic texture” are used synonymously in accordance with the reviewed literature. Soft PC and non-dilated pancreatic duct have also been associated with an increased production of pancreatic juice (Hamanaka *et al.*, 1996), postoperatively elevated levels of serum C-reactive protein (Murakami *et al.*, 2008) and high concentrations of drain amylase (Shyr *et al.*, 2003; Okabayashi *et al.*, 2007). The importance of soft PC as risk predictor has been known for almost 30 years; a soft PC was the main reason to favor a total pancreatectomy in order to avoid a difficult PJ (Brooks, 1976). That soft PC could constitute a risk factor for POPF was mentioned in a discussion by Longmire in 1984

(Longmire, 1984). Causative physiological mechanisms and the biological plausibility of soft PC being a risk factor for POPF were systematically investigated and discussed by Yeo (Yeo *et al.*, 1995; Yeo *et al.*, 2000). A ‘‘soft’’ or ‘‘normal’’ PC indicates a strong risk for the development of POPF, whereas a ‘‘hard’’ pancreas has been considered as a protective factor. A soft friable pancreas, more frequently seen in periampullary, endocrine, and cystic lesions, is characterized by the absence of fibrosis and the presence of edema and inflammatory cell infiltration into the pancreatic parenchyma. Technically, it is associated with difficulties in performing the pancreatico-enteric anastomosis (Brooks, 1976), whereas a hard fibrotic PC facilitates the construction of a good anastomosis (Yang *et al.*, 2005). A fibrotic pancreatic remnant is thought to have reduced exocrine function, making it less likely to induce leakage of pancreatic juice (Ho *et al.*, 2005). A soft pancreas was found to be associated with a higher incidence of POPF in both retrospective (Lin *et al.*, 2004; DeOliveira *et al.*, 2006; Liang *et al.*, 2007; Okabayashi *et al.*, 2007; Lee *et al.*, 2007) and prospective studies (Ansorge *et al.*, 2012a; Kamoda *et al.*, 2008). Also the diameter of the pancreatic duct has been recognized to have a significant impact on the risk of POPF development by several reports, and small pancreatic duct diameter has been considered to complicate the construction of a safe pancreatico-enteric anastomosis (Crippa *et al.*, 2007). In several retrospective series, pancreatic duct sizes less than 3 mm (Poon *et al.*, 2007; Pratt *et al.*, 2008b; Yang *et al.*, 2011), less than 2 mm (de Castro *et al.*, 2005a) or non-visible ducts (Choe *et al.*, 2008) were considered to be risk factors for developing clinically relevant POPF.

Table 9. Causes and consequences of different types of pancreatic consistency.

	Soft consistency	Hard consistency
Tumor pathology	Duct non-obstructive	Duct obstructive
Pancreatic parenchyma	Normal	Fibrosis, desmoplasia
Exocrine function	Normal	Reduced / terminated
Circulation / Perfusion	Normal	Reduced
Suturing conditions	Difficult	Easy
Acinar cells	Normal	Decreased

A few experimental studies in the field (Tomaszewska *et al.*, 2000; Nevalainen & Aho, 1992; Lamsa *et al.*, 2008; Lamsa *et al.*, 2009; Lamsa *et al.*, 2006) provide valuable information on the causative mechanisms of POPF development. In an animal model it could be demonstrated that experimental transection with ultrasonic scissors or electrocautery induced more pancreatic injury than scalpel transection (Lamsa *et al.*, 2006). The acinar cell damage and inflammation induced by the resection spread into the entire gland with intensity depending on the extent of injury at the site of transection (Lamsa *et al.*, 2009). A high frequency of acinar cells in the cut edge of the pancreas (CEP) increased the risk for immediate postoperative complications following PD, whereas extensive fibrosis at the CEP proved to be a protective factor. The authors questioned the reliability of digital evaluation of pancreatic consistency and suggested that the risk for postoperative complications should be determined by histological analysis, proposing a CEP frozen section counting the number of acinar cells as stratification tool for future randomized RCTs (Laaninen *et al.*, 2012).

Treatment-related risk factors

Neoadjuvant treatment

One of the first studies on neoadjuvant radiation suggested that the treatment might prevent POPF after PD by demonstrating a POPF incidence of 5% in the radiation group and 19% in the conventional group (Ishikawa *et al.*, 1991). A more recent retrospective study on 24 patients undergoing neoadjuvant chemotherapy revealed no in-hospital or 30-day mortality, low surgical morbidity, and POPF occurring in one patient (Heinrich *et al.*, 2008). A study comparing 46 patients undergoing neoadjuvant chemoradiation to 64 patients with conventional treatment showed similar POPF rates for both groups (Lowy *et al.*, 1997). A study on 79 patients showed that neoadjuvant radiochemotherapy was associated with a marked reduction in the incidence and severity of POPF (10% vs. 43% in the control group) and associated morbidity (Cheng *et al.*, 2006).

Preoperative biliary drainage (PBD)

The role of PBD as a risk factor for postoperative morbidity and POPF following PD has been discussed extensively. Unrelieved tumor-induced jaundice has been regarded as an intolerable symptom and a risk factor for postoperative complications. PBD was introduced in order to improve the patients' preoperative quality of life and postoperative outcome (van der Gaag *et al.*, 2009). However, PBD has been demonstrated to have its own risk of post-interventional morbidity, and the possible contamination of the biliary system by drain-introduced bacteria might contribute to postoperative infectious complications (van der Gaag *et al.*, 2009). A randomized controlled multicenter trial advised against the routine performance of PBD (Velanovich *et al.*, 2009). Retrospective studies demonstrated higher postoperative morbidity rates in patients undergoing PBD (Povoski *et al.*, 1999). Two meta-analyses were inconclusive regarding the impact of PBD on the outcome of pancreatic surgery (van der Gaag *et al.*, 2007; Saleh *et al.*, 2002) and the POPF rate did not seem to be affected (Velanovich *et al.*, 2009; van der Gaag *et al.*, 2007). However, a recent randomized trial demonstrated significant increased complication rates after PBD (74%) compared to early surgery without PBD (39%), suggesting that routine PBD should be avoided (van der Gaag *et al.*, 2010).

Pylorus preserving pancreaticoduodenectomy

Since the introduction of PPPD (Traverso & Longmire, 1980), numerous studies have compared this procedure to classic PD, including multiple RCTs and meta-analyses (Ramacciato *et al.*, 2011a).Three systematic review and meta-analyses were published in the last two years, none of them could demonstrate the superiority of one procedure over the other in decreasing POPF rates (Diener *et al.*, 2007; Iqbal *et al.*, 2008; Karanicolas *et al.*, 2007); both techniques are accepted and have similar POPF rates.

Extended Resections

Extended lymphadenectomy and retroperitoneal soft tissue clearance in association with PD were proposed as an option to improve long-term outcome and survival in patients with periampullary and pancreatic cancer (Farnell *et al.*, 2005). The results of a multicenter RCT

of 81 patients did not reveal any differences in the incidence of POPF or other morbidity or mortality between standard and radical procedures (Pedrazzoli *et al.*, 1998). A subsequent trial demonstrated significantly higher morbidity (43%) and a higher rate of DGE and POPF in patients undergoing extended resections compared to standard resections (29%); the survival being similar between the two groups (Yeo *et al.*, 2002; Yeo *et al.*, 1999). Two meta-analyses demonstrated higher morbidity rates following extended PD but no survival benefits (Iqbal *et al.*, 2009; Michalski *et al.*, 2007).

Blood loss

Several studies have investigated whether increased intraoperative blood loss could be a risk factor for POPF. A study on 233 PDs reported intraoperative hemorrhage greater than 1000 mL to be a risk factor for clinically relevant POPF with a relative risk by a factor of nine compared to patients with limited blood loss (Pratt *et al.*, 2008a). A study comparing a POPF group with a non-POPF group demonstrated that the POPF group had a significantly greater blood loss (1584 ± 862 mL) than the non-POPF group (794 ± 387 mL), proposing that blood loss exceeding 1500 mL implied an increased POPF risk (Yeh *et al.*, 1997). A series of 295 PDs found a significant association between blood loss and intra-abdominal complications (Cheng *et al.*, 2007). In a retrospective review of 1891 patients, increased blood loss and transfusions were associated with a higher POPF incidence (Lin *et al.*, 2004). Extended operative duration was found to be associated with POPF in three studies (Lin *et al.*, 2004; de Castro *et al.*, 2005a; Yeo *et al.*, 1995). However, lack of standardized measurement and possible strong interactions with other relevant factors including more advanced stages of disease, patient obesity, jaundice-induced coagulopathy and concurrent pancreatitis could not be excluded (Yeh *et al.*, 1997; Shrikhande & D'Souza, 2008; Lai *et al.*, 2009).

Intra-abdominal drainage

Surgically placed prophylactic drains have been associated with increased rates of abdominal and wound infections, increased abdominal pain, decreased pulmonary function, and prolonged hospital stay in studies on other gastrointestinal procedures (Ramacciato *et al.*, 2011a). Regarding PD, a retrospective study on 89 PDs comparing 38 patients without drains to 51 patients with routinely placed intraabdominal drains demonstrated similar rates of POPF, abscesses, reoperations and CT-guided interventions following PD, which led the authors to assume that routine use of prophylactic drains might not be necessary (Heslin *et al.*, 1998). A subsequent RCT of 179 patients could not demonstrate differences in mortality, morbidity, interventional radiologic drainage, or surgical exploration between the drainage and the non-drainage group, asserting that surgical drains following PD should not be considered mandatory (Conlon *et al.*, 2001). A more recent prospective study on 104 patients comparing early drain removal (POD 4) to delayed removal (POD 8) demonstrated a lower POPF-incidence in the early-removal group; however, the early removal group was enrolled consecutively after the delayed removal group and the results could have been influenced by increased surgical experience (Kawai *et al.*, 2006). A randomized trial comparing early (POD 3) to standard drain removal (POD 5 or later) with deviant outcome criteria demonstrated that drains could be safely removed in patients at low POPF risk and

that prolonged postoperative drainage was associated with a higher rate of postoperative complications, increased hospital stay and costs (Bassi *et al.*, 2010). However, several studies have emphasized the importance of drainage fluid analyses for the prediction of POPF (Facy *et al.*, 2012; Molinari *et al.*, 2007; Nissen *et al.*, 2012; Shinchi *et al.*, 2006; Sutcliffe *et al.*, 2012; Winter *et al.*, 2007).

Postoperative nutrition

The loss of gastric pacemaker activity following PD has been explained by the removal of the interstitial Cajal pacemaker cells with the duodenum and distal stomach, which, together with the physiological consequences of biliary and pancreatic diversion, resulted in a postoperative gastric stasis and DGE (Takaki, 2003). A recent systematic review of the current literature showed that routine total parenteral nutrition (TPN) was not beneficial and should be avoided (Goonetilleke & Siriwardena, 2006). It was demonstrated that early postoperative enteral nutrition was associated with a lower incidence and severity of infectious complications compared to TPN after pancreatic surgery (Di Carlo *et al.*, 1999). The role of TPN in the development of POPF is barely studied; a retrospective analysis of 50 PDs found that early postoperative administration of enteral nutrition was associated with a lower incidence of POPF (Okabayashi *et al.*, 2007).

POPF-preventive approaches

Various reconstruction techniques have been evaluated with the aim to reduce anastomotic leakage and the incidence of POPF following PD. These include different jejunal sites (end vs side), and different anastomosis types (duct-to-mucosa vs invagination) for the pancreaticojejunal reconstruction, as well as different organs for the pancreatico-enteric reconstruction (PG vs PJ). Moreover, the use of fibrin glue, pancreatic duct stents and other adjunct procedures have been investigated. RCTs on the technical modifications are rare (Yang *et al.*, 2011), and as a result, there is no consensus about which operative technique is less prone to POPF development (Ramacciato *et al.*, 2011a). A recent systematic review did not reveal one single pancreatic reconstruction technique to be applicable to all kinds of pancreatic remnants (Yang *et al.*, 2011).

Pancreatico-enteric reconstruction techniques

Pancreaticojejunostomy

PJ is the oldest and most commonly used technique of pancreatico-enteric reconstruction following PD. The jejunum is surgically easy to manage due to a good blood supply and a usually mobile mesentery. The traditional duct-to-mucosa PJ technique was first described by Cattell (Cattell, 1948) and later revised (Blumgart, 1996). The method re-establishes the flow of pancreatic juice in a near-physiological manner by uniting the remnant pancreas with a jejunal segment. The rationale behind the duct-to-mucosa technique was to obtain a direct communication between the pancreatic duct and jejunal mucosa in order to protect the open CEP from the effect of proteolytic enzymes, and, thus to provide optimal healing conditions and prevent POPF (Shrikhande & D'Souza, 2008; Lai *et al.*, 2009; Callery *et al.*, 2009). The anastomosis is considered as technically difficult to perform and was originally recommended for glands with dilated pancreatic duct; however, in recent years the technique has been preferred regardless of the duct diameter (Shrikhande & D'Souza, 2008; Lai *et al.*, 2009; Stojadinovic *et al.*, 2003).

The invaginating end-to-end PJ is an established and well-proven alternative to Cattel's duct-to-mucosa technique that has been used for over 40 years (Aston & Longmire, 1974). In the early 70’s, there were four established alternatives to treat the remnant pancreas after pancreatic head resection; a pancreaticojejunal duct-to-mucosa anastomosis, an inversion of the transected end of the pancreas into the jejunal lumen, a ligation of the pancreatic duct with oversewing of the transected pancreas, or a TP (Aston & Longmire, 1974). During the past 30 years, the traditional PJ has been consistently reported to have an average POPF rate of 10% and ranging between 2 and 19% (Strasberg *et al.*, 1997). Multiple variations of the PJ technique have been described; end-to-end PJ’s with invagination of the mobilized part of the remnant pancreas into the jejunum, end-to-side PJ’s with or without duct-to-mucosa sutures, in antecolic or retrocolic jejunal loops, and with or without separation from the hepato-enteric anastomosis. One of the most recent variants is the binding PJ, which was originally reported to significantly decrease postoperative complications and POPF

rates when compared with the conventional PJ (Peng *et al.*, 2007). The authors achieved excellent results with this anastomosis, but a subsequent validation of the technique was difficult (Maggiori *et al.*, 2010; Buc *et al.*, 2010; Kennedy & Yeo, 2011). According to a comprehensive review, the duct-to-mucosa anastomosis was regarded as a safer technique than invagination anastomosis (Poon *et al.*, 2002). With small ducts and soft textures the POPF rate was lower in duct-to-mucosa PJ's than in invaginated PJ's (Suzuki *et al.*, 2002). However, a prospective RCT could not demonstrate differences in morbidity or POPF rate between duct-to-mucosa and single-layer end-to-side anastomosis (Bassi *et al.*, 2003). In a recent texture-and-duct-stratified RCT the lateral invagination technique had a considerably lower POPF rate than the duct-to-mucosa anastomosis (Berger *et al.*, 2009). The conclusion was that additional studies were needed to define the optimal technique of pancreatic reconstruction following PD.

Isolated Roux loop pancreaticojejunostomy

Separation of the pancreaticojejunal and hepaticojejunal anastomosis by an isolated Roux loop reconstruction was advocated to avoid a bile-induced activation of pancreatic enzymes and thereby reduce anastomotic erosion (Kingsnorth, 1994; Khan *et al.*, 2002; Sutton *et al.*, 2004; Kaman *et al.*, 2008; Perwaiz *et al.*, 2009; Ballas *et al.*, 2010). Potential disadvantages were increased operating time and the need for an additional anastomosis. Several cohort studies had reported low fistula rates; however, recent studies could not reveal advantages over the traditional use of a single jejunal loop (Kaman *et al.*, 2008; Perwaiz *et al.*, 2009; Ballas *et al.*, 2010).

Pancreaticogastrostomy

Since the technique was introduced in clinical practice (Waugh & Clagett, 1946), PG has been extensively investigated as a possible means of reducing POPF rates (Yeo *et al.*, 1995; Sauvanet *et al.*, 1992; Takano *et al.*, 2000; O'Neil *et al.*, 2001; Aranha *et al.*, 2003; Bassi *et al.*, 2005b; Duffas *et al.*, 2005; McKay *et al.*, 2006; Wente *et al.*, 2007c; Bock *et al.*, 2012). The inactivation of pancreatic enzymes by gastric acid and the absence of enterokinase in the gastric environment were considered as potential mechanisms that might contribute to preventing autodigestion of the pancreatico-gastric anastomosis. The thickness and rich blood supply of the stomach wall provided favorable conditions for suturing and anastomotic healing (Machado, 2012). However, three RCTs (Yeo *et al.*, 1995; Bassi *et al.*, 2005b; Duffas *et al.*, 2005) were unable to demonstrate significant differences between PG and PJ outcomes regarding POPF rates, other morbidity or mortality. The findings of a meta-analysis of 11 studies suggested that PG was safer after PD, but much of the evidence came from cohort studies (McKay *et al.*, 2006). The results of a recent comprehensive meta-analysis indicated that all cohort studies reporting PG-superiority most likely had been influenced by publication bias (Wente *et al.*, 2007c). In conclusion, the results of current research suggest that PG and PJ are techniques with equally good outcomes (Machado, 2012).

Gastric partition

A PPPD with a technical modification of the pancreatico-gastric reconstruction (gastric partition), has been described (Fernandez-Cruz *et al.*, 2008). A gastric segment, 12–15 cm in length, was prepared and placed in close proximity to the CEP, followed by the construction of an end-to-side, duct-to-mucosa anastomosis. The incidence of POPF was significantly lower in the gastric partition group (4%) compared to the PJ group (18%). According to the author, an advantage of this technique compared to conventional PG was the location of the anastomosis outside the gastric cavity so that contents could empty unhindered into the jejunum, and pancreatic juice could drain directly into the stomach (Fernandez-Cruz *et al.*, 2008). At the time of writing this thesis, the modification has not yet been validated in other cohorts.

Binding pancreaticogastrostomy

Two problems with the binding PJ (Peng *et al.*, 2004) were reported recently; discrepancies between the circumferential size of the remnant pancreas and the jejunal lumen, and the exudation of pancreatic juice caused by fixation sutures in the pancreatic capsule (Peng *et al.*, 2011). In order to avoid these problems, a technical variant, the binding PG, was reported. The modification was designed and successfully performed with encouraging results, and considered as feasible for managing large pancreatic remnants (Peng *et al.*, 2011). At the time of writing this thesis, the modification has not yet been validated in other cohorts.

Total Pancreatectomy

TP allows a more extensive lymphadenectomy, obviates the risks of POPF and of positive pancreatic resection margins, but at the cost of intractable diabetes mellitus, compromised immunity, and complete loss of pancreatic exocrine function (Parsaik *et al.*, 2010; Billings *et al.*, 2005; Sarr *et al.*, 1993; Karpoff *et al.*, 2001). After its enthusiastic introduction (Fallis & Szilagyi, 1948), the following evaluation showed poor outcome results and TP as alternative to PD was abandoned (Andren-Sandberg & Ihse, 1983). Today, long-term outcomes are equally bad or even worse compared to pancreatic resection and a different but considerably impaired outcome profile makes TP an option to consider only in selected patients, but not with the aim to prevent POPF (Machado, 2012).

Additional preventive surgical measures

Optimizing blood supply to the pancreatic remnant

A method to optimize the blood supply to the remnant pancreas is one of the modifications that have been reported to substantially reduce the POPF rate. The method is based on a concept of vascular watershed in the pancreatic neck and the significance of ischemia in the CEP for the POPF development. A series applying the method in PD patients resulted in a POPF rate of 1.6% (Strasberg *et al.*, 2002). At present, the method awaits external validation.

Use of fibrin sealants

An early RCT including 97 mixed resections showed no differences in POPF rates between the fibrin and non-fibrin groups (D'Andrea *et al.*, 1994). A recent trial randomized 125 high-risk pancreatic anastomoses to either application of fibrin glue sealant application on the anastomosis surface or not, with results showing similar POPF rates for both groups (Lillemoe *et al.*, 2004).

Pancreatic duct occlusion (PDO)

Although being one of the oldest techniques to deal with the remnant pancreas (Whipple, 1945), there is still no evidence that PDO could replace a pancreatico-enteric reconstruction. In a small series comparing PDO (primary closure of the pancreatic duct, oversewing of the pancreatic remnant and external drainage) to a PJ group, the PDO group had lower morbidity, decreased mortality, and shorter hospital stay (Reissman *et al.*, 1995). A comparison of 86 chemical and suture occlusions of the pancreatic duct in 83 PJ's revealed no significant difference in postoperative complications, mortality, or exocrine insufficiency. However, the PDO group had a significantly higher POPF rate (17% vs 5%) and a significantly higher incidence of postoperative diabetes mellitus after 3 and 12 months, respectively (Tran *et al.*, 2002). A RCT of 182 mixed pancreatic resections randomized to PDO with fibrin glue or conventional anastomosis could not reveal differences in POPF rates or other morbidity (Suc *et al.*, 2003).

Pancreatic duct stenting and external pancreatic drainage

The rationale behind transanastomotic stenting was to protect the duct-to-mucosa PJ or PG from contact with pancreatic secretions; moreover it was considered to facilitate a more precise suture placement, and thereby to protect the pancreatic duct from suture injury and iatrogenic occlusion (Machado, 2012). However, stent obstruction and migration were significant drawbacks, and studies on pancreatic stenting revealed discordant results (Ramacciato *et al.*, 2011a; Machado, 2012). A cohort study on end-to-side PJ's in soft pancreatic remnants comparing stented (internal or external) and non-stented methods showed no difference in POPF rates (Imaizumi *et al.*, 2006). A randomized trial of 234 patients showed that internal pancreatic duct stenting did not decrease incidence or severity of POPF (Winter *et al.*, 2006).

External pancreatic drainage or complete pancreatic diversion was thought to optimize anastomotic healing by preventing bile-induced activation of pancreatic enzymes (Machado, 2012). A cohort study showed equivalent outcomes for external and internal pancreatic stenting of duct-to-mucosa PJ (Ohwada *et al.*, 2002). A RCT of 120 patients showed significant lower fistula rates in the external drainage group than in the non-stented group (Poon *et al.*, 2007). A recent RCT of 158 patients randomized to external stent or conventional anastomosis revealed that the stented group had a significantly lower rate of POPF, overall morbidity, and DGE (Pessaux *et al.*, 2011b).

Omental wrapping

In order to protect surrounding organs from the autolytic activity of leaking pancreatic juice, vascularized structures such as the omentum or falciform ligament have been wrapped around the anastomosis. A recent nationwide survey of the Japanese Society of Pancreatic Surgery evaluated the POPF-preventive benefits of anastomosis-wrapping using the omentum or falciform ligament (Tani *et al.*, 2012). Their analysis of 2597 cases could not reveal POPF reduction by omental wrapping (POPF 43% in the wrapping group, 37% in the non-wrapping group), and the incidence of clinically relevant POPF (B/C) was lower in the non-wrapping group (17% vs 22%). According to the authors, it was not possible to conclude whether the wrapping itself constituted a risk factor for POPF due to the retrospective character of the study (Tani *et al.*, 2012).

Surgical loupes

Surgical loupes allow a precise reconstruction technique and minimize technical errors such as suture crossing, inadequate amounts of duct and jejunal mucosa or incorrect knot placement. Significantly reduced POPF rates with an operating microscope (3%) compared to operating loupes (15%) have been reported (Wada & Traverso, 2006).

Surgeon volume

Volume/outcome studies in complex surgical procedures have demonstrated that surgeons with higher caseloads achieve lower mortality and improved outcomes than general surgical units (Begg *et al.*, 1998; Halm *et al.*, 2002; Birkmeyer *et al.*, 2002). High procedure volume was found to correlate with improved outcome following PD (Mukherjee *et al.*, 2009; Ho & Heslin, 2003; van Heek *et al.*, 2005; Balzano *et al.*, 2008). A study of 145 PDs demonstrated a significant association between surgical volume and POPF incidence and reported low surgical volume as an independent risk factor for POPF development (Yeo *et al.*, 1995). Similar findings were reported in a study comparing the outcomes of surgeons demonstrating an overall morbidity of 52% in PDs performed by surgeons with limited experience (less than 50 PDs) compared to and 27% for surgeons that had performed more than 50 PDs (Cheng *et al.*, 2007).

Preventive pharmacological approaches

The pharmacological inhibition of the pancreatic exocrine secretion has been proposed to reduce the incidence of pancreatic fistula by multiple studies (Gurusamy *et al.*, 2012), and the use of somatostatin or its analogues in order to prevent POPF after PD has been studied for over 20 years (Hackert *et al.*, 2011b). The discordant results of multiple RCTs on the protective impact of prophylactic somatostatin were summarized in a recent Cochrane meta-analysis which concluded that the evidence in the current literature could not provide a recommendation about the routine use of prophylactic somatostatin or octreotide (Gurusamy *et al.*, 2012).

Management of pancreatic fistula

According to the reviewed literature, sufficient drainage and prevention of its progression are the cornerstones of managing POPF once the complication is recognized. Appropriate treatment measures have to be instituted immediately and with highest priority (Bassi *et al.*, 2001; Yang *et al.*, 2005; Shrikhande & D'Souza, 2008; Lai *et al.*, 2009; Callery *et al.*, 2009; Cameron *et al.*, 2006).

According to two series, non-operative management including treatment for postoperative bowel paralysis and drainage of intra-abdominal collections has been successful in about 90% of cases (Kazanjian *et al.*, 2005; Munoz-Bongrand *et al.*, 2004). It has to be ensured that adequate hydration is provided; TPN is recommended in patients not having tolerated oral feeding after POD 10 (Yang *et al.*, 2005; Shrikhande & D'Souza, 2008; Callery *et al.*, 2009). If signs of infection are present, empiric antibiotics are recommended and adjusted according to gram stains or culture results (Machado, 2012). Cautious drain management is indicated in patients with POPF and high-output drainage (>200 ml/day) or amylase rich effluent (Bassi *et al.*, 2001; Lai *et al.*, 2009). The administration of octreotide with therapeutic intent has been recommended by some authors (Machado, 2012); however, according to a recent meta-analysis there is no solid evidence that somatostatin analogues result in a higher closure rate of pancreatic fistula compared with other treatments (Gans *et al.*, 2012). In contrast, percutaneous drainage of CT-verified collections has been considered to be crucial (Halloran *et al.*, 2002). Post-pancreatectomy hemorrhage is favorably managed by angiographic embolization (Puppala *et al.*, 2011; Sato *et al.*, 1998b). Surgical intervention has to be considered in cases of suspected anastomotic dehiscence or in clinically deteriorating patients with non-drainable abscesses.

Severe POPF leads to an accumulation of secondary morbidity and mortality (Denbo *et al.*, 2012; Fuks *et al.*, 2009; Pessaux *et al.*, 2011a) and remains an unresolved surgical problem. The prevention and management of severe POPF have been main objectives of recent POPF research (Pessaux *et al.*, 2011a; Reid-Lombardo *et al.*, 2007b; de Castro *et al.*, 2005a; Farley *et al.*, 1996; Bachellier *et al.*, 2008; Hasegawa *et al.*, 2008; Blanc *et al.*, 2007; Ribero *et al.*, 2013). Failure of conservative management might necessitate repeat surgery (Yekebas *et al.*, 2007; de Castro *et al.*, 2005b) but current treatment concepts have high failure-to-rescue rates (de Castro *et al.*, 2005a; Ho *et al.*, 2005; Farley *et al.*, 1996; Bachellier *et al.*, 2008; Ribero *et al.*, 2013; Smith *et al.*, 1992; Gueroult *et al.*, 2004; van Berge Henegouwen *et al.*, 1997). Surgical options include wide peripancreatic drainage of abscesses or fluid collections, revision of the initial pancreatico-enteric anastomosis, conversion to an alternative anastomosis, or completion pancreatectomy (Machado, 2012). In patients with PJ disruption, simple peripancreatic drainage might not be effective (Bachellier *et al.*, 2008; van Berge Henegouwen *et al.*, 1997). Completion pancreatectomy (CP), the standard treatment of severe POPF (Farley *et al.*, 1996; Smith *et al.*, 1992; Gueroult *et al.*, 2004), has a high procedure-associated mortality (38-64%) and leads to complex secondary morbidity with poor short term and long term outcomes (Ribero *et al.*, 2013).

II OBJECTIVES

The current thesis comprises two published papers and two submitted manuscripts. The general aims were to study the preconditions for developing clinically relevant pancreatic fistula following PD, and to propose POPF-predictive models that might facilitate the clinical management of patients undergoing PD.

The specific aims were

1. To evaluate the extent to which metabolite changes and protease activation in the proximity of the pancreaticojejunostomy provided pathophysiological information on the risk of postoperative pancreatic fistula formation after PD (study I).

2. To assess the importance of postoperative analyses of pancreatic amylase in the contents of prophylactic intraabdominal drainage for the prediction of pancreatic fistula following PD (study IV).

3. To develop a practical, structured PD-specific protocol for the intraoperative assessment of pancreatic gland consistency and main pancreatic duct diameter; and to evaluate the predictive impact of this assessment on the development of postoperative pancreatic fistula (study II).

4. To assess the importance of procedure-specific risk factors for the risk adjustment of PD outcomes by comparing the predictive value of a procedure-specific pancreatic risk model versus an established generally applicable model consisting of other risk factors for postoperative morbidity and mortality (POSSUM, study III).

III PATIENTS AND METHODS

All patients included in the cohort studies of this thesis underwent elective PD at the Department of Upper Abdominal Surgery, Karolinska University Hospital, Sweden, which is a tertiary referral surgical center for pancreatic diseases. The decision for surgical intervention was made at the Karolinska multidisciplinary pancreatic tumor board. The tumor board holds weekly structured conferences where surgeons, radiologists, oncologists and pathologists discuss each individual case and tailor diagnostic measures and treatments to the specific clinical context based on current evidence. Demographical and peroperative parameters were recorded prospectively during the preoperative surgical and anesthesiological evaluations that all patients had to undergo after the decision for surgery was made. The Pancreatic Intention-To-Resect Register (PITR) is a prospectively maintained database that is classified as an internal quality register. The register in its current form was started in January 2008 and includes demographics, operative parameters and postoperative morbidity data of all patients undergoing elective pancreatic surgery at Karolinska.

Table 10. Study parameters.

	Study I	Study II	Study III	Study IV
Identifier	Microdialysis measurement	Intraoperative risk assessment	POSSUM risk adjustment	Drain pancreatic amylase
Design	Prospective OCS	Prospective OCS	Prospective OCS	Prospective OCS
Data source	µD database	PITR + IPRA register	PITR + POSSUM	PITR + lab register
Patients	48	110	195	315
Recruitment	non-consecutively	non-consecutively	consecutively	consecutively
Time period	March 2007 – April 2010	January 2008 – July 2010	January 2008 – December 2010	January 2008 – June 2012

Pancreaticoduodenectomy

In all patients included in the studies of this thesis, a standardized Kausch-Whipple PD was performed with radical lymphadenectomy excluding stations 9 and 14d (Pedrazzoli *et al.*, 1999b). Selective sampling of station 16b1 (para-aortic nodes) was done for tumor staging. If considered necessary a resection of the superior mesenteric/portal vein was performed with curative intent.

Resection

The procedure followed a standardized sequence. A midline laparotomy provided adequate exposure of the resection field. The liver and peritoneal surfaces were examined for unexpected tumor dissemination (liver metastasis or peritoneal carcinosis). Suspicious lesions and enlarged lymph nodes outside the planned resection field were biopsied and examined by frozen section; if positive for dissemination, the resection was aborted or converted to a double bypass. The separation of the falciform ligament from the abdominal wall enabled the placement of a self-retaining retractor system (Omnitract®) in the laparotomy, which was affixed to the operating table beneath the left arm board. The caudal liver surface and the gallbladder were released from adhesions and the gallbladder was included in a liver retractor and reflected superiorly to provide adquate exposure to the subhepatic compartment.

Pancreaticoduodenal mobilization

The mobilization of the pancreaticoduodenal area started from right lateral by mobilizing the ascending colon and the hepatic flexure, in some cases extending to a Cattell-Braasch maneuver (Cattell & Braasch, 1960). Kocher's maneuver was performed by reflecting the duodenum medially and separating it from the Gerota's fascia and perinephric fat, developing the dissection plane down to the ventral aspect of the caval vein and left renal vein. The transverse mesocolon was retracted medially and separated from the duodenum and the uncinate process. The SMV was identified medial to the uncinate process in the root of the mesentery.

The inferior medial mobilization of the pancreaticoduodenal area included a resection of the greater omentum and gastrocolic ligament which allowed a complete mobilization of the transverse mesocolon and exposure of the middle colic vein down to the SMV confluence. The whole infra-pancreatic portion of the SMV was exposed up to the inferior aspect of the pancreatic neck. The right gastroepiploic vein was ligated to prevent avulsion, while the large inferior pancreaticoduodenal branch to the SMV was preserved in order to avoid venous stasis in the specimen. An opening of the avascular plane between the anterior aspect of the SMV and the posterior aspect of the inferior pancreas was developed bluntly and the inferior portion of the pancreatic neck was undermined.

The cranial mobilization of the pancreaticoduodenal area started with a cholecystectomy and the dissection of the cystic-duct/CBD confluence. The left hepatic artery (LHA) was

exposed in the hepatoduodenal ligament to its origin from the common hepatic artery (CHA).

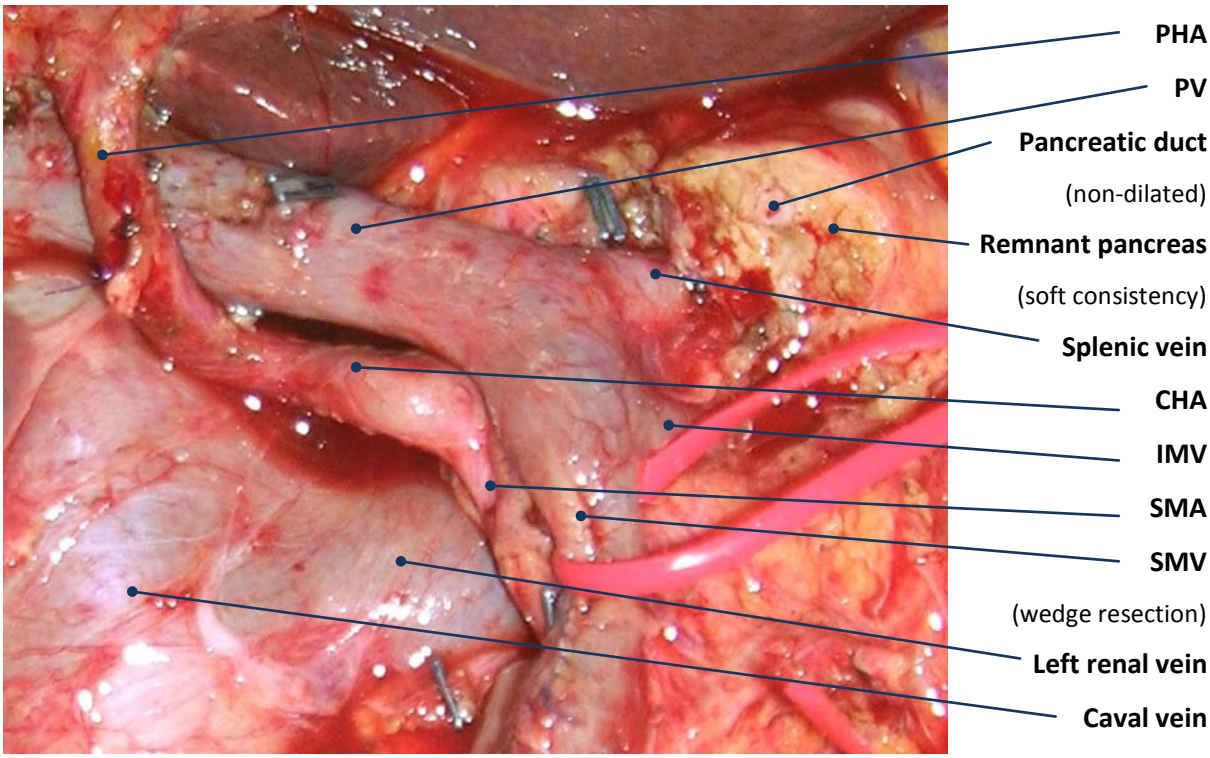
Table 11. Michel Classification of anatomic variants of arterial liver blood supply.

Type	Arterial configuration	Occurrence
I	Regular: CT – CHA – GDA / PHA – RHA / LHA	84%
II	Replaced LHA: LGA – LHA	1%
III	Replaced RHA: SMA – RHA	6%
IV	Replaced LHA + RHA	0.5%
V	Accessory LHA: PHA – LHA1 and LGA – LHA2	3.5%
VI	Assessory RHA: PHA – RHA1 and SMA – RHA2	1%
VII	Assessory LHA and RHA	0
VIII	Replaced RHA + Assessory LHA or Replaced LHA + Assessory RHA	0.5%
IX	Replaced CHA (SMA – CHA)	1%
X	Replaced CHA (LGA – CHA)	0

The extirpation of lymph node stations 8a and 12a allowed access to the central parts of the CHA and the anterior aspect of the PV. Potential anatomical variants of the right hepatic artery (RHA) had been identified preoperatively so that the CBD could be isolated from connective tissue while preserving the RHA. The CBD was divided 1-2 cm proximal to the cystic duct confluence. The distal lumen (specimen side) was sutured to limit potential spillage of cancer cells, while the proximal duct was left unclamped. The division of the CBD allowed exposure of the PV and access to the space under the proper hepatic artery (PHA), the GDA and the right gastric artery. After ensuring that pulsatile flow through the hepatic arteries was retained, the GDA was divided and suture ligated. The right gastric artery was divided and ligated. The CHA and the PV were exposed completely. Superior pancreatico-duodenal branches to the PV were divided and ligated, and the PV was followed to the superior aspect of the pancreatic neck. The avascular plane between SMV and pancreatic neck was developed from the superior aspect and the pancreatic neck was undermined on the ventral SMV using a blunt instrument ("the forceps that does not exist"). The pancreatic neck above the SMV was sometimes looped to minimize pancreatic manipulation under the subsequent transection of the pancreas.

The mobilization of the pancreatoduodenal area from the left was carried out by the transection of the stomach and the division of the jejunum. Transection points were chosen at the junction of the left and right gastro-epiploic arteries on the greater curvature and at the incisura angularis of the lesser curvature. The omentum was divided between the gastroepiploic vessels and the stomach was transected using a linear cutting stapling device (GIA®, Ethicon). The lesser omentum was divided and suture ligated. The stapler line of the remnant stomach was oversewn with continuous 4-0 PDS. The ligamentum of Treitz was opened and the jejunum was mobilized by full exposure of the duodenojejunal flexure. The jejunum was divided 10 cm distal to the ligamentum of Treitz with a GIA® stapler and the remnant jejunum was oversewn with 4-0 PDS. The proximal jejunal segment was devascularized and dislocated behind the mesenteric vessels through the duodenal fossa into the subhepatic compartment.

Figure 1. Vascular structures in the hepaticoduodenal ligamnet and central mesentery. Patient with a Michel IX variant; a replaced CHA (branching from the SMA).



Pancreatic transection

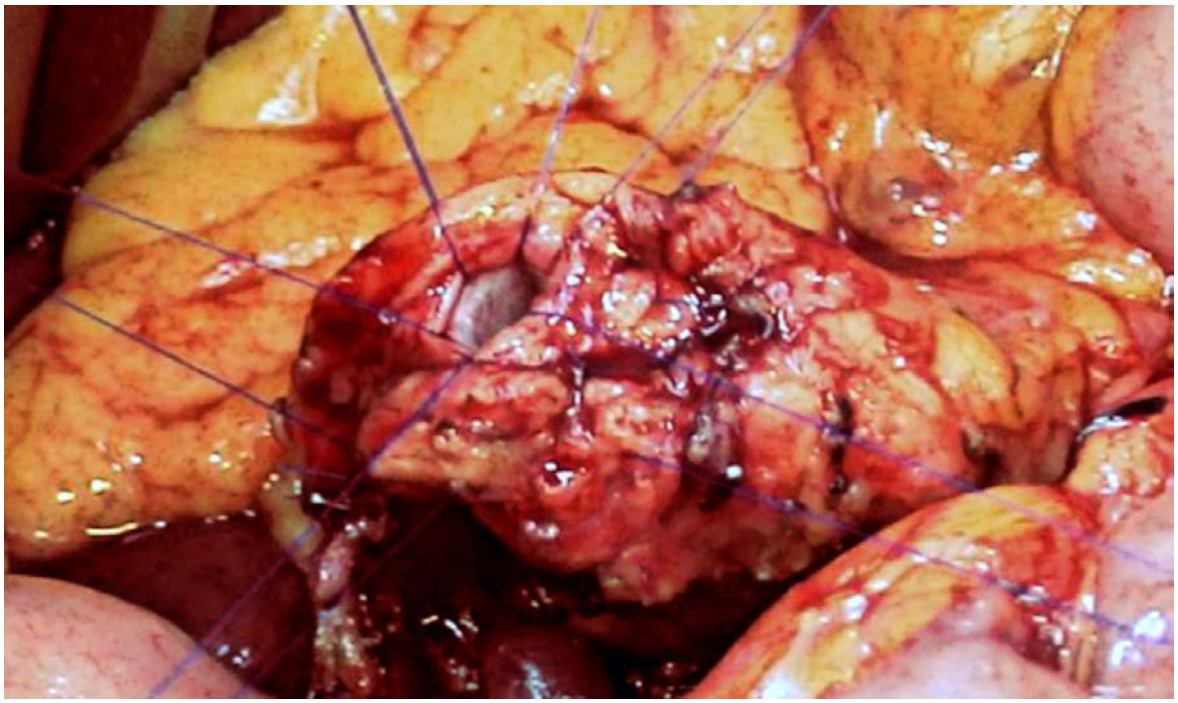
The pancreas was transected to the left of the SMV. Bleeding from the intrapancreatic arteries was controlled by electro cauterization or by hemostatic sutures with 6-0 polypropylene. To separate the specimen from the mesenteric vessels the mesopancreas was transected usually using a lateral-inferior approach. At the inferior aspect, the first jejunal tributary vein was identified and preserved. The SMA could be identified usually posteromedial to the first jejunal tributary branch. After separating the specimen from the venous pancreaticoduodenal branches by individual clips ligations, the SMV was carefully retracted from the specimen by the assistant, allowing access to the retroperitoneal attachment of the uncinate process to the SMA. To achieve full tumor clearance the complete mesopancreas was separated from the SMA by exposing the SMA inferiorly and towards the aortic origin. The superior and inferior pancreaticoduodenal branches were divided and clips ligated. The para-aortic lymph node station 16b1 was sampled for staging purposes and the remaining nodes from station 12a, b and p were removed.

Reconstruction

For the pancreaticojejunal reconstruction, the remnant pancreas was mobilized above the splenic vein and the portal confluence. The proximal jejunum was advanced through a mesenteric defect that had been created to the left of the middle colic vessels. The pancreatico-jejunal anastomosis was carried out by a non-stented two-layer duct-to-mucosa PJ according to Cattel's technique (Cattell, 1948). Both the outer (between the pancreatic

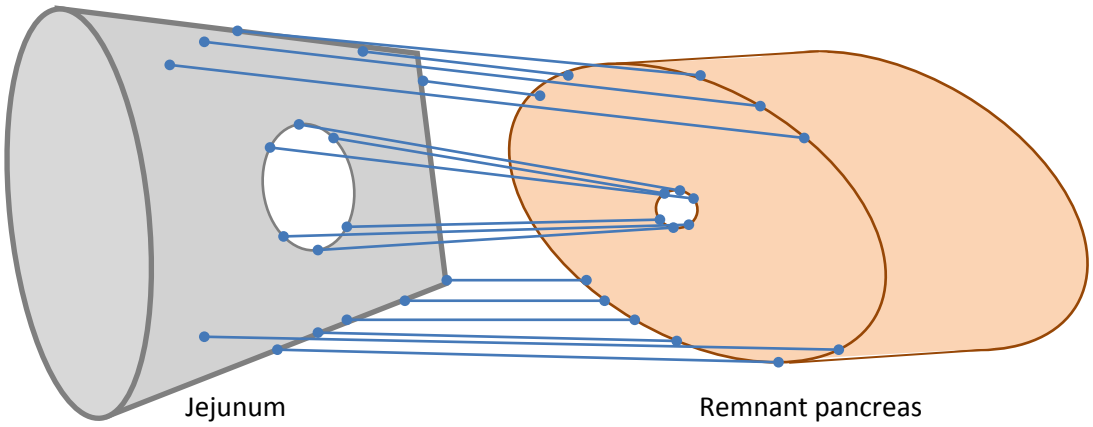
parenchyma and jejunal seromuscularis) and inner (between the main pancreatic duct and the whole jejunal wall) layers were constructed as posterior and anterior rows of interrupted sutures with 5-0 polypropylene.

Figure 2. Remnant pancreas with six duct sutures. Typical intermediate risk gland (dilated main duct and soft consistency).



When the ductal diameter was small, the inner layer was sutured with 6-0 polypropylene. The surgery was completed by a standard end-to-side single layer hepatico-jejunostomy using interrupted 5-0 polydioxanone (PDS) sutures according to the technique described by Blumgart and Kelley (Blumgart & Kelley, 1984), an antecolic stapled side-to-side gastrojejunostomy on a jejunal 'omega' loop, and a stapled side-to-side entero-enterostomy. Two four-channel Blake® drainage tubes were placed in front of the PJ and behind the hepaticojejunostomy.

Figure 3. Inner and outer layers of the duct-to-mucosa pancreaticojejunal anastomosis. Blue lines indicate sutures.



Postoperative treatment

In all patients in the four studies, the postoperative management followed a standardized protocol. The patients were evaluated twice daily by the attending surgeon in the high-dependency unit or regular ward to identify possible deviations from the expected postoperative course. White blood cell count, serum levels of pancreatic amylase and C-reactive protein were determined daily, along with the volume of drainage fluid and concentrations of drain pancreatic amylase. Computed tomography was carried out if clinical symptoms or signs suggested the occurrence of an intraabdominal complication. Accessible fluid collections were drained percutaneously under ultrasonographic guidance. POPF, peripancreatic abscesses, and fluid collections with or without pancreatic amylase were treated equally according to a single standard care algorithm. Based on the patient's clinical condition, this could involve a spectrum of radiological interventions and/or surgical procedures ranging from optimization of abdominal drainage to completion pancreatectomy.

Intraoperative pancreatic risk assessment

In the studies II-IV, a PD-specific intraoperative pancreatic risk assessment (IPRA) was used to classify characteristics of the pancreatic gland, in order to relate those to the risk of developing POPF. After the pancreatic transection the consistency (PC) and the main pancreatic duct diameter (PDD) were assessed according to a four-grade scale for each variable. A PDD grade of 1 (more than 4 mm) was assigned when the lumen of the pancreatic duct at the point of transection exceeded the diameter of two 2-mm buttoned probes, a PDD grade of 2 (3–4 mm) when one probe could be inserted with room to spare but not enough to allow the insertion of a second probe, a PDD grade of 3 (less than 3 mm) when one probe would fit precisely in the duct, and a PDD grade of 4 (less than 2 mm) when a probe could not be inserted without significant force. In contrast to PDD, the surgeon's PC assessment was subjective, based on visual and tactile information gathered during pancreatic manipulation, from mobilization and transection of the gland to mobilization of the remnant and placement of sutures during the pancreatico-enteric reconstruction. The PC grade was declared before the anastomosis had been completed. A PC grade of 1 was assigned for a very hard consistency (such as in patients with severe chronic pancreatitis), PC 2 for hard (fibrotic or atrophic obstructed pancreatic gland), PC 3 for soft (unaffected compact gland), or PC 4 for very soft consistency (unaffected fatty pancreas).

Table 12. Peroperative pancreatic risk assessment. Classification of pancreatic consistency (PC) grades and pancreatic duct diameter (PDD) grades.

PC grade	Subjective surgical assessment	Risk factor
PC1 (very hard)	as in severe chronic pancreatitis	no
PC2 (hard)	as in a fibrotic or atrophic obstructed pancreatic gland	no
PC3 (soft)	as in an unaffected compact gland	yes
PC4 (very soft)	as in an unaffected fatty gland	yes

PDD grade	Surgical assessment with 2-mm buttoned probes	Risk factor
PDD1 (>4mm)	PDD exceeds the diameter of two probes	no
PDD2 (3-4mm)	One probe can be inserted with room to spare	no
PDD3 (<3mm)	One probe fits precisely in the duct	yes
PDD4 (<2mm)	A probe cannot be inserted without significant pressure	yes

Risk estimation of postoperative pancreatic fistula or associated morbidity. No risk factors - low risk for postoperative pancreatic fistula or associated morbidity (2%). One risk factor (softer PC or PDD < 3 mm) - intermediate risk (26%). Both risk factors (softer PC and PDD < 3 mm) - high risk (51%).

Microdialysis

The blood concentrations of a substance may not reflect its concentrations at the cellular level; differences depend on the extent of protein binding, capillary permeability, and kinetics in the distribution volumes (Chaurasia *et al.*, 2007). Microdialysis is an atraumatic minimally-invasive sampling technique of measuring concentrations of unbound substrates in the extracellular tissue fluid. The concept of microdialysis is based on attempts from the 1960s to directly study biochemistry and notably transmitter release by using push-pull cannulas, dialysis sacs, and dialytrodes in animal tissues (Chaurasia *et al.*, 2007). In 1974, the use of hollow fibers was reported (Ungerstedt & Pycock, 1974). A major breakthrough was the report on in situ microdialysis of the rat brain used to measure metabolic events at the cellular level; the atraumatic technique permitted stable dialysis conditions for several days (Zetterstrom *et al.*, 1982; Ungerstedt *et al.*, 1982). Improvements of this techniques resulted in the development of the microdialysis needle probe. Microdialysis was rapidly used for pharmacokinetic studies and further adopted in clinical settings. Clinical microdialysis has been shown to be a safe and reliable technique for studying tissue biochemistry and drug distribution applicable to most organs in appropriate clinical situations (Ungerstedt, 1991; Muller, 2002). It is the only tool available that explicitly provides data on the extracellular space. Microdialysis methods have been used mostly in intensive care research, clinical pharmacology, dermatology and metabolic research (Chaurasia *et al.*, 2007).

The microdialysis technique requires the insertion of a probe directly or via a guide cannula into a specific tissue or fluid-filled space (Ungerstedt, 1991). The probe is designed to mimic a blood capillary. It consists of a shaft with a semipermeable hollow fiber membrane at the tip, which is connected to inlet and outlet tubing. Semipermeable membrane materials used in probe construction range from low- to high-molecular weight cutoff. A physiologically compatible perfusion fluid is delivered through the probe at a low and constant flow rate (0.1-5 μL/min). Solutes are exchanged by passive diffusion across the semipermeable membrane of the probe depending on the concentration gradient. By that, amounts of solutions can be sampled. Microdialysis has been widely employed in metabolic studies of various human tissues in vivo, particularly with regard to adipose tissue and skeletal muscle metabolism (Chaurasia *et al.*, 2007; Magkos & Sidossis, 2005).

In patients of study I, an intraperitoneal (IP) gastrointestinal microdialysis catheter was used (CMA 62, CMA® Microdialysis AB, Solna, Sweden) with a 180-mm shaft and a 30-mm membrane in length, molecular weight cut-off at 20 kDa. After the intraabdominal drains had been placed, the catheter was introduced through a small incision in the abdominal wall and the microdialysis membrane was placed in the proximity of the PJ. The catheter outlet tubes were fixed to the skin. Microdialysis was performed as previously described (Jansson *et al.*, 2003) starting at 12:00 pm on POD 1. Samples were collected in microvials every 4 hours and were analyzed immediately for glycerol, lactate, pyruvate and glucose in a CMA 600 Microdialysis Analyzer (CMA® Microdialysis AB, Solna, Sweden) using a kinetic enzymatic analysis technique.

Blood levels of lactate and glucose were measured every 4 hours concomitantly with the microdialysis sampling. Trypsinogen activation peptide (TAP) was analyzed in microdialysates as a marker of protease activation on POD 1-2. Plasma pancreatic amylase was analyzed on POD 1-2. Postoperative complications were recorded according to the Clavién-Dindo Classification. Three study groups were stratified; the group of patients developing clinical POPF (ISGPF A-C and Clavién-Dindo ≥ II), a group a patients developing other surgical complications and a group without surgical complications. The IP concentrations of glycerol, lactate, pyruvate, glucose, and TAP, and the systemic concentrations of lactate and glucose, along with the IP lactate/pyruvate ratio (L/P ratio), were compared between the study groups.

Analysis of proteolytic activation peptides in microdialysates

Since trypsin was too large (approximately 25 kDa) to pass through the membrane with a weight cut-off at 20kDa, other markers of proteolytic enzyme activation had to be evaluated. Enterokinase activates trypsinogen in the duodenum cleaving off trypsin activation peptide (TAP) with a molecular weight of 1 kDA. Trypsin in turn activates carboxypeptidase B cleaving off carboxypeptidase B activation peptide (CAPAP) with a molecular weight of 10 kDa. In a pilot subgroup of ten patients, TAP and CAPAP were analysed in microdialysates sampled from the pancreatic duct and duodenum during surgery and the IP microdialysates. TAP was measured by a radioimmunoassay and CAPAP by a double-antibody ELISA test (Appelros *et al.*, 1998; Petersson & Borgstrom, 2006). As expected (Rinderknecht, 1993b), high levels of TAP were detected in the duodenum whereas it was absent in the pancreatic duct. Since TAP values were higher than CAPAP values, only TAP was measured in the rest of the patients. TAP concentrations were used to report IP protease activation, except in one patient with POPF, in whom CAPAP was detected but technical difficulties hampered TAP measurement. The analysis of TAP was performed in microdialysates stored at -20° C; TAP being a stable peptide could be stored safely at this temperature.

Postoperative drain and blood sample analysis

In patients recruited into study IV, levels of serum C-reactive protein (CRP), an acute-phase reactant and marker of systemic inflammation, and plasma pancreatic amylase (PPA), a marker of pancreatic injury or inflammation, were recorded. From the 24-hour output of the abdominal drains concentrations of pancreatic amylase (DPA) were determined together with the respective drain volumes. The DPA levels that study IV refers to were obtained from the left abdominal drain. Drains were removed earliest on POD 4, if the drain volume was below 30-50 ml or if drain output did not contain amylase. The CRP concentrations were measured by an immunoturbidimetric assay and displayed as mg/L (normal range 0–3 mg/L). The catalytic activity concentrations of PPA and DPA were measured by an enzymatic colorimetric assay after inhibition of the salivary-type α-amylase by monoclonal antibodies, and was displayed in katal ($mol \cdot s^{-1}$)/ L according to the International System of Units (Dybkaer, 2002). The SI unit formed the basis of all statistical calculations of PPA and DPA in the current study, the concentration of the enzyme unit (U/L) as adopted by the International Union of Biochemistry (1965, no authors listed) was calculated using the converting factor 1 U = 16.667 x 10^{-9} kat (Dybkaer, 2002). The normal range for PPA was 0.15-1.1 µkat/L (9-66 U/L), and the lowest measurable level for pancreatic amylase was 0.13 µkat/L (7.8 U/L), levels below that had been referred to as "<0.13" in the laboratory report and due to statistical reasons were defined as 0.12 µkat/L (7.2 U/L) throughout the study.

POSSUM score calculation

The use of outcomes to address surgical quality implies the need for detailed clinical data for risk adjustment, either based on administrative systems (Charlson *et al.*, 1987; Elixhauser *et al.*, 1998) or on prospectively maintained clinical databases (Greenblatt *et al.*, 2011; Parikh *et al.*, 2010a; Venkat *et al.*, 2011). In pancreatic surgery, different methods have been used for the risk adjustment of surgical procedure cohorts (Pratt *et al.*, 2008b; Parikh *et al.*, 2010a; de Castro *et al.*, 2009; Grendar *et al.*, 2012; Khan *et al.*, 2003; Knight *et al.*, 2010; Zhang *et al.*, 2009; Tamijmarane *et al.*, 2008).

The well-established "Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity" (POSSUM) estimates individual morbidity and mortality risk based on 12 parameters describing the patient's clinical condition and on 6 parameters describing the extent of the surgical procedure (Copeland, 2002; Copeland *et al.*, 1991). The complete scoring system is shown in table 13. The authors nominated the ratio between observed and POSSUM-estimated morbidity as quality indicator for surgical performances. The risk adjustment was recognized as most effective for general surgery (Jones & de Cossart, 1999). Five years after its introduction, the logistic equation of the score was modified (P-POSSUM) due to mortality overestimation (Whiteley *et al.*, 1996; Prytherch *et al.*, 1998). Accordingly, variants were developed for several surgical sub-specialties (Dutta *et al.*, 2011; Lam *et al.*, 2004; Neary *et al.*, 2003; Tekkis *et al.*, 2004), however, not for pancreatic surgery. POSSUM, originally considered as suitable for pancreatic procedures, has subsequently been applied with divergent results (Pratt *et al.*, 2008b; de Castro *et al.*, 2009; Khan *et al.*, 2003; Zhang *et al.*, 2009). However, it is still a widely used scoring system (Copeland *et al.*), and in 2010, it had been incorporated into the Swedish National Register for Pancreatic Tumors. An online POSSUM calculator is available at http://www.vasgbi.com/riskpossum.htm.

In study III, all clinical, radiological and blood chemistry data required to calculate the POSSUM physiological score had been recorded at patient enrollment. Cardiac and respiratory criteria were evaluated based on the preoperative radiological work-up (CT-scan or chest X-ray). The parameters of the operative severity score were concomitantly recorded. PD was considered as "major+" (score 4) as originally proposed (Copeland *et al.*, 1991). Individual morbidity and mortality risks were calculated. Data recording and score calculation were done by a research fellow who was not involved in the surgery and blinded for the outcomes (P.L.).

Table 13. Physiological and operative assessment of the POSSUM system (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity).

		POSSUM score		
Physiological	1	2	4	8
Age (years)	<60	61–70	>70	NA
Cardiac signs	Normal	Cardiac drugs	Edema; warfarin	JVP
Chest X-ray	Normal	NA	Borderline cardiomegaly	Cardiomegaly
Respiratory signs	Normal	SOB exertion	SOB stairs	SOB rest
Chest X-ray	Normal	Mild COAD	Moderate COAD	Other change
Systolic blood pressure (mm Hg)	110–130	131–170 100–109	>170 or 90–99	<90
Pulse (b/min)	50–80	81–100 40–49	101–120	>120 or <40
Glasgow coma score	15	12-14	9-11	<9
Urea nitrogen (mmol/L)	<7.5	7.6-10	10.1-15	>15
Sodium (mEq/L)	>135	131-135	126-130	<126
Potassium (mEq/L)	3.5-5	3.2-3.4 5.1-5.3	2.9-3.1 5.4-5.9	<2.9 or >5.9
Hemoglobin (g/dL)	13–16	11.5–12.9 16.1–17	10–11.4 17.1–18	<10 or >18
White blood cell count (x1012/L)	4–10	10.1–20 3.1–3.9	>20 or <3	NA
Electrocardiogram	Normal	NA	AF (60–90)	Other changes
Operative	1	2	3	4
Operative magnitude	Minor	Intermediate	Major	Major+
No. of operations within 30 days	1	NA	2	>2
Blood loss per operation (ml)	<100	101-500	501-999	>999
Peritoneal contamination	No	Serous	Local pus	FBC, pus or blood
Presence of malignancy	No	Primary cancer only	Node metastases	Distant metastases
Timing of operation	Elective	NA	Emergency <24 h	Emergency <2 h

Adopted from the revised score (Copeland, 2002). JVP, jugular venous pressure; SOB, shortness of breath; COAD, chronic obstructive airway disease; FBC, free bowel content.

Main outcome parameters

POPF

In the studies of this thesis, POPF was defined according to the ISGPF definition (Bassi *et al.*, 2005a). Different sub-criteria were used, among others, a widely used modification of the ISGPF definition; the categories of grade B and C were merged and labeled as "clinically-relevant fistula" (Reid-Lombardo *et al.*, 2007b; Ansorge *et al.*, 2012a; Facy *et al.*, 2012; Moskovic *et al.*, 2010; Noji *et al.*, 2012; Malleo *et al.*, 2012). The measurement of plasma pancreatic amylase instead of serum amylase was considered as unproblematic, since the ISGPF definition was based on the relation between the drain and serum levels of amylase, and serum and plasma levels of pancreatic amylase were considered as identical.

Table 14. Main study outcome parameters.

	Definition	Paper
Postoperative pancreatic fistula (POPF)	ISGPF grade A-C	IV
	ISGPF grade A-C and CDC ≥ grade II	I
	ISGPF grade B or C	II; III; IV
Symptomatic peripancreatic collections (SPPC)	Drainage improves patient condition regardless of amylase content	II; III
Pancreaticojejunostomy-associated morbidity (PJAM)	POPF ISGPF grade B or C or SPPC	II; III
Severe pancreaticojejunostomy associated morbidity (PJAM)	POPF ISGPF grade C or SPPC and CDC grade IIIb-V	II
Other surgical complications (OSC)	Postoperative intra-abdominal complication CDC ≥ grade II	I
Total morbidity	CDC ≥ grade II	II; III; IV
Mild morbidity	CDC grade I-II	III
Moderate morbidity	CDC grade IIIa	III
Severe morbidity	CDC grade IIIb-IVb	III
	CDC grade IIIb-V	IV
Mortality	CDC drade V	II; III
	CDC grade V or 30-days mortality	IV

ISGPF, International study group of pancreatic fistula, table 1; CDC, Clavién-Dindo Classification.

SPPC and PJAM

In study II and III, the ambition was to capture all relevant morbidity resulting from pancreatic surgery. Therefore, also radiologically verified postoperative abscesses or fluid collections not containing pancreatic amylase were recorded if they were adjacent to the PJ and if their drainage improved the patient's condition; these were defined as symptomatic postoperative peripancreatic collections (SPPC). PJAM was defined as POPF (ISGPF grade B/C), or SPPC.

Clavién-Dindo Classification

The Clavién-Dindo Classification of surgical complications adopted for pancreatic surgery (CDC) was used to classify postoperative complications (Dindo *et al.*, 2004; DeOliveira *et al.*, 2006). In study I, surgical complications other than POPF (OSC) were defined as any other postoperative intra-abdominal complication with a grade of II or higher according to CDC. In study II, severe morbidity was defined as CDC grade ≥ IIIb. In study III, the severity of postoperative morbidity was classified according to CDC, and morbidity was divided into mild (requiring bed-side treatment, CDC II), moderate (requiring additional intervention without general anesthesia, CDC IIIa), or severe (requiring additional intervention in general anesthesia and/or intensive care, CDC IIIb-IV). CDC V entailed in-hospital mortality. In study IV, relevant postoperative morbidity was classified according to established definitions (Dindo *et al.*, 2004; Bassi *et al.*, 2005a; Wente *et al.*, 2007a; Wente *et al.*, 2007b; Bone *et al.*, 1992).

Mortality

In study I-III, PD-associated mortality was defined as in-hospital-mortality corresponding to CDC V. In paper IV, PD-associated mortality was defined as either death occurring within 30 days after surgery (30-days mortality) or death in hospital, regardless of the time after surgery (in-hospital mortality).

Statistics

Study I

Data were presented as median and 10-90th percentile in graphs, and as mean with standard deviation as the measurement for statistic dispersion. The coefficient of variation between time points per day and patient indicated that it was appropriate to use the mean values as central tendencies for the analysis of aggregated data. Differences between groups were analysed by a two-way mixed model (Brown & Prescott, 2006) with study groups, POD and measurement type as factors. Logarithmic or square root transformations were performed before statistical analyses when needed. The Spearman rank correlation coefficient was used to measure the association between the metabolite variables. The study was considered to be a descriptive and explorative investigation and included neither power estimation nor randomization. $P<0.05$ was considered to be statistically significant.

Study II

The incidence and risk estimate of POPF and SPPC were calculated for each grade of PDD and PC. Patients were grouped according to PC and PDD characteristics. Based on the presence of risk factors, three groups were stratified: a group of no risk factors, a group with one risk facto and a group with two risk factors. Risk estimates for POPF, SPPC, PJAM and severe PJAM were determined for each group and reported as odds ratios. Two-tailed Pearson's correlation test and McNemar's χ^2 test were used to examine the association between PC, PDD and endpoint parameters. Interobserver agreement was tested using Cohen's κ statistic.

Study III

POSSUM morbidity estimation calculates individual risk estimates based on a complex scoring system, and it can be difficult to interpret the predictive value of these individual scores. For a simplified risk categorization it has been assumed to group patients with similar scores. In accordance with previous publications (Pratt *et al.*, 2008b; Zhang *et al.*, 2009) the study cohort was grouped based on the POSSUM morbidity risk into quintiles (0-19%, 20-39%, 40-59%, 60-79% and 80-99%) which were labeled as standard risk (SR) groups. The cohort was additionally divided into low-risk (0-59%) and high-risk (60-99%) groups which were labeled as split cohort (SC) groups. Due to a non-normal patient distribution the cohort was further grouped into quintiles of near-equal sample size (POSSUM morbidity risk 0-48%, 49-59%, 60-69%, 70-75% and 76-99%) which were labeled as equal risk quintiles (ERQ). POSSUM mean values were calculated for the groups of SR, SC and ERQ and compared according to the observed morbidity. The ratio between observed and POSSUM-estimated morbidity (O/E ratio) was calculated. SR, SC and ERQ were correlated to total morbidity and severity of postoperative morbidity according to CDC. The study cohort was grouped by IPRA results, and the IPRA low-risk and high-risk

groups were compared to POSSUM low-risk and high-risk groups regarding total morbidity and CDC. Finally the associations between POSSUM SR groups, total morbidity and CDC were tested for the IPRA high-risk and low-risk groups, respectively. The associations between categorical variables were tested in binary logistic regression or by Pearson's R bivariate correlation. The differences of distribution levels and medians in groups of continuous variables were assessed by Mann-Whitney U tests for two samples, and Kruskal-Wallis analysis of variance or independent median tests for several samples.

Study IV

Summary data were analyzed using frequency tables for category variables. The continuous variables were non-normally distributed (Kolmogorov-Smirnov and Shapiro-Wilk tests), therefore central tendency was displayed as median and statistic dispersion as interquartile range. Chi-square tests were used for comparing category variables, non-parametric tests (Kruskal-Wallis and Fisher's exact for 5-sample, Mann-Whitney U for 2-sample) for comparing level distributions and level medians in continuous variables. To test the predictive accuracy (% of correctly predicted cases) receiver operating characteristic (ROC) analyses were performed. An area under the curve (AUC) greater than 0.8 was considered as of a high diagnostic accuracy, a p value <0.05 (two-sided) was considered as significant. Cut-off levels for the samples with the greatest AUC and a balanced high accuracy were identified by using the visualization and coordinates of the ROC-curve. Regression analyses for the cut-off-stratified subgroups were performed in order to identify risk models describing the dependent variable states with optimum accuracy. The actual risk estimates were reported as odds ratios. Postoperative day (POD) was displayed as subscript number after the sample name (PPA_1 = plasma pancreatic amylase on the first postoperative day).

Software

The Karolinska Pancreatic Intention-to-Treat Register is a JMP® database. Statistical analysis was done using the SAS® System 9.1, (SAS Institute Inc., Cary, NC, USA) and Statistica 9.0, (StatSoft® Inc., Tulsa, OK, USA) in study I, using SPSS® 19 (SPSS, Chicago, Illinois, USA) in study II, using SPSS® 20.0 (IBM Corp., NY, U.S.) in study III and IV. All papers and the thesis were written using Microsoft Word® 2007/2010 and Adobe Acrobat® IX. References were managed using Thompson Reuters Endnote® 5/X6. Figures were scaled using GIMP 2.8.2. For literature search, NCBI Pubmed, Google Scholar® and the Karolinska Institutet library resources were used. Manuscript files were stored on Google Drive®.

IV RESULTS

Study I

Forty-eight patients were enrolled. Mortality was 4.1% (2/48) and overall surgical morbidity 31% (15/48). Seven patients (15%) developed clinically significant POPF. Two patients underwent CP on POD 4 and POD27, respectively, followed by ICU treatment. Five patients had clinical and radiological symptoms of POPF on POD 8-9; of those, one patient was treated successfully with intravenous antibiotics, two patients received IV antibiotics and ultrasound-guided drainage, and two were re-operated due to surgical complications other than POPF; one for bile leakage, and one for intra-abdominal hemorrhage. Eight patients had other surgical complications (OSC). One patient was re-operated for leakage from the hepaticojejunostomy, three patients were re-explored due to suspected intra-abdominal bleeding; one patient was treated successfully by surgical hemostasis, one patient underwent a negative exploration, was re-operated for wound dehiscence and succumbed to circulatory arrest, and one patient died of multi-organ failure. Three patients with bleeding from the gastrojejunostomy were treated endoscopically. One patient developed a delayed leakage from the gastrojejunostomy.

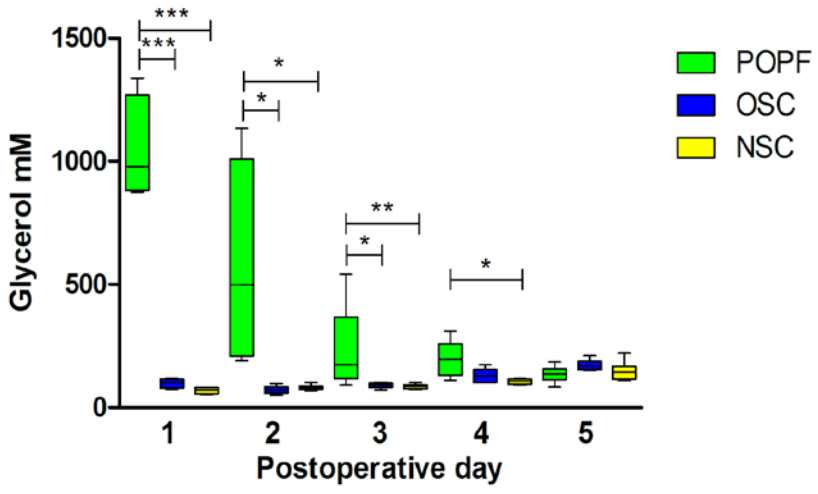


Figure 4. Intraperitoneal glycerol levels for POD 1-5 following PD, grouped by POPF (n=7), other surgical complications (OSC, n=8) and no surgical complications (NSC, n=33). Median (10-90 percentile) of median values for each time-point in each of the groups are presented (line at median), *P<0.05, **P<0.01, ***P<0.001.

The POPF group had higher IP glycerol levels than the OSC (p=0.013) and NSC group (p=0.006, Fig. 1), while there were no differences in IP glycerol levels between OSC and NSC. The POPF group had higher IP L/P ratios than the OSC (p=0.049) and NSC group (p=0.024, Fig. 2), IP L/P ratios were similar in OSC and NSC. The POPF group had a significant increase in IP L/P ratios between POD 1 and 2 (p=0.003). IP lactate levels were higher in POPF compared with OSC (p=0.035) and NSC (p=0.015). IP glucose levels were lower in POPF than in OSC (p=0.014) and NSC (p=0.001). There were no differences in IP lactate and glucose levels between OSC and NSC. All groups had higher pyruvate levels on POD 1 than on POD 2 (p< 0.001). IP pyruvate levels did not differ between the groups.

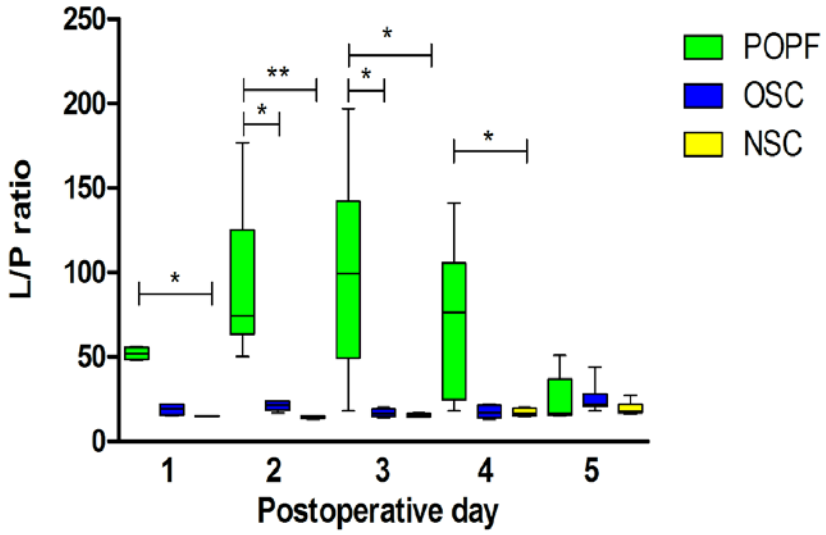


Figure 5. IP lactate / pyruvate (L/P) ratio for POD 1-5 following PD, grouped by POPF (n=7), other surgical complications (OSC, n=8) and no surgical complications (NSC, n=33). *P<0.05, **P<0.01.

TAP and/or CAPAP were detected in microdialysates in six of seven patients with POPF. All patients had similar TAP levels regardless of the CDC grade. In 6 of 8 OSC patients, TAP was below 0.1 µg/L. In 31 of 33 NSC patients, TAP was below 0.1 µg/L on POD 1-2 (table 15). Systemic lactate or glucose levels did not differ between groups or PODs. IP lactate levels were significantly higher than systemic levels on POD 1-5 ($p<0.001$, Fig. 3). Systemic glucose concentrations were significantly higher than IP levels in the POPF group ($p< 0.001$).

Table 15. Intraperitoneal (IP) TAP and plasma pancreatic amylase (PPA). OSC (other surgical complications), NSC (no surgical complications).

	Total (n=48)	POPF (n=7)	OSC (n=8)	NSC (n=33)
IP TAP (µg/L) POD1	1.49 ± 8.24	11.18 ± 22.22	0.30 ± 0.78	0.001 ± 0.03
IP TAP (µg/L) POD2	1.12 ± 6.23	8.63 ± 16.73	0.08 ± 0.25	0.002 ± 0.01
PPA (µkat/L) POD1	2.02 ± 3.30	5.21 ± 5.96	1.55 ± 2.73	1.44 ± 2.22
PPA (µkat/L) POD2	1.19 ± 2.02	2.44 ± 2.84	0.92 ± 1.87	0.98 ± 1.81

Study II

A total of 110 patients were included in the analysis. There was excellent inter-observer agreement for both PC and PDD assessment in a series of ten consecutive patients (Cohen's $\kappa = 0.86$). Sixty-eight patients (62%) developed postoperative complications and two (2%) died. Surgical morbidity was observed in 48 patients (44%) and pancreaticojejunostomy-associated morbidity (PJAM) in 24 patients (22%). POPF, which occurred in 17 patients (15.5%; 9 ISGPF grade B, 8 grade C), was the most common complication and three-quarters of these patients developed POPF-induced secondary morbidity. Patients with POPF had a significantly higher incidence of severe morbidity than patients with SPPC or other complications (8 of 17 vs 12 of 51; p=0.033). SPPC, the third most common complication (7 patients, 6.4%), was also associated with a high incidence of secondary morbidity (3 of 7 patients).

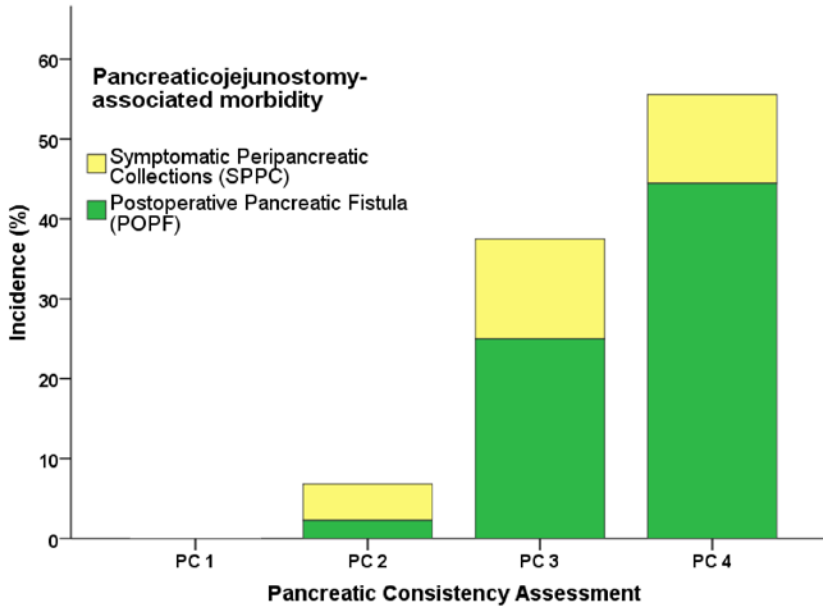


Figure 6. Incidence of pancreaticojejunostomy-associated morbidity according to the various assessment grades of pancreatic consistency (PC) grouped into post-operative pancreatic fistula and symptomatic peripancreatic collections.

POPF occurred in none of 23, one of 44, four of 16 and 12 of 27 patients with grades PC 1, PC 2, PC 3 and PC 4 respectively (p<0.001, fig 1). SPPC occurred in none of 23, two of 44, two of 16 and three of 27 patients with these grades (p=0.070). POPF developed in none of 14, three of 50, ten of 37 and four of nine patients, and SPPC in none of 14, one of 50, five of 37 and one of nine patients, with duct diameter grades PDD 1, PDD 2, PDD 3 and PDD 4 respectively (p<0.001, p=0.034, Fig. 2).

When PC 1 and PC 2 were merged into a 'harder PC' group, and PC 3 and PC 4 into 'softer PC' group, the softer PC group had a significantly higher incidence of POPF (p<0.001) and a higher incidence of SPPC (p=0.071) than the harder PC group. When PDD 1 and PDD 2 were merged into a 'larger PDD' group, and PDD 3 and PDD 4 into a 'smaller PDD' group (duct less than 3 mm), patients with a smaller PDD had a significantly higher incidence of POPF (p<0.001) and SPPC (p=0.015). Softer PC and smaller PDD emerged as risk factors for developing POPF or SPPC. Three different risk groups were defined; a group without risk factors (harder PC/larger PDD), patients with one risk factor (softer PC/larger PDD or harder PC/smaller PDD) merged into one risk group as they had identical risk profiles, and

a group with two risk factors (softer PC/smaller PDD). There were significant differences between the groups regarding the incidence of POPF (p<0.001), SPPC (p=0.019), PJAM (p<0.001) and severe PJAM (p=0.001). Patients with a high-risk pancreatic gland had a 25-fold higher risk of developing associated postoperative morbidity than patients with a low-risk gland. Severe PJAM developed in 20% of patients with two risk factors, in 11% with one risk factor and in 0% without risk factors. All patients with severe PJAM had a PDD smaller than 3 mm. The risk factor groups also had different distributions of histopathology. In patients with a high-risk gland, ductal adenocarcinoma was found in 17%, compared with 37% in intermediate risk patients and 73% in patients with low-risk glands.

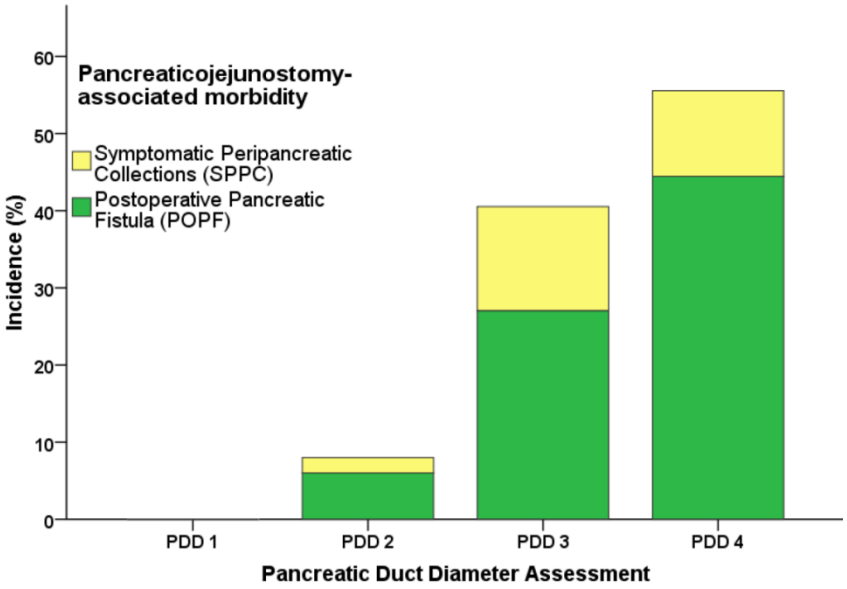


Figure 7. Incidence of pancreaticojejunostomy-associated morbidity according to the various grades of the pancreatic duct diameter (PDD) grouped into POPF and symptomatic peri-pancreatic collections (SPPC).

Table 16. Postoperative risk of pancreaticojejunostomy-associated morbidity. Incidence of postoperative pancreatic fistula (POPF) and symptomatic postoperative peripancreatic collections (SPPC). Patients grouped by presence of risk factors "soft pancreatic consistency" (SPC) or "small pancreatic duct diameter" (SPDD, < 3mm).

	No Risk Factors	One Risk Factor (SPC or SPDD)	Two Risk Factors (SPC and SPDD)	*P*
POPF (B/C) or SPPC	2%	26%	51%	*< 0.001*
Odds ratio (95% CI)	0.025 (0.003 – 0.19)	1.4 (0.43 – 4.2)	12 (4.2 – 35)	
POPF (B/C)	0%	22%	37%	*< 0.001*
Odds ratio (95% CI)		1.7 (0.49-6.0)	10 (3.1-35)	
SPPC n	2%	5%	14%	*0.019*
Odds ratio (95% CI)	0.14 (0.017 – 1.3)	0.79 (0.089 – 6.9)	6.1 (1.1 – 33)	
Severe POPF or SPPC	0%	11%	20%	*0.001*
Odds ratio (95% CI)		1.4 (0.27 – 7.4)	9.1 (1.8 – 47)	

Severe POPF or SPPC is defined as POPF (B/C) or SPPC with a CDC ≥IIIb.

Study III

A total of 195 patients met the inclusion criteria for the analysis. One hundred twenty-six patients developed postoperative complications (total morbidity 65%); 33 of those (17%) were considered to have moderate, and 29 (15%) to have severe morbidity. The in-hospital mortality rate was 3.1%. POPF occurred in 30 patients (15.4%), delayed gastric emptying in 12%, systemic inflammatory response syndrome in 9% and SPPC in 7%. POPF and SPPC together accounted for the major part (22%) of the postoperative morbidity.

The POSSUM algorithm calculated a mean morbidity risk for the study cohort of 62.5% (95% confidence interval 61-65) and a mean mortality risk of 18.2% (95% CI 16.8 – 19.6). P-POSSUM calculated a mean cohort mortality risk of 5.5% (95% CI 4.8 – 6.2). With the observed morbidity of 65% the O/E ratio for the entire study cohort was 1.04. There were no systematic associations between estimated and observed numbers in the risk groups; the O/E ratio decreased with increasing morbidity risk since all risk groups had similar observed morbidity rates (table 5). The individual POSSUM scores did not reveal associations with the occurrence of postoperative morbidity (Mann Whitney, U=4326, p=0.956) or the severity according to the Clavién-Dindo classification (Kruskal-Wallis, p=0.908, Independent median, p=0.964).

Table 17. POSSUM groups, patient distribution, morbidity risk range, estimated and observed morbidity, ratio between observed and estimated morbidity (O/E ratio).

		Morbidity		
POSSUM Groups	N	Estimated	Observed	O/E ratio
Standard risk				
1 (0-19%)	0	0	0	-
2 (20-39%)	19	6 (4-7)	14 (74%)	2.33
3 (40-59%)	56	28 (22-33)	33 (59%)	1.18
4 (60-79%)	92	64 (55-72)	58 (63%)	0.91
5 (80-99%)	28	25 (22-27)	21 (75%)	0.84
Equal quintiles				
1 (0-48%)	38	9 (0-18)	23 (61%)	2.55
2 (49-59%)	37	20 (18-22)	24 (65%)	1.2
3 (60-69%)	41	26 (25-28)	29 (71%)	1.12
4 (70-75%)	32	23 (22-24)	21 (66%)	0.91
5 (76-99%)	47	41 (36-47)	29 (62%)	0.71
Split cohort				
Low-risk (0-59%)	75	22 (0-44)	47 (63%)	2.14
High-risk (60-99%)	120	95 (72-119)	79 (66%)	0.83

N displays number of patients assigned to the risk groups, 'Estimated' displays number of patients with median estimated morbidity, group dispersion in parentheses. 'Observed' displays number of patients with observed morbidity, percent of each risk group in parentheses.

The IPRA groups showed significant differences in their morbidity profiles (table 7). The rates of total, moderate and severe morbidity in the high-risk group exceeded the rates in the low-risk group by a factor of 1.6-, 2.0- and 3.1, respectively. Mortality was 6% in the high-risk and 0% in the low-risk group. None of those differences were captured by the POSSUM risk estimates. Unadjusted and POSSUM-adjusted morbidity rates were found to be nearly identical. Patients with high-risk classified pancreatic glands did not have higher POSSUM scores than patients with low-risk pancreatic glands.

Table 18. Outcome parameters, morbidity profiles and POSSUM morbidity estimation in IPRA and POSSUM risk groups.

	POSSUM			Intraoperative pancreatic risk assessment		
	low risk N=75	high risk N=120	*P*	low risk n=98	high risk n=67	*P*
Observed						
Total morbidity	47 (62.7)	79 (65.8)	*ns*	49 (50)	56 (83.6)	*< 0.001*
Mild (DCC II)	23 (30.7)	36 (30)		31 (31.6)	18 (26.9)	
Moderate (DCC IIIa)	14 (18.7)	19 (15.8)	*ns*	12 (12.2)	16 (23.9)	*< 0.001*
Severe (DCC IIIb-IV)	9 (12)	20 (16.7)		8 (8.2)	17 (25.4)	
Mortality (DCC V)	1 (1.3)	5 (4.2)	*ns*	0	4 (6)	*0.015*
Surgical morbidity	29 (38.7)	62 (51.7)	*ns*	29 (29.59)	46 (68.66)	*< 0.001*
POPF[b]	12 (16)	18 (15)	*ns*	0	24 (35.8)	*< 0.001*
SPPC[c]	4 (5.3)	9 (7.5)	*ns*	4 (4.1)	7 (10.4)	*ns*
DGE[d]	4 (5.3)	19 (15.8)	*0.027*	13 (13.3)	6 (9.0)	*ns*
Estimated						
POSSUM (95% CI)	46% (44-48)	73% (71-75)	*< 0.001*	65% (62-68)	59% (55-63)	*ns*
P-POSSUM (95% CI)	2% (2-3)	8% (7-9)	*< 0.001*	6% (5-7)	5% (3-6)	*ns*

Study cohort grouped by POSSUM-estimated morbidity risk into low-risk and high-risk, and grouped by the surgical pancreatic risk assessment into low-risk, intermediate-risk and high-risk. Intermediate-risk data not shown. POSSUM, physiological and operative severity score for the enumeration of morbidity and mortality. Values in parenthesis are percent and, if indicated as range, 95% confidence intervals. DCC, Dindo-Clavién Classification of surgical complications adopted for pancreatic surgery; POPF, Postoperative pancreatic fistula; SPPC, symptomatic postoperative peripancreatic collections; DGE, delayed gastric emptying.

Patients with high-risk glands had no association between the POSSUM SR group estimates and the observed incidence or severity of post-operative morbidity (p=0.782 and 0.486, respectively.). This was exemplified by a stepwise decrease of the O/E ratio concomitantly with increase of estimated morbidity (3.05, 1.67, 1.16 and 0.98, respectively). However, in the low-risk group, associations between the SR groups and the incidence (p=0.44) and severity (p=0.026) of postoperative morbidity could be observed. This was characterized by a more constant O/E ratio in the SR groups (1.69, 0.62, 0.79 and 0.74, respectively).

Table 19. Association between POSSUM morbidity estimation and incidence and severity of total morbidity. Association between the peroperative pancreatic risk assessment (PPRA) risk groups and incidence and severity of total morbidity.

	Total morbidity *P*	Clavién-Dindo *P*
POSSUM risk estimation		
Individual POSSUM score	*0.956*[a]	*0.908*[b]
Standard risk groups	*0.637*[c]	*0.321*[d]
Equal cohort quintiles	*0.950*[c]	*0.601*[d]
Split cohort	*0.653*[c]	*0.319*[d]
PPRA groups	*< 0.001*[c]	*< 0.001*[d]

[a]Mann-Whitney test, [b]Kruskal-Wallis analysis of variance, [c]Regression analysis, [d]Pearson correlation

Study IV

Three hundred-twenty four out of 379 scheduled patients underwent PD (resection rate 86%). Of those, 315 met inclusion criteria and were included in the analysis. Two hundred-four patients (65%) developed postoperative morbidity, 18% considered severe (Clavién-Dindo classification≥ IIIb). Clinically -relevant POPF was the predominant primary morbidity occurring in 15%, and the associated mortality rate was 3.5%. A total of 76 patients developed POPF according to the ISGPF definition. 17 patients with subclinical fistula (grade A, 5.4%) had a median length of hospital stay (14 days) comparable to those without POPF. Out of 59 patients with clinically-relevant POPF (grade B/C, 19%), 11 developed POPF as a complication to another surgical morbidity. Of 23 patients with severe POPF (grade C, 7%), 7 were treated conservatively and 17 patients (5%) required a CP. Mortality in this latter group exceeded cohort mortality by a factor of 10.

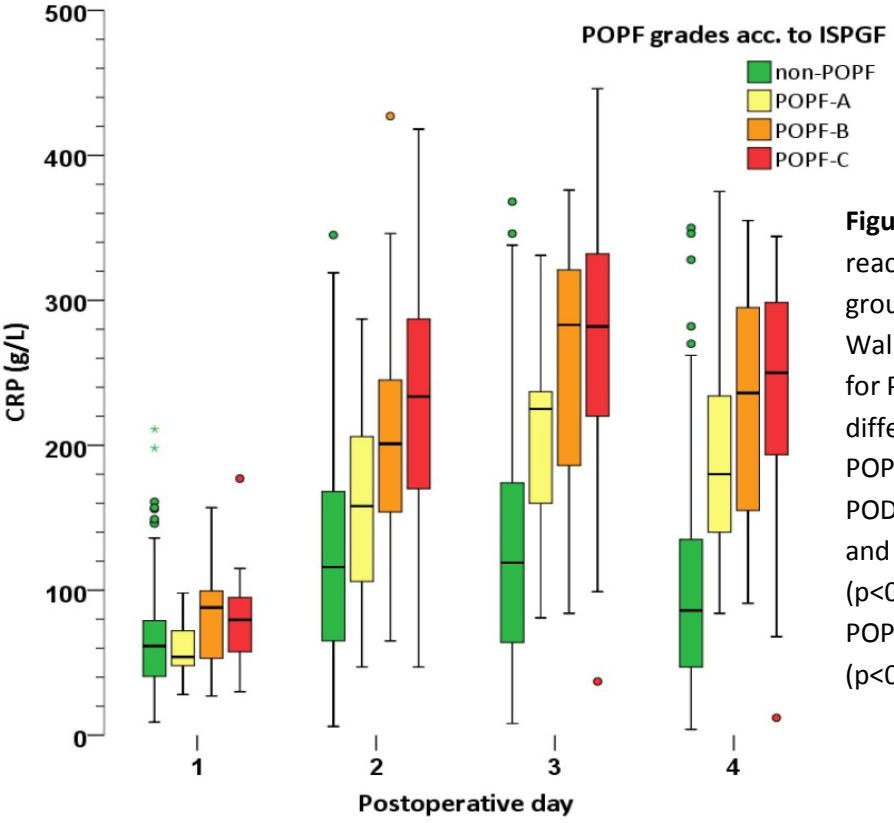


Figure 8. Levels of C-reactive protein POD 1-4, grouped by POPF. Kruskal-Wallis 5-sample calculated for POD1-3. Significant differences between non-POPF and POPF-B/C on POD1 ($p<0.05$), non-POPF and POPF-A on POD3 ($p<0.05$), non-POPF and POPF-B/-C on POD2+3 ($p<0.001$).

For POD1-2, CRP level distributions revealed significant differences between non-POPF and POPF-B and –C, and for POD3 between non-POPF and all POPF groups. In the non-POPF group, the initial increase of CRP levels subsided after the first two postoperative days. Only 7% of patients with declining CRP levels after POD2 developed POPF-B/C, whereas 84.5 % of all patients with POPF-B/C had persistent or increasing CRP levels after POD2. PPA and DPA level distributions showed significant differences between non-POPF and all POPF groups for POD1-3. For the further analysis, subclinical fistulas (POPF-A) were assigned to the control group (non-POPF/POPF-A) and POPF-B/C was selected as dependent variable. Median levels of CRP, PPA and DPA for POD 1-3 differed significantly between non-POPF/POPF-A and POPF-B/C; median CRP in POPF B/C

exceeded median CRP in non-POPF/POPF-A by a factor of 2, median PPA and DPA levels of POPF B/C exceeded non-POPF/POPF-A by a factor of 6 to 62 ($p<0.001$).

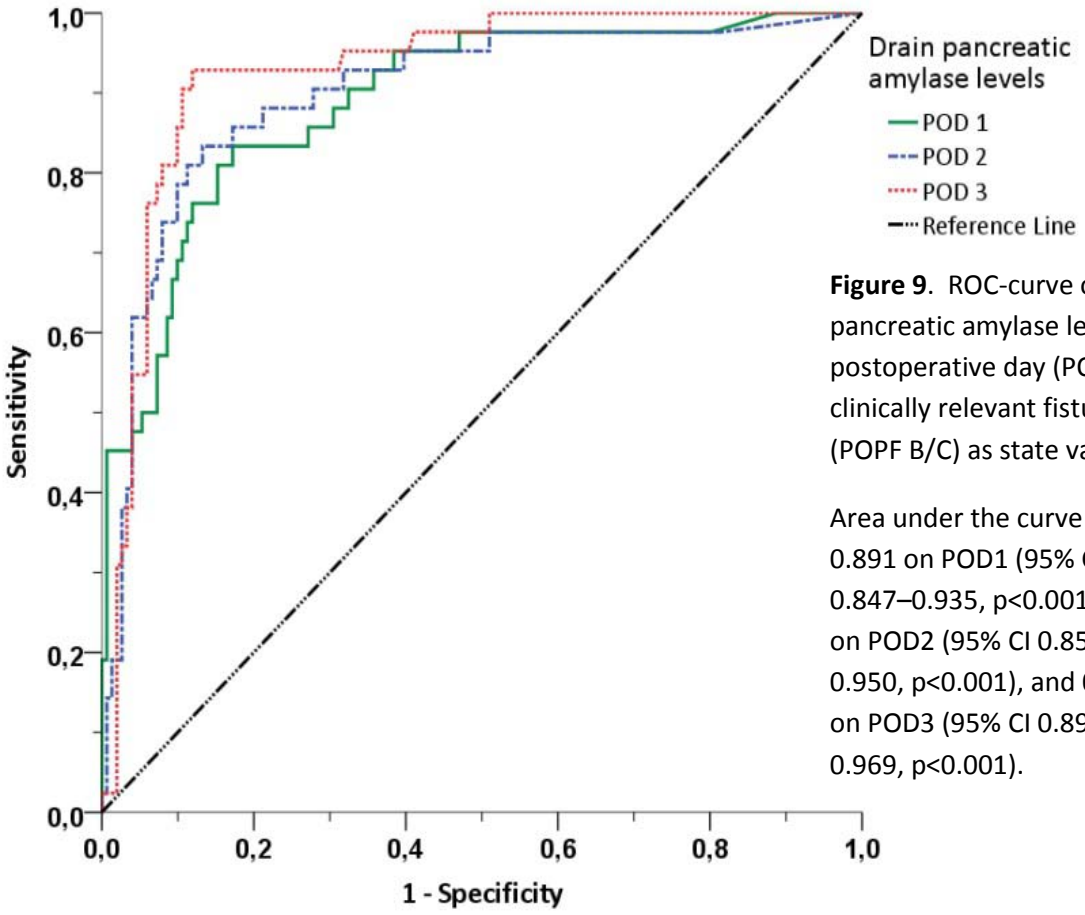


Figure 9. ROC-curve of drain pancreatic amylase levels for postoperative day (POD) 1-3; clinically relevant fistula (POPF B/C) as state variable.

Area under the curve was 0.891 on POD1 (95% CI 0.847–0.935, p<0.001), 0.903 on POD2 (95% CI 0.855–0.950, p<0.001), and 0.933 on POD3 (95% CI 0.897–0.969, p<0.001).

In a receiver operating characteristic (ROC) analysis, CRP-, PPA- and DPA levels for POD 1-3 revealed a high diagnostic accuracy for POPF B/C with an area under the curve (AUC) > 0.8 except CRP_1 (figures 2a-c), and the highest accuracies for the levels of CRP_3, PPA_2, PPA_3, DPA_1 and DPA_2. Since POPF-prediction based on DPA_3 levels could be confounded by the actual POPF definition, DPA3 was excluded from the cut-off analysis. In 21 coordinates of the eight ROC curves the highest balanced accuracy (high sensitivity + high specificity) for POPF-B/C prediction was determined. Cut-off levels were selected for CRP3 at 202 mg/L (sensitivity 77.6%, specificity 83.1%, OR 16.978, 95% CI 8.425-34.213), for PPA_1 at 2.955 µkat/L (177.3 U/L, sensitivity 81.5%, specificity 75.7%, OR 13.671, 95% CI 6.460-28.935), for PPA_2 at 1.625 µkat/L (97.5 U/L, sensitivity 79.7%, specificity 81.2%, OR 16.972, 95% CI 8.328-34.590), for DPA_1 at 18.115 µkat/L (1086.9 U/L, sensitivity 83.6%, specificity 83.5, OR 25.818, 95% CI 11.686-57.039) and at 22.035 µkat/L (1322.1 U/L, sensitivity 80.0%, specificity 86.0%, OR 24.606, 95% CI 11.551-52.416), and for DPA_2 at 5.235 µkat/L (314.1 U/L, sensitivity 87.8%, specificity 83.2%, OR 35.446, 95% CI 14.065-89.331) and at 7.125 µkat/L (427.5 U/L, sensitivity 83.7%, specificity 85.0%, OR 29.042, 95% CI 12.499-67.480). A multivariate regression of the parameters increased the specificity and thereby the accuracy for the POPF-B/C prediction. Four different prediction models were calculated. Model 1, solely based on PPA samples,

identified many non-POPF patients. By stepwise regression, the sensitivity could be increased and the high specificity retained by substituting PPA_1 with CRP_3 (model 2). The DPA model was comparable to PPA_2/CRP_3 regarding the accuracy (88.5%) but had a stronger OR (31.885, 95% CI 13.945-72.906). The inclusion of PPA_1 in the DPA model could not improve accuracy (86.1%), however, the inclusion of CRP_3 (model 4) increased the sensitivity to 80% without impairing the specificity (92%), and by that the accuracy to 90.3% (OR 44, 95% CI 16.889-115.379). The peroperative pancreatic assessment had a lower sensitivity and accuracy in predicting POPF than the selected cut-off levels of PPA, DPA and CRP. In fact, 37 out of 87 patients with high-risk glands developed POPF-B/C, yielding a sensitivity of 42.5% (accuracy 75.8%, OR 8.616, 95% CI 4.314-17.209), and adding intermediate-risk to the high-risk cases, 50 out of 143 patients developed POPF-B/C (sensitivity 35%, accuracy 64.4%). However, in patients with low-risk pancreatic glands the risk of developing POPF was negligible (1 out 121 patients with low-risk classified patients developed POPF, specificity of 99.2%, OR 64.516, 95% CI 8.750-475.713).

Table 20. Multivariate binary logistic regression of plasma pancreatic amylase (PPA), serum C-reactive protein (CRP) or drain pancreatic amylase (DPA) with selected cut-off levels. Different prediction models that describe the risk of developing clinically-relevant POPF following pancreaticoduodenectomy (odds ratio with 95% confidence interval).

	Cut-off level	OR (95% CI)	Sensitivity %	Specificity %	Accuracy %
Model 1: PPA		**13 (6.3-25)**	51	92	81
PPA_1	3.0 µkat/L (177 U/L)	4.0 (1.4-11)			
PPA_2	1.6 µkat/L (98 U/L)	5.3 (2.0-14)			
Model 2: PPA and CRP		**19.0 (9.4-38)**	65	91	86
PPA_2	1.6 µkat/L (98 U/L)	6.7 (3.0-15)			
CRP_3	202 mg/L	7.4 (3.4-16)			
Model 3: DPA		**32 (14-73)**	64	95	88
DPA_1	22 µkat/L (1322 U/L)	6.5 (2.4-17)			
DPA_2	5.2 µkat/L (314U/L)	11 (3.8-33)			
Model 4: DPA and CRP		**44 (17-115)**	79	92	90
DPA_1	22 µkat/L (1322 U/L)	6.6 (2.5-18)			
DPA_2	5.2 µkat/L (314U/L)	6.2 (2.1-18)			
CRP_3	202 mg/L	6.3 (2.5-16)			

Accuracy indicates % of correctly predicted cases. Subscript numbers specify the postoperative day when the sample is obtained.

V DISCUSSION

The aims of this thesis were to elucidate the contributing factors and early diagnostic markers of POPF following PD, and to formulate predictive models that might facilitate a more individualized postoperative management of patients undergoing PD. In study I, local metabolite changes and protease activations in the proximity of the PJ were measured using intraperitoneal microdialysis technique. The profile that was seen in patients subsequently developing POPF (a combination of high glycerol, high L/P ratio and low glucose) was clearly distinct from the profile seen in patients with a normal postoperative course. In study II, a structured pancreatic assessment was proposed that provided a practical way to obtain good estimates of the risk of POPF or associated morbidity following PD. In study III, the capability of a generally applicable risk estimation model (POSSUM) in predicting incidence and severity of PD-associated morbidity was compared to that of the intraoperative pancreatic risk assessment model proposed in study II. The results demonstrated that POPF-associated risk factors assessed by the procedure-specific pancreatic model had stronger impacts on overall postoperative morbidity than the risk factors incorporated in POSSUM. In study IV, the data could prove drain pancreatic amylase at selected cut-off levels to be a superior diagnostic marker than plasma pancreatic amylase regarding the prediction of clinically relevant POPF following PD. A model combing drain pancreatic amylase (> 22 µkat/L or 1322 U/L on POD 1 and >5.2 µkat/L or 314 U/L on POD 2) and C-reactive protein (>202 mg/L on POD 3) had the highest POPF-predictive value.

ISGPF definition

The establishment of an internationally accepted definition of POPF provided by the ISGPF has been one of the major advances in POPF research. Multiple studies discuss postoperative pancreatic morbidity using the term “clinically relevant” fistula, which comprises ISGPF grades B and C, and excludes A-grade fistulae (Bassi *et al.*, 2005a). In study II, it could be observed that ISGPF-defined clinically relevant POPF and clinically relevant peripancreatic fluid collections (not covered by the ISGPF definition) had similar associations with the discussed risk factors. This suggests an interrelationship between these differently defined morbidities at some level and a potential to enhance the sensitivity for the capture of relevant postoperative morbidity data, but the exact details of this have to be clarified.

The general acceptance of the ISGPF definition has facilitated communication between pancreatic researchers. However, reviewing the recent literature, uncertainties in the usage of the definition may have contributed to some confusion. A more recent paper co-authored by one the ISGPF authors defined POPF as “output rich in amylase content confirmed by fistulography, stadiation by ISGPF” (Molinari *et al.*, 2007) which is not consistent with the original definition. Reading the original definition carefully it says *“Output via an operatively placed drain (or a subsequently placed, percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content greater than*

3 times the upper normal serum value" (Bassi *et al.*, 2005a). However, multiple studies, among them one of the most systematic POPF reviews in recent literature refers to the ISGPF-definition as *"POPF was defined as failure of healing/sealing of a pancreatic–enteric anastomosis or a parenchymal leak not directly related to an anastomosis with a drain output of any measurable volume of fluid on or after postoperative Day 3 with an amylase content greater than three times the serum amylase activity"* (Ramacciato *et al.*, 2011a). The discrepancy between upper normal serum value being an absolute value (in our institution 1.1 µkat/L or 66 U/L) and serum amylase activity being an individual and time-dependent parameter may produce significant variations in the outcomes of PD and to some extent contribute to confusion in the understanding of the definition.

Intraoperative pancreatic risk assessment

In study II, a simple protocol for intraoperative risk assessment of pancreatic characteristics was demonstrated to have a significant predictive value on the subsequent development of POPF. Significantly higher incidences of general and severe pancreatic morbidity following PD were found in patients whose remnant pancreas had the risk factors of softer PC and PDD less than 3 mm. Of the patients with both risk factors, 51% developed associated postoperative morbidity in contrast to 21% with one risk factor and 2% without risk factors. The consistency and duct size assessment and classification into low-risk, intermediate-risk and high-risk glands revealed different relative risks of developing POPF by a factor of 25.

Table 21. Overview over studies investigating pancreatic risk factors for POPF after PD.

Author, study type, patients/year (patients/years)	Type of study, patients/year (patients/years), POPF definition	Pancreatic risk factors			
		PC classification	*p*	PDD classification	*p*
(Choe *et al.*, 2008)	R, 17 (172/10), POD 7	no	*0.392*	non-dil./dil.	*0.001*
(Pratt *et al.*, 2008a)	P, 42 (233/5.5), ISGPF	soft/hard	*0.001*	1 mm decrease	*0.011*
(Liang *et al.*, 2007)	R, 50 (100/2), ISGPF	soft/hard	*0.017*	3.4mm/ 5.8mm	*<0.001*
(Poon *et al.*, 2007)	P, 20 (120/6), POD 3	no	*0.084*	≤3mm/ >3mm	*0.032*
(Yang *et al.*, 2005)	R, 15 (62/4), POD 3	soft/hard	*0.004*	<3mm/ ≥3mm	*0.002*
(Okabayashi *et al.*, 2007)	R, 3 (50/15), other	non-fibr/fibr	*0.01*	no	*0.14*
(DeOliveira *et al.*, 2006)	R, 253 (633/2,5), POD 10	soft/hard	*0.005*	no	-
(Lin *et al.*, 2004)	R, 12 (235/20), POD 10	soft/mod/hard	*<0.001*	no	-

R, retrospective; P, prospective; POD, postoperative day; PC, pancreatic consistency; PDD, pancreatic duct diameter; fibr, fibrotic. POD 7 (Yeo *et al.*, 1997b); ISGPF (Bassi *et al.*, 2005a); POD 3 (Buchler *et al.*, 1992); POD 10 (Yeo *et al.*, 1995).

Both characteristics, softer PC and smaller PDD, have been recognized as significant POPF risk factors by numerous previous reports (Pratt *et al.*, 2008a; Liang *et al.*, 2007); however, previous results are difficult to summarize due to the mixed use of endpoint definitions (Bassi *et al.*, 2005a; Yeo *et al.*, 1997b; Yeo *et al.*, 1995; Buchler *et al.*, 1992) as shown in table 8. Other problems are small study inclusion numbers per year (Lin *et al.*, 2004; Liang *et al.*, 2007; Okabayashi *et al.*, 2007; Choe *et al.*, 2008), retrospectively collected material from an extended time period, lack of standardized surgical protocols for the study cohort, several resection or reconstruction techniques (Lin *et al.*, 2004; Liang *et al.*, 2007; Okabayashi *et al.*, 2007; Yang *et al.*, 2005; Poon *et al.*, 2007) or incomplete pancreatic characteristics data sets (Lin *et al.*, 2004; Choe *et al.*, 2008). Study II used standardized protocols, added clinically relevant parameters to the established endpoint definitions and proposed different pancreatic risk profiles that allow quantifying the risk of associated postoperative morbidity for each individual case.

The original categorization of the pancreatic consistency and duct assessment to four grades was meant to provide an optimal demarcation between the grades, allowing a nuanced categorization, and resulting in groups comparable in size. It has repeatedly been shown that the surgical consistency assessment and classifications into “soft” or “hard”, despite of its subjectivity, is strongly associated with the histological grades of fibrosis (Reid-Lombardo *et al.*, 2007b; Wellner *et al.*, 2010). The 4-grade scale for the subjective consistency assessment chosen in this study was meant to enforce a nuanced categorical decision-making by the surgeon avoiding an inconclusive “intermediate” category. The grading of the main pancreatic duct was done from a similar point of view based on earlier investigations on normal and dilated duct size (Hadidi, 1983; Hastier *et al.*, 1998). In study II, 17% had one risk factor, either a smaller PDD (10%) with a hard consistency, or a softer PC (7.3%) with a larger PDD. Five patients of this subgroup (21%) developed associated morbidity (4 POPF, 1 SPPC), two patients that both had a harder PC developed severe complications. POPF-prediction based on pancreatic consistency alone would have substantially compromised the prediction sensitivity by missing 22% of all severe complications. All the 9 patients that developed severe pancreatic remnant-associated postoperative morbidity had a smaller PDD, regardless of the consistency.

Limitations of POSSUM

POSSUM was originally designed as a generally applicable ready-to-use risk scoring system for surgical procedures, and also suitable for pancreatic surgery. The intraoperative pancreatic risk assessment proposed in study II is a PD-specific tool for surgical decision making, designed to identify patients with a high risk for POPF, and based on validated and biologically plausible risk factors. POPF has been confirmed by multiple studies to be the predominant factor for postoperative complications following PD. In study III, the predictive impact of the intraoperative pancreatic risk assessment discussed in study II was tested on the same outcome parameters that are used for generally applicable risk adjustment models such as POSSUM. By comparing the morbidity predictions of both models, it was demonstrated that the risk factors incorporated into the intraoperative

pancreatic risk assessment had a significantly stronger predictive impact on the incidence and severity of overall morbidity than the factors incorporated into the POSSUM system.

Also previous studies have raised conceptual issues concerning the predictive value of the POSSUM scoring system for pancreatic procedures. A series of 50 PDs reported morbidity overestimation and risk adjustment failure (Khan *et al.*, 2003), and a series of 241 PDs morbidity underestimation and potential for systematic inaccuracy in predicting complications (Tamijmarane *et al.*, 2008). In a series of 326 pancreatic resections with deviant outcome criteria, a correctly estimated cohort morbidity was observed but over- and underestimation were seen in low-risk and high-risk groups, respectively (Pratt *et al.*, 2008b), whereas in a series of 652 PDs a significant lack of fit was found (de Castro *et al.*, 2009). The results of a recent review of 1734 pancreatic operations suggested that POSSUM overpredicted postoperative morbidity in patients undergoing pancreatic surgery, and both POSSUM and P-POSSUM failed to offer significant predictive value for mortality in pancreatic surgery. This had implications for clinical practice because there appeared to be insufficient evidence to promote the use of POSSUM in pancreatic surgery (Wang *et al.*, 2013). In study III, POSSUM underestimated postoperative morbidity in patients with a high risk for POPF and overestimated morbidity in low-risk patients.

However, the idea behind POSSUM is still relevant. The ambition was to facilitate the assessment of surgical quality, allowing for comparative surgical audits to provide reliable outcome measures, and, in a wider perspective, to promote institutional transparency and a scientific environment in daily clinical practice. In the original report, POSSUM was introduced as a preoperative system "*designed to predict the risk of morbidity or complications"* (Copeland *et al.*, 1991). In a re-publication, POSSUM was described as a "*system developed to allow an assessment of surgical quality that was risk adjusted for the patient's acute and chronic physiological status and for the nature of the operation"* (Copeland, 2002). These statements imply semantic differences in their definitions of POSSUM. In the reviewed literature, "morbidity prediction" and "risk adjustment" are often used synonymously; however, the terms have different origins and meanings. Morbidity prediction has been an objective in medical science and as a term, has also been used by health authorities. However, risk adjustment is a health-economic term that has been developed by insurance companies as an actuarial tool to calibrate payments to health plans or other stakeholders based on the relative health of the at-risk populations (Lodh *et al.*, 2010). Available clinical data are converted into individual risk scores which are then aggregated into overall scores for each insurance plan. Risk adjustment has been developed as a method by which health insurance plans could be compensated based on the underlying health status of the people enrolled, and thereby protected against losing money by covering people with high-cost conditions. Much of the practical knowledge that exists about implementing risk adjustment comes from experience with the US Medicare program (Pope *et al.*, 2000). In practice, individual risk scores, built from data on patient demographics, disability, institutional status, and diagnoses, are used to help determine monthly payments made to plans for each person enrolled in state Medicaid managed care programs. The POSSUM paper proposed an individual O/E ratio as an indicator for surgical performance. This individual ratio has some similarities to the individual risk scores used in health insurances. However, it is difficult to use or interpret in a clinical context. Medical

treatment or monitoring strategies cannot be dosed like payment plans. In contrast to the intraoperative assessment, POSSUM is not an instrument for clinical decision making as it depends also on postoperative data.

Regarding risk adjustment for surgical audit, the use of a "one size fits all" system in a specific clinical context might have certain disadvantages. Some factors included in the score appeared to be limited by imprecise definitions, arbitrarily grouping, or are of questionable relevance. For instance, the routine use of preoperative chest radiographs is not generally accepted and rarely provides evidence to really modify therapy (Munro *et al.*, 1997). The risk scoring adjusted for systolic blood pressures has neither been proven to be predictive of perioperative cardiac events or other morbidities except for systolic pressures greater than 180 mm Hg (Casadei & Abuzeid, 2005). The grouping of hemoglobin or electrolytes levels appears to be irrelevant since chemical derangements are routinely corrected prior to elective or semi-acute surgery. On the other hand, conditions that have been associated with postoperative morbidity such as reduced cognitive function (Brooks-Brunn, 1997), obesity (Archer & Jacobson, 1993; Littleton, 2012), creatinine as a marker of kidney function (Brooks-Brunn, 1997), or albumin, a marker of malnutrition and disease (Goldwasser & Feldman, 1997), have not been incorporated into POSSUM. Moreover, in the operative severity score, the terms "operation" and "procedure" suffer from imprecise definition. The malignancy scores have not proven to represent comprehensive risk factors for postoperative morbidity. Finally, POSSUM outcome criteria do not match current definitions and as a measure for surgical performance, the O/E ratio has not shown to be sufficiently robust in patient samples of smaller sizes. However, the idea behind the POSSUM score continues to be relevant. Centralization of complex surgery needs to be accompanied by an ongoing audit of results (Simunovic *et al.*, 2010). Health care providers who benefit from centralization processes have to adapt to a greater demand of performance transparency and updated treatment standards to be able to provide credibility to buyers. Outcome measurement as a transparent method of quality assessment has become important even from an economic perspective (Birkmeyer & Birkmeyer, 2006), but a comprehensive interpretation of outcomes is dependent on a properly risk-adjusted patient cohort. This necessitates strict definitions, robust statistical processes and the identification of relevant risk factors. The results of the current study indicated that a useful risk adjustment model for pancreatic surgery needs to be procedure-specific, not generally applicable.

Early diagnostic markers of POPF

Local markers of subsequent POPF development

Typically, intermediate- or high-risk classified pancreatic glands are not affected by duct-obstructive processes and have an unimpaired exocrine activity. The early induction and persistence of the pancreatic inflammatory response to surgical trauma in unaffected glands has been demonstrated as a precondition for POPF development (Hashimoto & Ohyanagi, 2002; Raty *et al.*, 2006). Accordingly, postoperatively elevated levels of drain amylase (Shyr *et al.*, 2003; Okabayashi *et al.*, 2007) or CRP (Murakami *et al.*, 2008) have been demonstrated for pancreatic glands with soft PC and non-dilated duct (study II), and a

normal density of acinar cells and corresponding normal exocrine activity (Hamanaka *et al.*, 1996). On the contrary, POPF risk decreased with increasing extent of fibrosis in the pancreatic remnant (Laaninen *et al.*, 2012; Uchida *et al.*, 2002). That tumor-induced alteration of pancreatic parenchyma and duct diameter had protective effects against postoperative morbidity had been noticed already over thirty years ago (Brooks, 1976). A fibrotic firm texture and a dilated pancreatic duct constitute improved conditions for the construction of a duct-to-mucosa anastomosis; in addition, the diffuse parenchymal fibrosis seen after ductal obstruction might decrease pancreatic enzyme production and thereby lower the potential for POPF development (Kloppel *et al.*, 2004). Other histological findings (duodenal/cystic/islet cell pathology) may be associated with a rather unaltered pancreatic gland but should not be considered as independent POPF risk factors (Pratt *et al.*, 2008a).

In study I and IV, consistent with these pathophysiological mechanisms, the pancreatic inflammatory response to the surgical trauma could be monitored by postoperative analyses of local metabolites near the PJ and of pancreatic enzymes in plasma and drains. However, it is unclear whether POPF establishes subsequent to the pancreatic inflammatory response or whether pancreatic inflammation and fistula formation might be concomitantly occurring processes. In study I, the levels of IP glycerol and TAP in microdialysate were initially high and then declined in the POPF group. The local presence of TAP close to the PJ could be a result of an enterokinase-induced trypsinogen activation at the intestinal brush border during the construction of the anastomosis (Rinderknecht, 1993b); alternatively of a premature intra-pancreatic trypsinogen activation, a process that may occur in the early phase of acute pancreatitis (Petersson & Borgstrom, 2006; Gudgeon *et al.*, 1990; Lerch & Gorelick, 2000). The initial high and then rapidly declining glycerol levels could be caused by lipase activity or by cell membrane damage due to pancreatic transection and suturing. The low levels of IP glycerol and TAP measured in patients without POPF suggest a form of pancreatic inflammation to be involved in the early process of fistula formation. TAP concentrations were <0.1 µg/l in 31/33 patients with no surgical complications (NSC), and glycerol levels were below 100 µmol/l in patients with other surgical complications and NSC, similarly to previously reported levels in patients without complications after colorectal surgery (Jansson *et al.*, 2005). Previous investigations in colorectal surgery suggest that IP L/P ratios repeatedly exceeding 20, or an absence of a L/P ratio decline during the first postoperative days, may serve as indicators of visceral ischemia and subsequent anastomotic leakage (Jansson *et al.*, 2004; Matthiessen *et al.*, 2007). In study I, the high IP L/P ratios in the POPF group could imply an impaired supply of glucose, which is the major provider of intracellular pyruvate. As a consequence, an impaired delivery of substrate and oxygen to the tissues shortly after surgery might predispose the subsequent development of POPF.

The importance of drain amylase for the diagnosis of POPF

The definition of POPF is based on the analysis of drain amylase (Bassi *et al.*, 2005a), and the diagnostic importance of drain fluid analyses for POPF has been previously investigated (Facy *et al.*, 2012; Conlon *et al.*, 2001; Molinari *et al.*, 2007; Nissen *et al.*, 2012; Shinchi *et al.*, 2006; Sutcliffe *et al.*, 2012). However, based on the findings of study III, some issues

could be raised concerning previous conclusions on the subject. That a drain amylase (DA) cut-off level > 5000 U/L on POD1 could be used as indicator for POPF development, as proposed in a prospective study of 137 mixed pancreatic resections with ISGPF outcome criteria (Molinari *et al.*, 2007), still needs validation in a PD-cohort (Sutcliffe *et al.*, 2012). Evaluating drain pancreatic amylase (DPA), not DA, the present series could observe associations with POPF at significant lower levels but failed to confirm that one single DPA cut-off level from POD1 distinctly could separate POPF-courses from non-POPF. A retrospective study of 65 mixed pancreatic resections with ISGPF outcome criteria investigated drain lipase levels on POD 3 and 5, which correlated with DA levels, but had a higher sensitivity for POPF than DA (Facy *et al.*, 2012). The current study avoided analyses of DPA samples from POD 3 or later, since the POPF-predictive impact of those analyses could be biased by the ISGPF-defined outcomes. Two cohort studies of 76 and 70 PD patients, respectively, both with ISGPF outcome criteria, showed that the risk of POPF development was excluded and drain removal suggested for DA levels < 100 U/L (Nissen *et al.*, 2012) or DA_1 levels < 350 U/L (Sutcliffe *et al.*, 2012), consistent with the findings of patients with intra-operatively classified low-risk pancreatic glands in the present study. A prospective cohort study of 177 mixed pancreatic resections and ISGPF outcome criteria showed that high rates of subclinical pancreatic fistula worsened the possibility of identifying clinical relevant POPF by analyzing DA postoperatively (Moskovic *et al.*, 2010). Published cut-off levels have to be validated in future studies but the monitoring of DA levels during the initial postoperative course revealed a POPF-predictive potential comparable to other more expensive methods (Ansorge *et al.*, 2012b).

The inherent effects of intraabdominal drainage on the outcome

In several studies the therapeutic value of abdominal drains in pancreatic resections drains has been questioned. The use of drains could increase the incidence of postoperative complications (Conlon *et al.*, 2001) and contribute to the development of infected intra-abdominal fluid collections; early removal could reduce morbidity (Kawai *et al.*, 2006; Bassi *et al.*, 2010). Moreover, the absence of drains in pancreatic resections was not associated with increased risk of abscess, pancreatic or biliary fistula, postoperative interventions, reoperations (Heslin *et al.*, 1998), morbidity or mortality; but with a decreased incidence of DGE and wound infections (Fisher *et al.*, 2011). It was concluded that improvements in image-guided percutaneous drainage techniques allowed for safe post-operative drainage in patients who developed significant abdominal collections (Heslin *et al.*, 1998), and therefore the routine use of abdominal drains was no longer considered mandatory (Conlon *et al.*, 2001). It is difficult to assess whether these conclusions are valid for all POPF risk groups; as most of the study cohorts were heterogeneous in this aspect (Heslin *et al.*, 1998; Conlon *et al.*, 2001; Kawai *et al.*, 2006; Fisher *et al.*, 2011). According to a recent review the evidence regarding the effectiveness of prophylactic drainage after pancreatic surgery was still unclear and a treatment recommendation could not be given (Diener *et al.*, 2011). In the current study, comparison with the results of the peroperative gland assessment emphasized the additional predictive value of the information gained from the drain analyses. Although not systematically investigated in the current study, a certain therapeutic value of abdominal drainage in these patients could not be disregarded. On the other hand, the risk of developing POPF was negligible in patients with intra-

operatively classified low-risk pancreatic glands, and low or even undetectable DPA and PPA levels in this patient group reinforced this conclusion but had no additional diagnostic value. From that perspective and considering that it might be harmful after some days (Heslin *et al.*, 1998; Conlon *et al.*, 2001; Kawai *et al.*, 2006; Bassi *et al.*, 2010; Fisher *et al.*, 2011), prophylactic abdominal drainage following PD could not be recommended for patients with low-risk glands.

Cum hoc non propter hoc

In the past decades, RCTs testing different POPF-preventive approaches have produced discordant results, and observational cohort studies (OCS) have postulated risk factors that later did not materialize as relevant medical advances. The reporting of new risk factors and risk factor scoring systems has increased significantly in recent years. Nationwide databases such as the US NSQIP have facilitated systematic epidemiological and observational risk factor research which has resulted in complex risk factor reports (Parikh *et al.*, 2010b). Indeed, the development of POPF is most likely a complex process, involving not only one single cause but multiple causal processes. However, knowledge of a risk factor does not automatically imply understanding the causation of a process. In other areas of medical research, it has been made clear that observational studies counting or scoring risk factors are important; however, they only initiate a process of fully elucidating pathophysiological causal chains (Kraemer *et al.*, 2001).

Table 22. Terms used to characterize associations.

Risk
Risk factor
Independent risk factor
Causal risk factor
Effect modifier
Mediator
Moderator
Indicator
Correlate

The term “risk factor” was coined by William B. Kannel in a publication of the Framingham Heart Study characterizing a condition that is correlationally, but not necessarily causally associated with an increased risk of disease (Kannel *et al.*, 1961). The definition was rapidly adopted in numerous areas of translational medical research, and the terms “risk factor”, and in particular “independent risk factor”, have facilitated the reporting and publishing of associations. However, their extensive use in POPF research might have resulted in an inflationary risk factor reporting with discordant results and unclear states of evidence. Consequently, the identification of reliable and relevant risk factors might have been hampered, and a focused research on the relevant causes of POPF development might have been delayed. In other research areas, an imprecise use of technical terms in risk research contributed to a certain confusion; more precise terminology would have revealed that most OCS actually evaluated correlates at the lowest level of causality, not risk factors, and by no means independent risk factors or causal factors (Kraemer *et al.*, 2001; Kraemer *et al.*, 1997). Minimal conditions required to establish a causal association between a factor and an outcome have been outlined in Bradford Hill’s Criteria of Causation (Hill, 1965), an accepted concept to evaluate the quality of associations in epidemiological studies. To test the quality of an association between a factor and an outcome, biological plausibility and temporal precedence have to

be confirmed, controlled confounders have to be accurately measured and further adjustment for potential unmeasured confounders has to be assessed.

Due to their study design, OCS evaluating potential risk factors for POPF might be unable to determine the extent of confounding, bias, or chance expected. As a consequence of these assumptions, the subsequent designing of interventions to be tested in RCTs that manipulate correlates, not risk factors, is likely to produce inconclusive results. Regarding the concept of evidence based medicine this consequence might have been particularly problematic as grading systems placing RCTs at the top of a hierarchy might have delivered misleading conclusions in cases where RCTs were insufficient or unnecessary (Howick *et al.*, 2009).

The many deviant results of studies in POPF risk factor research illustrate the need to completely elucidate the causal processes of POPF development. The pancreatic factors that were investigated in this thesis have been validated as risk factors for POPF by multiple studies and reach up to the level of "biologic plausibility" and "experimental evidence" according to the causation concept of Bradford Hill. They constitute essential factors to be considered in the risk adjustment of PD outcome measurement as well as in the stratification of study cohorts for future POPF-preventive clinical trials.

Table 23. Modified Bradford Hill Criteria of Causation. Strength of evidence in observational studies that supports causation (Johnson, 2012).

1	Statistical significance
2	Strength of the association (odds ratio, relative risk)
3	Dose–response relationships
4	Temporal sequence of exposure and outcome
5	Consistency of the association (internal validity)
6	Replication of results (external validity)
7	Biologic plausibility
8	Experimental evidence

VI CONCLUDING REMARKS

Postoperative pancreatic fistula is the predominant morbidity following pancreaticoduodenectomy. Until now, one single condition has been confirmed to fulfill the criteria to be an independent risk factor for POPF development at the level of biological plausibility: the preoperative physiological integrity of the pancreatic gland. An unaffected gland with unimpaired exocrine activity, typically characterized by a soft consistency and a small duct, responds to surgical trauma with a pancreatic inflammatory reaction. This response is monitorable by microdialysis of local metabolite concentrations in the proximity of the remnant pancreas or by analysis of pancreatic amylase levels in intraabdominal drainage.

As a tool of surgical decision making, the intraoperative assessment of pancreatic consistency and pancreatic duct diameter represents a mandatory component in the procedure sequence of pancreaticoduodenectomy, and constitutes a step towards a tailored postoperative patient management. Intraoperatively, the identification of "high risk" characteristics may favor alternative surgical strategies for patients with poor clinical condition in whom POPF would be considered as a life-threatening complication; alternatively, when a primary POPF significantly increases the risk of inducing severe secondary morbidity due to the extension of the surgical procedure performed.

Prophylactic abdominal drainage following pancreaticoduodenectomy is recommended in patients with intermediate or high risk classified pancreatic glands. Postoperatively, drain pancreatic amylase samples in combination with analyses of C-reactive protein can predict the subsequent or concomitant development of clinically relevant pancreatic fistula with high accuracy. The results of this thesis contribute to identifying patients in whom aggressive drainage strategies might be considered in order to prevent the development of severe fistula formation; however, this question should be addressed systematically in prospective randomized and POPF-risk adjusted clinical trials.

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