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ISSUES RELEVANT TO THE ENDOSCOPIC AND SURGICAL
MANAGEMENT OF PANCREATIC CARCINOMA

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To Nazafarin, Dorna, Damon and Ava

“There are no incurable diseases, only the lack of knowledge.”

Avicenna, Persian physician and philosopher (980–1037)

ABSTRACT

Background: A substantial proportion of the patients with pancreatic cancer require palliative decompression of the extrahepatic bile duct obstruction by endoscopic stent insertion. Only 20% of patients with pancreatic cancer are suitable for resection, which is considered to be a high-risk procedure with postoperative pancreatic fistula (PF) formation in a central role. The main objectives of this thesis were divided into two parts: i.e. to determine whether a covered self-expandable metal stent (cSEMS) was preferable to a conventional uncovered self-expandable metal stent (uSEMS) for palliation of jaundice in patients with an unresectable distal malignant biliary obstruction (Study I). The second part addressed factors that may affect the PF formation rate after distal pancreatectomy (DP) (Study II) and pancreaticoduodenectomy (PD) (Study IV) and the alleged PF preventive effect of pancreatic duct stenting (Study III) after DP.

Method and Patients: I: 400 patients with unresectable distal malignant biliary obstruction were enrolled in a randomized controlled trial to compare a cSEMS with a uSEMS. Outcome measures were time to stent failure, survival time and complication rate.

II: In a hypothesis-generating study, 51 consecutive patients undergoing DP were analysed regarding the impact of demographic factors, clinicopathological features and radiological parameters on the risk of developing PF.

III: 58 patients were randomized to either intraoperative pancreatic duct stent insertion (DP+stent) or not to elucidate the effect of the stent on the PF rate after DP.

IV: 182 consecutive patients undergoing PD were recruited to define predictive radiological variables that affected the risk for PF after PD.

Results: I: The median survival time in the palliative patients was short with 116 days and 174 days, respectively, in the covered and uncovered stent group. The first quartile period with a patent stent was 154 days in the cSEMS group and 199 days in those having a uSEMS ($p = 0.326$). Stent migration occurred in 6 cSEMS patients (3%) and in none of the patients in the uncovered group ($p = 0.036$).

II: Pancreatic fistula was diagnosed in 17 (33%) of the DP patients, and it occurred more frequently after hand suturing of the transection area than after the use of a stapler (69.2% vs. 21.1%; OR, 40.4; 95% CI, 3.36–486; $p = 0.004$). The preoperative radiological estimate of the alleged pancreatic remnant indicated that a large volume of the pancreatic remnant was associated with a higher PF risk (57.1% vs. 20.8%; OR, 6.14; 95% CI, 1.14–39.0; $p = 0.035$).

III: Clinically significant PF occurred in 6 DP patients (22.2%) and in 11 (42.3%) DP+stent (OR, 2.57; 95% CI, 0.78–8.48; $p = 0.122$). Operating time and hospital stay were significantly longer in the DP+stent group.

IV: Clinically significant PF were diagnosed in 35 of the 182 (19.2%) PD patients. CT and MRI-based measurements of the volume of the pancreatic remnant predicted the subsequent risk of PF (OR, 3.712, 95% CI: 1.582 - 8.710, $p=0.003$), as did a small duct diameter (OR: 8.459; 95% CI, 3.106–23.04; $P \leq 0.001$). The size of the pancreatic remnant and width of the pancreatic duct maintained their impact on leakage risk also in a multivariate analysis.

Conclusions: cSEMS and uSEMS are equally effective in palliating patients with malignant extrahepatic biliary obstruction, but with a tendency for the former to migrate. Preoperative radiological analyses and estimates of the remnant gland after resection seem to be a useful instrument to predict PF formation after DP as well as PD. Prophylactic pancreatic stent insertion does not reduce PF after a standardized resection of the body and tail of the pancreas.

LIST OF PUBLICATIONS

- I. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study

Eric Kullman, MD, PhD, Farshad Frozanpor, MD, Claes Söderlund, MD, PhD, Stefan Linder, MD, PhD, Per Sandström, MD, PhD, Anna Lindhoff-Larsson, RN, Ervin Toth, MD, PhD, Gert Lindell, MD, PhD, Eduard Jonas, MD, PhD, Jacob Freedman, MD, PhD, Martin Ljungman, MD, Claes Rudberg, MD, PhD, Bo Ohlin, MD, PhD, Rebecka Zacharias, MD, Carl-Eric Leijonmarck, MD, PhD, Kalev Teder, MD, Anders Ringman, MD, Gunnar Persson, MD, PhD, Mehmet Gözen, MD, Olle Eriksson, PhD

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- II. Impact of pancreatic gland volume on fistula formation after pancreatic tail resection

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- III. The effect of prophylactic transpapillary pancreatic stent insertion on clinically significant leakage rate following distal pancreatectomy: Results of a prospective randomized trial

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- IV. Preoperative pancreas CT/MRI characteristics predict fistula rate after pancreaticoduodenectomy

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Submitted.

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LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiology
BMI	Body mass index
CONSORT	Consolidated standards of reporting trials
cSEMS	Covered self-expandable metallic stent
CT	Computed tomography
DGE	Delayed gastric emptying
DP	Distal pancreatectomy
EP	Endoprosthesis
ERCP	Endoscopic retrograde cholangiopancreatography
GI	Gastrointestinal
ISGPF	International study group of pancreatic fistula
MRI	Magnetic resonance imaging
n.s.	Non-/not significant
OR	Odds ratio
PD	Pancreaticoduodenectomy
PDW	Pancreatic duct width
PF	Pancreatic fistula
POD	Postoperative day
PRV	Volume of the pancreatic remnant
PTC	Percutaneous transhepatic cholangiography
RCT	Randomized controlled trial
SEMS	Self-expandable metallic stent
uSEMS	Uncovered self-expandable metallic stent

1 THESIS SUMMARY - MAIN SECTION

Pancreatic ductal adenocarcinoma is presently the fourth leading cause of cancer-related death in the Western world.¹ The most common pancreatic cancer is of epithelial, exocrine cell origin.² The incidence of pancreatic cancer correlates with increasing age with a peak incidence of the disease in the 65–75-year-old age range. The majority of patients with pancreatic cancer are diagnosed with an advanced disease stage, making curative therapy impossible and determining the poor prognosis and the exceedingly high mortality.³

During the past decade there have been significant improvements in the diagnosis and the surgical, as well as endoscopic treatments, along with the development of adjuvant therapeutic regimens. Although improved survival has recently been reported, the results are still far from satisfactory with an overall 5-year survival of about 20% even for patients who undergo resection with a curative intent.⁴

This clinical research project contains basically two parts: one includes a prospective controlled randomized study that addresses issues relevant to palliative treatment of patients with cancers of the perampullary region, most of which are pancreatic cancers (Study I). In that pivotal study the question was addressed of whether covered (cSEMS) or uncovered (uSEMS) biliary metallic stents should be used for the palliation of patients with unresectable cancer.

In the second part, the hypothesis was explored as to whether the volume of the remaining pancreatic gland could adversely affect the risk of developing leakage after a distal pancreatic resection (DP) (Study II), as well as after a pancreaticoduodenectomy (PD) (study IV). The structure and methodology of that clinical research project was based on analyses of the prospective, controlled collection of data captured in a single institution on DP and PD operations, with particular emphasis on the pre- and intraoperative evaluation of the size of the gland as well as the diameter of the main pancreatic duct. This part of the thesis also incorporated a hypothesis-testing RCT (Study III) addressing the preventive effect of pancreatic duct stenting with the objective of decreasing the risk of leakage after resection of the body and tail of the pancreas .

The outcomes of these studies can be summarized as follows:

- cSEMS and uSEMS are equally effective in palliating patients with malignant extrahepatic biliary obstruction, but with a tendency of the former to migrate.
- Preoperative radiological analyses and estimates of the remnant gland volume and duct width seem to be a useful instrument to predict PF formation after DP as well as PD.
- Prophylactic pancreatic stent insertion does not reduce PF after a standardized resection of the body and tail of the pancreas.

2 HISTORICAL PERSPECTIVE

2.1 HISTORY OF THE BILIARY STENT

In the nineteenth century users of the principal dental impression procedure were struggling with significant problems related to the weakness of the material. The London dentist, Charles Stent (1807–1885) improved the plasticity as well as the stability of the material by adding gutta percha, which was used as a denture base. Since the development of this material and basic principle, several pioneers have contributed, together with industrial partners, to the non-surgical techniques to drain and decompress the biliopancreatic duct systems either using the percutaneous transhepatic cholangiography (PTC) approach or through the intraluminal transduodenal pathway using ERCP.

Plastic biliary stents were introduced in 1979 and have been widely used owing to their relatively low cost and ease of placement. The use of the plastic stent has been hampered by early occlusion requiring replacement every 3 to 4 months, stent migration and difficulties to deploy stents with a diameter larger than 10F using standard side-viewing duodenoscopes. As a result of the deficiencies of plastic stents, large-bore self-expanding metallic stents (SEMS) have been developed in the hope of prolonging stent patency and reducing the need for repeat intervention. The Wallstent, a stainless steel SEMS was introduced in 1990 and later the Ultraflex Diamond biliary stent, a nitinol-based SEMS (both from Boston Scientific, Watertown, Mass, USA), were FDA-approved. These latter stents have subsequently dominated the market for SEMSs. Since the launch of these expandable stents, several other biliary SEMSs have been developed, resulting in a reduction of prices and increased usage rates. Another important chapter in the history of stent development was the development of the covered self-expandable metal stent (cSEMS). The underlying idea was to prevent tumour ingrowth by means of the covering sheath. The cSEMS was first developed in 1994 in Japan, with a metallic skeleton bound to a synthetic covering sheath consisting of polyether type polyurethane, silicone or ePTFE.⁵ These stents have subsequently been designed and manufactured to be both biocompatible and resistant to the potentially deleterious effect of bile, gastric juice and pancreatic secretions. During the last decade, several companies that manufacture endoscopic and radiological devices have been involved in marketing an almost ever-lasting array of new stent designs with semi-covered and fully covered devices in addition to their uSEMSs.

The critical question of whether these covered stents really offer an effective barrier against tumour ingrowth remains unanswered.^{5,6} Moreover, additional information is needed regarding the clinically important question of whether there is a downside to these cSEMSs with an elevated tendency to dislodge.⁷

2.2 SURGERY FOR PANCREATIC TUMOURS

Surgery of the pancreas is at least four hundred years old and dates back to the Dutch physiological experimentalist R. de Graaf (1641–1673), who created canine pancreatic fistulas to determine the nature of the pancreatic secretion and initiated early experimental pancreatic surgery.⁸ At the age 23, de Graaf published his study, *De Succo Pancreatico*, in 1664, which attracted much attention.

In the 19th century the lack of technical expertise and knowledge limited pancreatic surgery to basically the evacuation of septic material. Pancreatic surgery was for a long time best characterized as being invariably fatal, given the unavailability of antibiotics and anaesthesiological skills and the primitive state of knowledge of fluid and electrolyte balance. The first successful distal pancreatic resection combined with splenectomy was probably performed by F. Trendelenburg in 1882, but the patient died during the first postoperative day. Alessandro Codivilla made a landmark achievement in pancreatic surgery when in 1898, he performed the first pancreaticoduodenectomy in Imola, Italy, but the patient did not survive the postoperative period. About one week later W. Halsted performed the first successful resection of an ampullary tumour at Johns Hopkins Medical School, Baltimore. Halsted described a local ampullary resection with associated reanastomosis of the pancreatic and bile duct into the duodenum.⁹ What Codivilla and Halsted demonstrated was that pancreatic surgery was feasible, albeit a risky undertaking. The discovery of endocrine tumours in the early twentieth century allowed Mayo and others to operate on patients with less aggressive and advanced lesions, which paved the way for a relatively large increase in pancreatic surgical activities. Accordingly, several case reports by Finney and Mayo described DP in the early twentieth century. Despite these limited pancreatic surgical success rates, the early 20th century tenet of the dominant contemporary European surgeon, Theodor Kocher (1841–1917), seemed most applicable when directed to the subject of pancreatic surgery:

“A surgeon is a doctor who can operate and knows when not to do so.”¹⁰ (Table 1).

Year, Introduced by	Procedure
1862, A. Le Dentu	Aspiration and external drainage of a cyst
1881, N. Bozeman	Excision of a cyst
1882, F. Trendelenburg	Distal pancreatectomy
1882, A. von Winiwarter	Palliative operation for pancreatic carcinoma
1882, K. Gussenbauer	Marsupialization of postnecrotic pseudocyst
1887, A. Socin	Treatment of acute pancreatitis at laparotomy
1888, B. Riedel	Pancreaticoduodenostomy for chronic pancreatitis
1891, A. Mayo Robson	Cholecystectomy for chronic pancreatitis
1894, W. Korte	Conservative surgical approach to acute pancreatitis
1895, T. Kocher	Sphincterotomy for gallstone removal
1898, A. Codivilla	First PD
1898, W.S. Halsted	Transduodenal ampullectomy for ampullary cancer
1902, B. Reynes	Resection of pancreas body for chronic pancreatitis
1903, T. Kocher	Kocherization of the head of the pancreas

Table 1. Historical perspective of the surgical contributions to the therapies for pancreatic disease.

2.3 ADVANCES IN PANCREATIC SURGERY IN THE 20TH CENTURY, WHIPPLE PROCEDURE AND ITS MODIFICATIONS

In February, 1935, A. O. Whipple (1881–1963) et. al. published “The Treatment of Carcinoma of the Ampulla Vateri” and in so doing laid the fundamental groundwork for modern pancreatic surgery.¹¹ The operation that he described was a two-stage procedure that initially involved a gastroenterostomy and a cholecystogastrostomy. Three to four weeks later the second stage was undertaken and included excision of the descending duodenum with a V-shape excision of the pancreatic head and over-sewing of the pancreatic duct. Initially, some dramatic failures occurred, but the procedure was eventually modified through a number of modifications and some revisions of the elaborate procedure are still in use today. The procedure that Whipple performed involved the resection of the stomach, jejunum, duodenum, pancreas and common bile duct. An important issue was the bleeding tendency resulting from obstructive jaundice until discovery and availability of vitamin K about 1939. In 1940 Whipple and his team had gained enough experience and refined the procedure to the extent that they were able to successfully undertake a one-stage pancreaticoduodenectomy. He judged his experience to be substantial and noted that in his initial eight two-stage procedures, the mortality had been 38%, whereas in the subsequent nineteen one-stage procedures, the postoperative mortality decreased slightly to 31%. Additional therapeutic surgical strategies have subsequently continued to evolve and, while successful, have been partly counterbalanced by the remaining low 5-year survival rates (< 5%). The recrudescence of pancreaticoduodenectomy began in the 1980s, when the surgical mortality rates dropped dramatically. The causes behind these improvements in surgical outcomes have been credited to the progress made in the fields of diagnostic imaging, perioperative and postoperative supportive care, and surgical techniques. The development and structuring of tertiary referral centres with a high caseload was also a major contribution to this phenomenon, adding to the low mortality (Table 2).

Year, Introduced by	Procedure
1909, W. Kausch	Two-stage PD
1937, A. Brunschwig	Radical 2-stage PD for carcinoma
1940, A.O. Whipple	One-stage PD
1944, K. Watson	Pylorus-preserving PD
1947, R. Cattel	Palliative lateral pancreaticojejunostomy
1951, G.E. Moora	Superior mesenteric vein resection for pancreatic cancer
1958, C.B. Puestow	Longitudinal pancreaticojejunostomy
1966, W.D. Kelly	Successful pancreatic transplant in human
1973, K. Kawai	Endoscopic papillotomy
1977, J. Najarian	Islet-cell autotransplant in chronic pancreatitis
1978, M. Claasen	ERCP with sphincterotomy and stone removal
1980, H.G. Beger	Duodenal preserving pancreatic resection
1994, M. Gagner	Laparoscopic PD
1996, L.A. Sussman	Laparoscopic distal pancreatectomy

Table 2. Landmark interventions in the management of pancreatic disease in the 20th century

3 SIGNIFICANT CHALLENGES IN PANCREATIC CANCER THERAPY

3.1 THE PROMINENT ROLE OF STENT TECHNOLOGY IN PALLIATIVE TREATMENT OF PATIENTS WITH UNRESECTABLE PANCREATIC CANCER

The median survival time of patients who present with pancreatic cancer has repeatedly been found to be in the vicinity of only 3-4 months with a tumour diameter at presentation of greater than 3 cm compared to 6-7 months in patients with smaller tumours.¹² The median survival has been found to be 5.3 months without hepatic metastases compared to 2.7 months in those with hepatic metastases.¹³ Other factors that may be associated with a reduced survival time include advanced age, poor performance status and exclusion of postoperative chemotherapy.¹⁴ Although “silent tumors” that present with only extrahepatic jaundice have a more favourable prognosis than those with additional symptoms such as pain,⁴ biliary drainage is an important primary goal for palliation in many patients with malignant obstructive jaundice. Jaundice causes major morbidity due to pruritus, hepatocellular dysfunction, cholangitis, coagulopathy and malabsorption.^{15, 16} Furthermore, jaundice remains a contraindication to chemotherapy and radiation. Drainage can be achieved non-surgically, either via PTC or ERCP. Non-operative techniques have the advantage of lower initial procedure-related morbidity and mortality, shorter hospital stay and lower cost. Since its inception in 1980, endoscopic biliary stenting has continued to evolve and is now a well-recognized predominant method of palliation. With experience and standardized equipment, endoscopic biliary drainage can be accomplished safely and successfully in more than 90% of cases.¹⁷ It effectively re-establishes the bile flow and alleviates jaundice and pruritus and improves the quality of life. Compared to open surgical and PTC, it carries an additional advantage of being safely performed in patients with poor performance status, metastatic disease, ascites, advanced age, associated liver cirrhosis and other co-morbidities.¹⁸ Compared to PTC, endoscopic biliary drainage has been shown to have fewer procedure-related complications.¹⁹ On comparing endoscopic drainage and surgical drainage, ERCP-guided drainage is found to have the advantage of initial low morbidity, low mortality and shorter hospital stays at the cost of relatively short-term patency of the stent, with a need for recurrent jaundice and cholangitis encountered in up to 25% of patients, especially in connection with use of a plastic stent.²⁰ In contrast, surgical drainage has the advantage of

long-term patency, up to 10–15% requiring re-intervention, but at the cost of high initial procedure-related morbidity, prolonged hospital stay and higher cost.²¹ To overcome the need for re-interventions with plastic stents, biliary SEMSs have gained popularity in recent decades.²² Plastic stents have been advocated for patients with potentially resectable disease since the patency benefits of SEMS over plastic stents may not be realized in this group of patients. However, this attitude, mainly based on cost analysis and the belief that initial SEMS placement could hinder subsequent Whipple resection, has been challenged and it has been demonstrated that SEMS can be safely removed at surgery.²³ Using SEMS for preoperative drainage could be worthwhile if there is a delay between diagnosis and surgery or for the group who could have neoadjuvant oncological therapy.

3.1.1 Covering of the biliary SEMS

Despite improved patency of SEMSs compared to plastic stents, there is still a need for reintervention in 13% to 44% of cases attributed to stent failure of SEMSs.²⁴⁻²⁷ To better counteract tumour ingrowth in uncovered SEMSs (uSEMSs), covered SEMSs (cSEMSs) were developed by placing a thin non-porous membrane on the inside of the metal mesh. Possible advantages of such a stent design have been addressed in relatively few small clinical studies, and the results have been partly conflicting (Table 3).

3.2 PANCREATIC FISTULA AFTER PANCREATIC SURGERY

Over the last three decades, advances in surgical technique and postoperative management have led to a substantial reduction of postoperative mortality. Although mortality rates have decreased to less than 5% in high-volume centres, postoperative morbidity remains to be a problem and challenge still ranging between 20 and more than 60%. Pancreatic fistula formation is still the Achilles heel of pancreatic surgery and continues to challenge clinicians since it is the main cause of postoperative morbidity and mortality. The fistula rate after DP and PD has been reported to range from 0% to 61% and from 0% to more than 30%, respectively.^{28, 29} PF has been attributed to several factors, such as a fatty, soft, non-calcified, non-fibrotic gland.^{30, 31} In addition, the underlying pathology, e.g. duodenal, ampullary and distal common bile duct lesions, has been shown to increase the risk. Despite this knowledge, the definition

of the details of the risk profile of each individual patient is still an enigma (Tables 4 & 5).

Author (Ref)	Krokidis et al. ³²		Yoon et al. ⁶		Isamaya et al. ⁵		Park et al. ⁷	
	cSEMS	uSEMS	cSEMS	uSEMS	cSEMS	cSEMS	cSEMS	cSEMS
Study design	RCT (PTC)		Retrospective		RCT (ERC/PTC)		Retrospective	
No. of patients	40	40	36	41	57	55	98	108
Stent material	Nitinol		Stainless steel		Different stents		Stainless steel	
Migration, no. (%)	3 (7.5)	1 (2.5)	2 (5.6)	1 (2.4)	1 (1.8)	0	6 (6.1)	0
Survival days	247 (N/A)*	203 (N/A)*	392± 60 [†]	308±4 [†]	255 (N/A)*	237 (N/A)*	209 (2– 667)*	207 (2– 917)*
Cholecystitis (%)	0	0	1 (3)	0	2 (4.8)	0	5 (6.1)	1 (1)
Pancreatitis (%)	0	0	0	0	5 (8.8)	1 (1.8)	6 (6.1)	2 (1.9)
Patency time (%)	–	–	83 [‡]	83 [‡]	–	–	92	92
At 1, 3, 6 and 12 months	97.5 92.5 87.6	77.5 69.8 69.8	78 [‡] 67 [‡] 54 [‡]	66 [‡] 54 [‡] 36 [‡]	100 91 74	81 68 55	72 56 47	77 54 37
Patency p-value	0.007		0.73		0.007		0.53	
Follow-up time [§]	192 (104–603)		109 (36–269)		246 (11–1115)		N/A	

Table 3. Previous studies comparing cSEMS and uSEMS.

* Median (IQR) or mean (range)

[†] Mean ± SD

[‡] At 100, 200, 300 or 400 days

[§]Days (range)

Author (year)	Number of patients	Fistula rate (%)	Mortality (%)	Prognostic factors
Lillemoe ³³ (1999)	235	5.0	1.0	None identified
Fahy ³⁴ (2002)	51	26.0	4.0	Trauma, suture closure
Pannegeon ³⁵ (2006)	175	23.0	0	Body transection, no ligation of PD
Thaker ³⁶ (2007)	40	13.0	0	No staple line reinforcement
Lorenz ³⁷ (2007)	46	19.0		None identified
Ridolfini ³⁸ (2007)	64	22.0	1.5	Pancreatic disease, preserving spleen, soft gland, not using octreotide
Sierzega ³⁹ (2007)	132	13.6	1.0	Nutritional risk index < 100
Kleef ⁴⁰ (2007)	302	12.0	2.0	OR time > 480 min / stapler
Olah ⁴¹ (2009)	70	14.3	1.0	None identified

Table 4. Previous studies on morbidity in connection with distal pancreatectomy and alleged risk factors.

Author (year)	Number of patients	Pancreatic fistula rate (%)	Mortality (%)	Prognostic factors
Fischer ⁴² 2006	164	6.1	2.2	None identified
Lee ⁴³ 2007	303	8.0	0	Texture, pathology
Poon ⁴⁴ 2007	120	13.4	3.4	Duct size, no stenting
Shirkhande ⁴⁵ 2008	267	10.1	2.6	Standardized anastomosis
Balzano ⁴⁶ 2008	252	24.8	3.2	None identified
Fernandez ⁴⁷ 2008	108	12.0	0	Pancreatico- gastrostomy
Seldzinki ⁴⁸ 2008	159	3.0	3.7	Pancreatico- gastrostomy
Pratt ⁴⁹ 2008	233	25.7	1.3	Texture, pathology, duct size

Table 5. Previous studies on morbidity in connection with pancreaticoduodenectomy and alleged risk factors.

4 THE AIMS OF THE THESIS

Study I To evaluate the possible advantages of a covered self-expandable metallic stent (cSEMS) compared to an uncovered self-expandable metallic stent (uSEMS) regarding stent patency in the palliative treatment of jaundiced patients with a malignant distal biliary obstruction.

Study II To determine factors that may affect the risk of pancreatic fistula (PF) after distal pancreatectomy (DP).

Study III To test if intraoperative insertion of a transpapillary pancreatic stent prior to DP reduces the risk of postoperative PF.

Study IV To evaluate whether the pancreatic remnant volume (PRV) and main duct width are important determinants of the risk of PF formation after pancreaticoduodenectomy.

5 METHODS

5.1 DEFINITIONS USED IN THIS THESIS

5.1.1 Pancreatic fistula

It has been difficult to compare previous studies on the PF rate due to the absence of a uniformly accepted definition of PF. In a review of studies from 1991 to 2000, 26 different definitions of a PF were identified.⁵⁰ The definition of PF emerging from the working group of ISGPF is the most widely accepted one and has subsequently been used in our studies as in many other published studies over recent years (Table 6). The ISGPF definition was modified in 2006 to allow grading of the severity of PF. Grade A explained the incidence of biochemical leakage defined as any measurable output on, or after, the 3rd postoperative day from an operatively positioned abdominal drain and displaying pancreatic amylase more than 3 times the upper limit normal serum amylase activity. A clinically significant pancreatic fistula is a fistula requiring any therapeutic intervention (grade B) or a fistula with severe clinical sequelae (grade C)(Table 7).²⁹

5.1.2 Delayed gastric emptying (DGE)

We used the ISGPF definition of DGE, which was defined to be present when the nasogastric intubation was maintained for 7 or more days, combined with at least one of the following: vomiting after removal of the nasogastric tube, reinsertion of a nasogastric tube or failure to restore oral feeding.

5.1.3 Postoperative morbidity

Adverse postoperative events were classified according to the Clavian-Dindo classification in Studies III and IV.⁵¹ This classification seems to be an easy and reliable way to record postoperative complications and has been used following pancreatic resection in several recent publications (Table 9).^{52, 53}

In Study I we used the WHO performance status classification to assess patients with unresectable malignant distal biliary obstruction. The American Society of Anesthesiologists (ASA) classification was applied in Study II–IV to assess patients' preoperative performance status (Table 8).⁵⁴

5.1.4 Post-ERCP complications

Complications of ERCP were defined according to the criteria presented by Cotton et al.⁵⁷ Post-ERCP pancreatitis was defined as new or worsened abdominal pain combined with elevation of s-amylase to more than 3 times the upper limit of normal and prolongation of the post-ERCP hospital stay. Radiological investigations were performed in the majority of patients with suspected mild, moderate or severe post-ERCP pancreatitis mainly to verify such differential diagnoses as perforation. Cholecystitis and perforation were in the majority of the cases verified by CT beside their clinical presentation.

	Description
ISGPF ⁵⁰	Drain output of any volume of amylase-rich fluid (greater than three times the upper normal limit serum amylase activity) on or after postoperative day (POD) 3.
Yeo et al. ⁵⁵	Drain output of greater than 50 mL/day of amylase-rich fluid (greater than three times the serum amylase activity) on or after POD 10 or radiological demonstration of pancreatic anastomosis disruption.
Sarr et al. ⁵⁶	Drain output of greater than 30 mL/day of amylase-rich fluid greater than five times the upper normal limit serum amylase activity on or after POD 5.

Table 6. Most frequently used definitions of PF.

Grade	A	B	C
Clinical conditions	Well	Often well	Ill
Specific treatment*	No	Yes/No	Yes
US/CT	Negative	Neg/Pos	Postive
Persistent drainage†	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to PF	No	No	Possibly yes
Signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/No	Yes/No

Table 7. PF Grading according to the modified ISGPF definition²⁹.

* Partial or TPN, antibiotics, somatostatin analogue and/or minimal invasive drainage.

† After 3 weeks.

ASA class.	Definition
I	Healthy patient
II	Mild systemic disease- no functional limitation
III	Severe systemic disease-definite functional limitation
IV	Severe systemic disease that is a constant threat to life
V	Moribund patient unlikely to survive 24 h with or without operation

Table 8. ASA classification.

Grade	Definition
I	Any deviation from the normal postoperative course without pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than ones allowed for grade I complications. Blood transfusion and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention.
IIIa	Intervention not under general anaesthesia.
IIIb	Intervention under general anaesthesia.
IV	Life-threatening complications. Requiring ICU management.
IVa	Single-organ dysfunction (including dialysis).
IVb	Multiorgan dysfunction.
V	Death of a patient.

Table 9. Postoperative complication grading according to Clavien-Dindo.

5.2 RADIOLOGICAL ANALYSIS

Preoperative CT or MRI was analysed by the same radiologist who was blinded to the postoperative course in Studies II and IV. In Study IV, two radiologists, blinded to the postoperative outcome, did the calculation for PRV and pancreatic duct width (PDW) using preoperative contrast-enhanced multidetector computed tomography (MDCT) and dynamic MRI investigations. The slice thickness was between 3 mm (with a reconstruction interval of 1.5 mm) and 5 mm (with a reconstruction interval of 2.5–5 mm). The PRV was analysed using a Voxar® 3D workstation (Toshiba Medical Visualization Systems, Edinburgh, UK) with 3D segmentation and volume calculation (Figs. 1–3). The caliber-width of the main pancreatic duct was measured at the resection plane. The calculations of PRV and PDW in 36 (Study II) and 157 patients (Study IV) were based on MDCT images and in the remaining patients using MRI images.

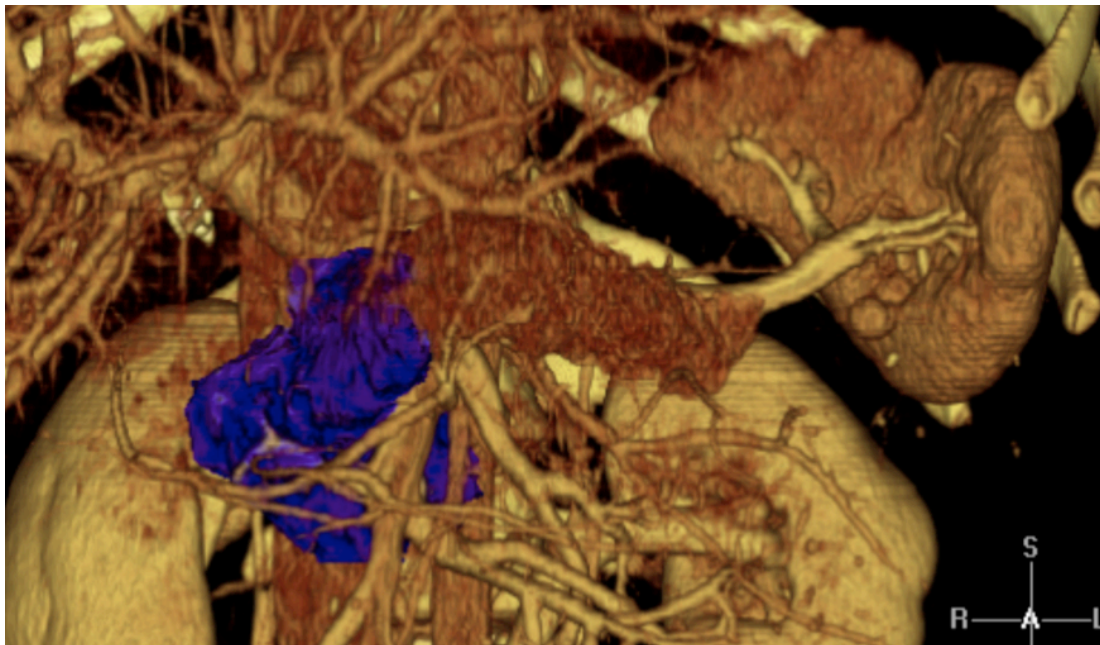


Figure 1. Computed tomography of the pancreas. 3D volume rendering image of the pancreas with the remaining pancreas shown in blue colour.

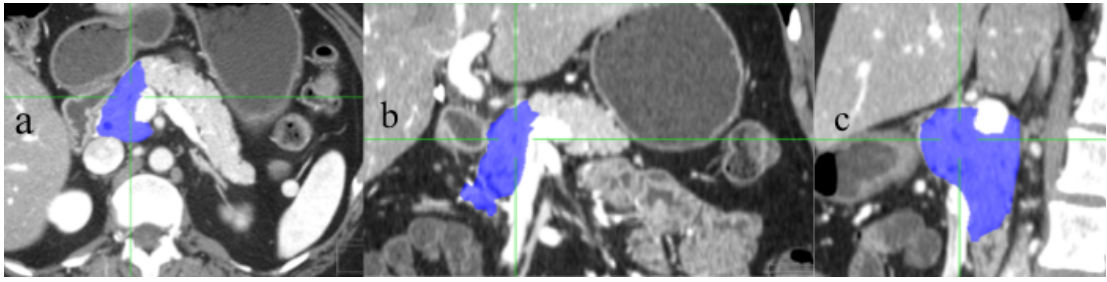


Figure 2. Measurement of the PVR of the head of the pancreas in Study II. Computed tomography of the pancreas showing 3D segmentation and volume calculation (blue color) in (a) transverse, (b) coronal and (c) sagittal images.

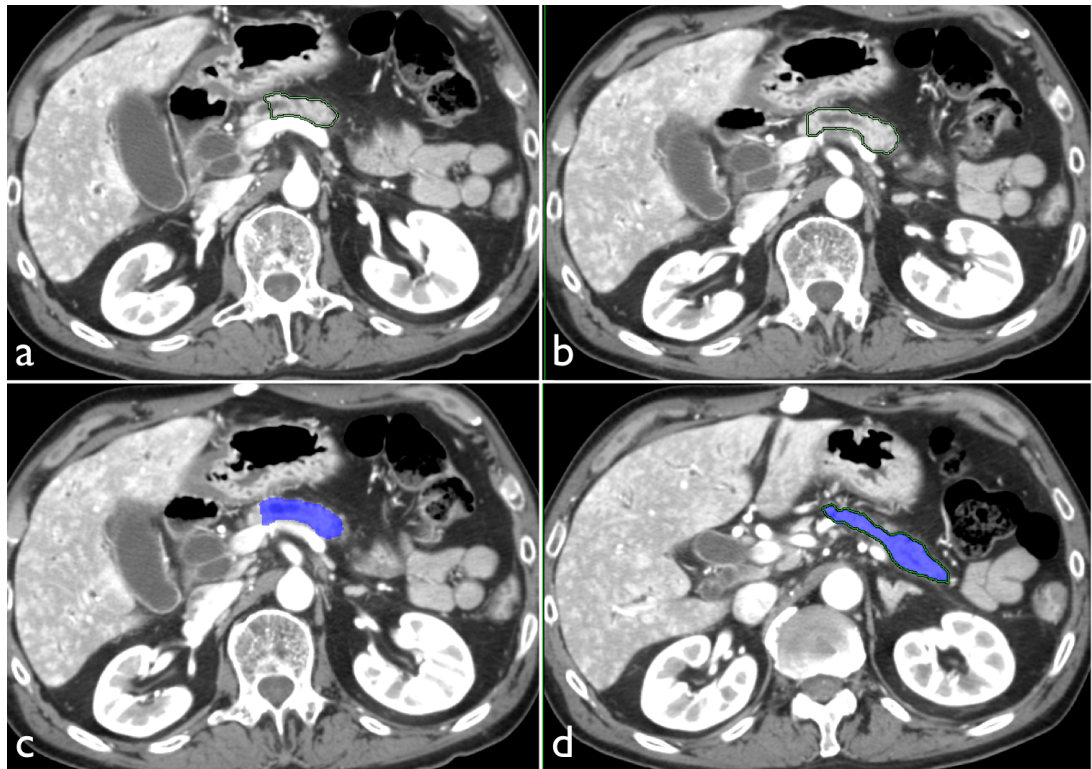


Figure 3. Measurement of PRV of body and tail of the pancreas in Study IV. A preoperative CT examination of the pancreas to measure the volume of the pancreatic remnant after a pancreaticoduodenectomy. Using a semiautomatic segmentation technique, the pancreas can be delineated (green line) first at the level of the alleged resection line (a) and then several sections towards the tail (b). The intermediate sections are automatically bordered (blue area) and have to be checked (c) before continuing segmentation of the caudal remnant (d).

5.3 ENDOSCOPIC, SURGICAL PROCEDURES AND FOLLOW-UP

Study I: This trial compared a polycarbonate-polyurethane covered nitinol stent with an uncovered nitinol metal stent (Nitinella; ELLA-CS, Hradec Kralove, Czech Republic). Fully expanded, the stents reached an inner diameter of 10 mm. When in an adequate position, the stents should be visible from the duodenal lumen. The membrane of the covered stent was placed inside the metal mesh, and only the distal 5 mm of the covered stent was uncovered. The delivery systems for the cSEMSs and uSEMSs were 8F and 7F, respectively. The endoscopist decided which SEMS length to use, being either 52 or 72 mm, depending on the anatomic circumstances and the length of the stenosis. To confirm a successful drainage procedure, liver function tests were performed before and at 2 to 5 days after stent insertion. The criteria for a successful stent insertion included radiological confirmation (at ERCP) that the stent was in an appropriate position and decrease in the bilirubin level during the first 5 days after stent insertion. Clinical follow-ups were performed once a month, starting at 1 month, and the endpoint was 12 months after randomization. Liver function tests were repeated at the 1-month follow-up. At the 2- to 12-month follow-ups, liver function tests were performed only if there had been any history or clinical signs of jaundice, cholangitis or itching during the past month. Patients who were not able to visit the outpatient clinic were contacted (or, when necessary, their caregivers) by a trained study nurse using a standardized questionnaire regarding symptoms recorded at hospices and other primary care facilities, which were evaluated. The study endpoints were an uneventful follow-up for 12 months, death with a patent stent, and confirmed stent failure (ERCP or PTC). However, in a few patients, radiological confirmation of stent failure was not possible, and these patients were considered to have suffered clinical stent failure based on symptoms and liver function test results indicating signs of stent dysfunction.

Studies II–IV: Preoperative management was standardized as far as possible. All patients received broad-spectrum antibiotics (combination cefaloprine type and metronidazole) and octreotide (Sandostatin 100 µg x 3, Novartis Pharm GmbH, Nuremberg, Germany) prior to and during the operation. The abdominal cavity was entered through a midline incision, after which a thorough examination of the peritoneal cavity and the liver followed to exclude metastases. In Study II, patients had the pancreatic neck transected by either a scalpel or by diathermy.

In cases of hand suturing of the resection line, it was closed by a monofilament suture and the suture sizes were USP 4/0 and USP 5/0. The closure of the pancreatic remnant was completed with a separate stitch ligation of the pancreatic duct, followed by a running suture closing the entire pancreatic remnant.

In Study III an endoscopic procedure was incorporated in patients who had been allocated to a DP+stent. To facilitate the insertion of the pancreatic stent, the surgeon applied a soft bowel clamp distal to the ligament of Treitz, which also prevented the distension of the bowel, which would complicate the subsequent surgical procedure. The transection line just above the mesenteric vein was marked to guide the endoscopist during the fluoroscopy in performing a pancreatic sphincterotomy and deploying an appropriate pancreatic stent. A 5 or 7-Fr pancreatic stent was placed depending on the diameter and length of the main pancreatic duct, positioned approximately 1 cm before the transaction line and with a portion of stent through the papilla visible in the duodenal lumen. The DP was performed in a standardized manner by transection of the gland just above the superior mesenteric vein by stapler (TLH 60 Proximate[®], Ethicon, Sommerville, NJ, USA). The pancreatic bed was drained and the fluid was continuously collected postoperatively and analysed daily for pancreatic amylase (Study III). All patients had a follow-up after 4 weeks and patients who received a pancreatic stent were also examined radiologically if the stent remained in the pancreatic duct. If so, it was removed endoscopically 4–8 weeks after surgery.

Study IV: Conventional PD with extended lymph node dissection (except for the lymph nodes to the left of the superior mesenteric artery) was performed in all patients.⁵⁸ The inner layer of the pancreaticojejunostomy was performed end-to-side, using duct-to-mucosa 5-0 or 6-0 sutures (Pronova[®], Ethicon, Somerville, NJ, USA). The outer layer, the remnant pancreatic parenchyma and the seromuscular layer of jejunum were adapted by using 4-0 or 5-0 sutures. Two intra-abdominal drains were inserted; one behind the pancreaticojejunostomy and the other drained the area behind the hepaticojejunostomy. All drain fluids and other collections drained postoperatively were analysed daily for amylase.

5.4 STUDY POPULATIONS

5.4.1 Study I

This study was designed as a multicentre, prospective, randomized controlled trial (RCT) involving 10 ERCP centres and 21 well-experienced endoscopists in Sweden. A total of 400 patients were randomized and enrolled at the 10 sites, 200 patients to the covered group and 200 to the uncovered group, between Januari 2006 and October 2008. A Consolidated Standards of Reporting Trials (CONSORT) flowchart, illustrating the progress of patients throughout the trial is summarized in Figure 4. The study groups were well balanced concerning their demographic and clinical profiles with no important differences emerging.

5.4.2 Study II

In this study a cohort of consecutive patients underwent distal pancreatectomy between March 1999 and December 2007 at the Karolinska University Hospital, Huddinge. During the study period, a total of 51 patients (39 females, 12 males) were included. All data on demographics, clinicopathological features, operative information, complications and in-hospital mortality were collected prospectively in the local pancreatic database. Radiological analyses were based on available CT investigations and preoperative MRI in 36 and 6 patients, respectively. Nine patients were excluded from the analyses due to unclear, extended or curtailed resection lines

5.4.3 Study III

All patients who were scheduled for DP between October 2006 and March 2011 at the Department of Surgery at Karolinska University Hospital were recruited for inclusion in the study. During the study period, a total of 64 patients were considered for DP and subsequently 58 patients were operated on according to the procedure allocated at the randomization. Excluded from inclusion were those in whom a transpapillary cannulation was not technically feasible (e.g. after Roux-en-Y reconstruction, bariatric gastric by-pass) and when the indication for the resection was a trauma. A CONSORT flowchart, illustrating the enrolment and processing of patients throughout the trial, is shown in Figure 5. The study groups were well balanced concerning their demographic and clinical profiles.

5.4.4 Study IV

The study cohort included all patients undergoing PD between September 2007 and November 2010 at the Karolinska University Hospital, Stockholm, Sweden. This database has been collected prospectively according to a standardized protocol and incorporates all pre-/intra- and postoperative information relevant to the management of similar patients. However, the present study protocol excluded patients who underwent extended resection of the pancreas (e.g. leaving only a small remnant close to the splenic hilum), which could compromise the current estimates of the PVR.

Furthermore, we censored the patients who received neoadjuvant chemotherapy prior to PD, given the potential confounding impact on the gland size and function after similar therapies. After censoring 15 patients who received neoadjuvant chemotherapy or extended pancreatectomies, 182 patients (94 males and 88 females), with a mean age of 65.8 years (range 22–87), were eligible for the actual study. The width of the main pancreatic duct was measured at the resection plane. The calculations of PRV and PDW in 157 patients were done using MDCT images and in the remaining patients using MRI images.

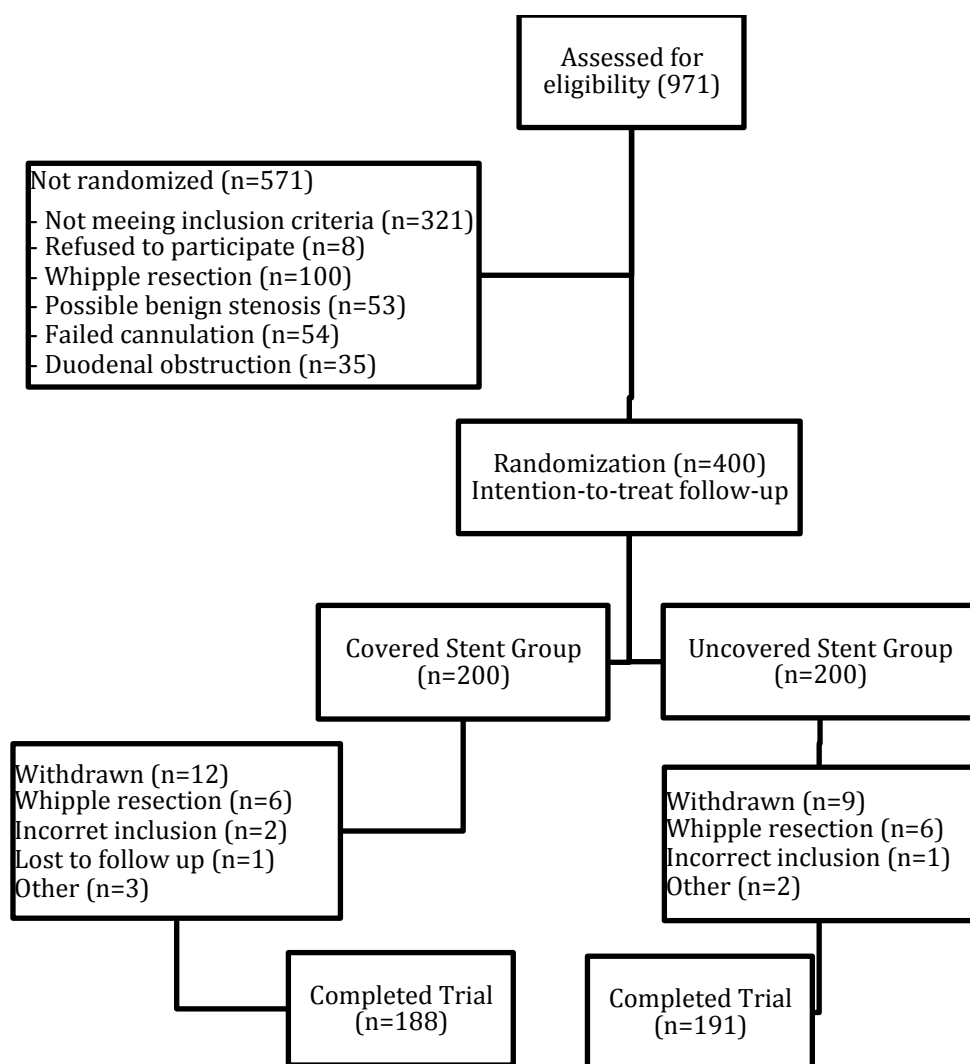


Figure 4. Flow chart study I.

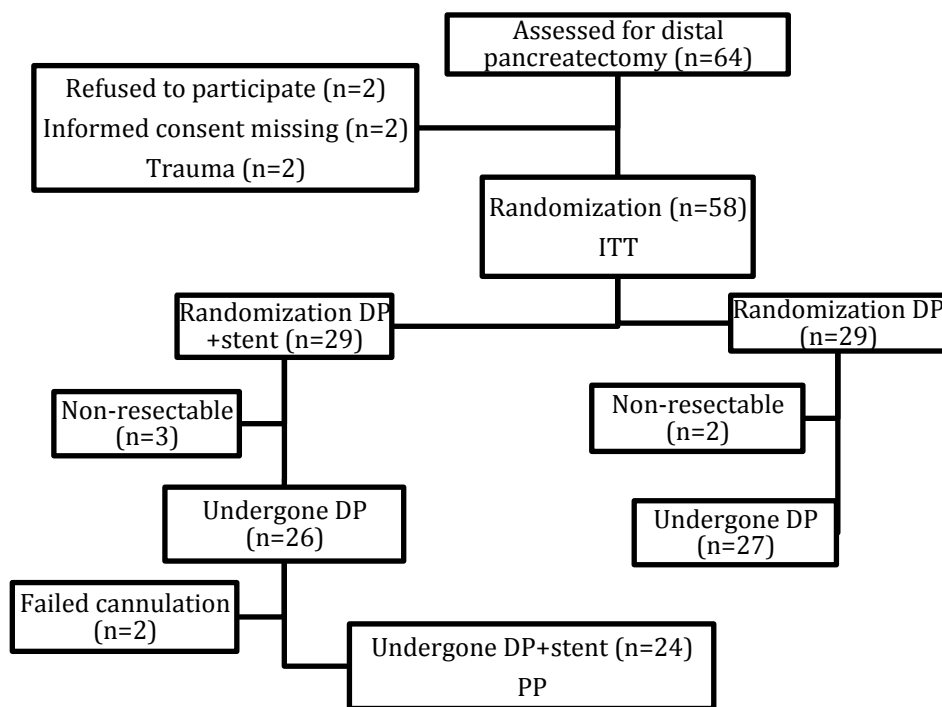


Figure 5. Flowchart, Study III.

5.5 STATISTICAL ANALYSES

The statistical analyses for the studies were performed using SPSS 17.0 or SPSS 19.0 software (SPSS Inc, Chicago, IL, USA). All tests of statistical significance were two-sided, and statistical significance was considered to occur at alpha less than 0.05. In Studies I and III, the principal analytic approach was the intention-to-treat, i.e. to compare those who were initially allocated to the respective therapeutic arm. In Study I stent patency and patient survival time were estimated using the Kaplan-Meier method, and the log-rank test was used to assess differences between the groups on an intention-to-treat basis. Either Fisher's exact test or the χ^2 test was used for comparisons of qualitative data, and continuous numerical data were compared using the Mann-Whitney U test. In Studies II–IV a logistic regression analysis was used to test significance. The associations were presented as odds ratios (OR) with two-sided 95% confidence intervals (CI).

Sample size in Study I was calculated based on a probability of stent failure while the patient was still alive (observed stent failure) of 22% and 10% in uSEMS and cSEMS groups, respectively. With a α -level of 0.05 and a power of 0.90, approximately 360 patients (180 in each group) were required. In Study III the sample size calculation was based on figures reported by Abe et al., who found no detectable PF after insertion of a pancreatic stent compared with our own reported incidence of any PF after DP in non-stented patients in Study II. With a 15% withdrawal rate or failure of stent insertion and a two-sided significance level of 0.05 and a power of 80%, 60 patients (30 in each arm) were required. Finally, in Study IV, based on a cut-off value of 34 cm³ (Study II), and assuming that the proportions of PF were 26% and 10%, respectively, 196 patients would need to be included in the study to detect this difference with a power of 80% and the level of significance set to 5% (two-sided), also with a withdrawal rate of 10%.

5.6 ETHICS

The study protocols conform to the ethical guidelines of the “World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects” adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo in 2004. The Ethics Committee of Southeast Sweden, M86-05, approved the study I protocol. Study I was registered at

Clinicaltrials.gov NCT00280709. The protocol for study III was approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden 2006/256-31 and the trial was registered at Clinicaltrials.gov NCT00500968. Studies I and III were reported according to Consolidated Standards for Reporting Trials (CONSORT), and after completion of the written informed consent form, the patients were randomized to ERCP or surgery using a computer-generated sealed envelope system. Studies II and IV were also approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden, 2009/82-31/3 and 2010/660-31/3.

6 RESULTS AND COMMENTS

6.1 STUDY I

The cSEMS group consisted of 88 males and 112 females with a median age of 79 (range 39–100). The corresponding figures were 91 males and 109 females for those allocated to uSEMS with a median age of 76 (51–95). A plastic stent was inserted prior to the randomization in 29 (15%) and 30 (15%) patients in cSEMS and uSEMS, respectively. A length of 52 mm was chosen for cSEMS in 93 (47%) patients and for uSEMS in 90 (45%), while the remaining patients received a 72mm stent.

In the cSEMS group, 90 patients (45%) had a hepatic and/or other metastases (metastases in lymph nodes, peritoneum and/or other organs) at the time of inclusion. The corresponding number for the uncovered group was 66 patients (33%) ($p = 0.018$). There was no significant difference in the cause of malignant biliary obstruction between the two groups. The most common cause of obstruction was pancreatic cancer, which occurred in 76% in the cSEMS group and 77% in the uSEMS group. Stratification of the disease groups was not done. Histological verification of malignant disease was obtained in 90 patients (45%) in the cSEMS group and 84 patients (42%) in the uSEMS group. In the remaining patients, the diagnoses of malignant disease were based solely on the results of US and/or CT findings, ERCP findings and the clinical course. Twenty-five patients (13%) in the cSEMS group and 27 (14%) in the uSEMS group also underwent MRI.

6.1.1 Patient survival

The median patient survival time was 116 days in the cSEMS stent group and 174 days in the uSEMS stent group ($p = 0.320$). There was no difference between intention-to-treat and per-protocol analyses.

6.1.2 Stent patency

Stent patency revealed no significant differences between the two groups. The first quartile stent patency time, i.e. the day when 25% of the stents had occluded, was 154 days in the cSEMS group and 199 days in the uSEMS group ($p = 0.326$). Stent patency at 1, 3, 6 and 12 months was 95%, 83%, 74% and 50% in the cSEMS group and 97%, 87%, 78%, and 56% in the uSEMS group.

As can be seen in Table 10, the majority of patients with a patent stent in both groups

died within 12 months, and 10% of the patients with a patent stent in the cSEMS group and 15% in the uSEMS group were alive at 12 months. Thus, observed stent occlusion during follow-up in the cSEMS and uSEMS groups occurred in 47 (24%) and 45 patients (23%), respectively. The cause of stent obstruction categorized by tumour overgrowth (above and/or below the stent) was observed in 18 (9%) cSEMS and 10 (5%) uSEMS patients (n.s.), by tumor ingrowth (through the mesh of the stent) in 9 (5%) cSEMS and 21 (11%) uSEMS patients ($p = 0.035$). Stent impaction because of sludge formation was observed in 12 (6%) cSEMS and 4 (2%) uSEMS patients ($p = 0.071$), and this was mainly based on the operator's endoscopic and cholangiographic findings at reintervention (Table 11). Stent migration occurred in 6 patients (3%) in the cSEMS stent group compared to none in the uSEMS group ($p = 0.030$).

6.1.3 Complications

There was no procedure-related mortality. The overall complication rates in the cSEMS and the uSEMS groups were similar, being 7% and 10%, respectively ($p = 0.370$). Acute cholecystitis occurred in 4 patients, 2 (1.1%) in each group. Two of these (in the cSEMS group) underwent cholecystectomy, and the other 2 were successfully treated with percutaneous drainage and lavage of the gallbladder. Post-ERCP pancreatitis developed in 3 patients (1.5%) in the cSEMS group and 4 (2.0%) in the uSEMS group. Four of these, 2 in each group, were classified as mild pancreatitis. The remaining 3 patients, 1 in the cSEMS group and 2 in the uSEMS group, had severe pancreatitis. During follow-up, 20 patients, 8 in the cSEMS group and 12 in the uSEMS group, had clinical symptoms suggestive of cholangitis. These patients responded to antibiotic treatment (orally or intravenously), whereupon liver function tests returned to normal.

	Covered (n=200)	Uncovered (n=200)	<i>p</i> value
Withdrawn, no. (%)	12 (6)	9 (5)	> 0.50
Death within 12 mo with patent stent, no. (%)	122 (61)	116 (58)	> 0.50
Alive at 12 mo with patent stent, no. (%)	19 (10)	30 (15)	> 0.127
Observed stent failure, no. (%)	47 (24)	45 (23)	> 0.50

Table 10. Mortality without stent failure and observed stent failures during follow-up.

	Covered (n=47)	Uncovered (n=45)	<i>p</i> value
Aetiology, no. (%)			
Stent migration	6 (3)	0	0.030
Encrustation (sludge)	12 (6)	4 (2)	0.071
Tumour over- and/or ingrowth	27 (13)	31 (15)	>0.50
Proximal overgrowth	11 (6)	3 (2)	0.053
Distal overgrowth	3 (2)	2 (1)	>0.50
Proximal and distal overgrowth	4 (2)	5 (3)	>0.50
Ingrowth	9 (5)	21 (11)	0.035
Unknown	2 (1)	10 (5)	0.036
Measures taken at stent failure, no.			
ERCP	41	33	
PTC	5	4	
None	1	8	

Table 11. Aetiology and measures taken in patients with observed stent failures.

6.1.4 Comments

This study is by far the largest comparative study conducted in this field. Before now it has been unclear whether cSEMSs offer a more durable and effective biliary drainage than uSEMSs.^{5, 59-61} We were unable to demonstrate a significant difference between uSEMSs and cSEMSs concerning stent patency. As might have been expected, we observed no significant difference regarding median patient survival time, which was 116 days (interquartile range, 242 days) in the cSEMS group and 174 days (interquartile range, 284 days) in the uSEMS group. This is also in accord with results reported by others.^{5, 7, 59-62} The frequency of observed stent failure occurred in the expected range, i.e. 24% and 23% for cSEMSs and uSEMSs, respectively.^{6, 7, 60, 63} It is notoriously difficult in some cases to distinguish between overgrowth, ingrowth and encrustation. In our study, as well as in previous reports, the mechanisms of stent dysfunction are mainly based on cholangiographic findings. Whether the mechanisms causing sludge formation are primarily dislocation and/or overgrowth or de novo formation of sludge similar to the biofilm formation in plastic stents has not been clarified so far.

Although not proven in clinical studies, it has been claimed that cSEMSs might increase the prevalence of cholecystitis and pancreatitis by blocking the cystic duct and the pancreatic duct orifice.^{5, 59, 61, 64, 65, 7, 60, 61} Therefore, another objective of this study was to assess the risk of these complications. We found cholecystitis in two patients (1%) in each group, which should be compared with the 1% to 7% incidence reported by others.^{7, 60, 66-68} Post-ERCP pancreatitis in this study developed in three patients (1.5%) in the cSEMS group and in four patients (2%) in the uSEMS group. Some authors have reported a zero incidence of pancreatitis after cSEMSs.^{6, 66} However, post procedural pancreatitis in our study seems to be of the same magnitude as that reported in the majority of previous studies, i.e. a 2% to 6% incidence of pancreatitis with cSEMSs, but with no significant difference between the two stent designs.^{7, 63, 69} Migration of covered GI stents is a well-known clinical problem,^{70, 71 72} which is usually associated with stent dysfunction. To decrease this risk with cSEMSs, these stents often have a semicovered design with an uncovered portion in the distal and/or proximal end of the stent. Migration of covered biliary stents has been reported to occur in 6% to 12% of cases.^{7, 60, 61, 63}

It may seem that this happens more frequently in stents made of stainless steel than in those made with nitinol. In our total series of 400 patients, migration of cSEMSs occurred in 6 out of 200 (3%) compared with none in the uSEMS group. Although of clinical importance, this did not affect the statistical significance of total stent patency between the two groups. In conclusion, there are no significant differences in patient survival or stent patency time between cSEMSs and uSEMSs in the palliative treatment of malignant distal biliary obstruction. CSEMSs migrated significantly more often than uSEMSs, whereas a trend towards increased tumour ingrowth was seen in uSEMSs.

6.2 STUDY II

A total of 51 patients (39 females, 12 males) with a median age of 59 years had undergone a distal pancreatectomy. The diagnosis was malignant tumour in 22 patients (43.1%) and benign or premalignant conditions in 29 (56.9%) patients. The transection area was closed by means of a stapler in 38 cases (74.5%) and by hand suturing in 13 (25.5%).

6.2.1 Surgical complications

Overall, 21 patients (41.2%) experienced postoperative complications. The most common complication was a pancreatic fistula, which was observed in 17 patients (33.3%). Three of the 7 patients with intra-abdominal abscesses had a local abscess without apparent pancreatic leakage. The occurrence of a pancreatic fistula increased the median length of hospitalization from 11 (range, 6–16 days) to 30 days (range, 14–110 days) ($p = 0.014$).

6.2.2 Risk factor analysis

PF occurred more frequently after hand suturing (9/13, 69.2%) than after the use of a stapler (8/38, 21.1%). At univariate analysis, hand suturing of the transected surface significantly increased the risk of a pancreatic fistula (OR, 8.44; 95% CI, 2.06–34.6; $p = 0.003$). The radiologically measured volume of the remaining gland at or exceeding the median value of 34 cm³ exerted a negative effect on the risk of a pancreatic fistula (OR, 5.07; 95% CI, 1.37–18.8; $p = 0.015$) (Table 12). In the subsequent multivariate analysis, both factors remained independent risk factors for PF (Table 13).

Variable	Fistula (%)	OR (95% CI)	P value
Gender:			
-Female	13/39 (33.3%)	1.0 (0.25–3.95)	1.000
-Male	4/12 (33.3%)	1	
Diagnosis:			
-Malignant	9/22 (40.9%)	1.82 0.56–5.90	0.320
-Benign	8/29 (27.6%)	1	
Resection margin for malignant*			
-R1 resection	3/8 (37.5%)	0.96 (0.16–5.90)	0.965
-R0 resection	5/13 (38.5%)	1	
Closure of transaction area:			
Hand suture	9/13 (69.2%)	8.44 (2.06–34.6)	0.003
Stapler	8/38 (21.1%)	1	
Pancreatic head volume ^{†‡}			
-Greater than or equal to 34 cm ³	12/21 (57.1%)	5.07 (1.37–18.8)	0.015
-Less than 34 cm ³	5/24 (20.8%)	1	
Pancreatic duct diameter [§]			
- Less than or equal to 2 mm	15/39 (38.5%)	1.56 (0.27–9.10)	0.620
- Greater than 2 mm	2/7 (28.6%)	1	
Transection line surface			
-Less than 27 mm ²	8/22 (36.4%)	1.14 (0.34–3.85)	0.829
-Greater than or equal to 27 mm ²	8/24 (33.3%)	1	

Table 12. Univariate analysis of risk factors for pancreatic fistula

* Resection margin was missing in one patient with a malignant diagnosis.

† Cut-off values were defined as the median values.

‡ Six patients were excluded due to an unclear resection line or lack of adequate radiological material.

§ Five patients were excluded due to an unclear resection line or lack of adequate radiological material.

Variable	OR (95% CI)	P value
Hand suture vs stapler	40.4 (3.36–486)	0.004
Pancreatic head volume greater than or equal to 34 cm ³ vs less than 34 cm ³	6.14 (1.14–39.0)	0.035

Table 13. Multivariate logistic regression analysis of variables associated with pancreatic fistula.

6.2.3 Study II: Comments

It has now been demonstrated, beyond any doubt, that DP is a surgical procedure that is followed by severe morbidity, which is very much related to the occurrence and perpetuation of a PF. The development of a fistula results in added burdens on the patient, as measured by more interventions and increased length of the hospital stay. Since many pancreatic resections are done due to malignancy, a fistula often delays or prevents a patient from receiving potentially beneficial adjuvant therapy. Additionally, fistulas are associated with increased health-care costs for each patient.⁷³ The nature of the present analysis and many other studies in the literature did not allow a comprehensive elucidation of issues and consequences related to fistula types A and B.⁷⁴ It is, however, pertinent to assume that abscess formation in close connection to the resection area may also be closely linked to phenomena like these. Accordingly, it is tempting to also include such abscesses in similar risk factor analyses, which in our cases would have further strengthened the association between our two main risk factors (see above) for the development of leakage after DP.

The debate has been quite extensive concerning the surgical technique to be used when sealing/closing the transection area of the gland. The current literature has been carefully surveyed and it was concluded that the quality of the studies which address this question was suboptimal and not adequately powered (Table 4). Thus, the authors concluded that well designed, randomized clinical trials are warranted. This was particularly the case when it came to the question about hand-sewn closure versus the use of staples. In our series we observed a strong association between leakage and the use of a manual suturing technique, whereas others have found the contrary,⁷⁵ again reinforcing the urgent need for a pivotal trial. Recently the DISPACT⁷⁶ trial group presented its results from a multicentre, multi-investigator setting, where a hand-sewn approach was compared to the use of stapler technique. The outcome was clear in that both methods were equivalent with 36% of patients having a pancreatic stump leak. The authors argue that the additional costs of staple devices cannot be justified but still the stapler technique will probably not be abandoned. The stapler technique has obvious advantages and allows a higher degree of standardization. Moreover, it is a prerequisite for the minimally invasive approach

to DP, which constitutes the preferred surgical approach in many institutions. However, this operative approach does not resolve the problem of leakage and the reported morbidity rate is comparable to that of open procedures.⁷⁷ Therefore, it is clear that further attempts have to be made to minimize the risk for PF.

A novel finding of the present study pertained to the plausible and logical association between the size of the remaining gland, as assessed by CT or MRI, and the PF risk. The larger the volume, the more active available gland tissue there is to secrete a digestive juice, which has the potential to exert detrimental effects on the sealed transection area of the gland. We were also unable to detect any impact of some other radiological variables defining the gland, such as the duct diameter, the area of the transected surface and the gross amount of resected tissue that affected the subsequent clinical course. In this context it is interesting to recall the recent observation that dynamic magnetic resonance imaging has been alleged to assess the texture of the gland tissue and thereby to potentially predict the risk of leakage after a Whipple resection.⁷⁸ Signal intensity measurements before and after contrast enhancement might offer a challenging research tool – again to be applied in well-designed clinical trial protocols. If this is combined with volume assessments, a novel and sharp instrument, with an obvious clinical potential, can be defined.

Another extension of this hypothesis-generating study brings attention to mechanisms by which the secreted juice from the remaining pancreatic head can perhaps be diverted away from the area of the sealed transection line. Downstream control by use of a pancreatic stent would be an option, again something which was explored in a subsequent clinical trial (Study III).

6.3 STUDY III

During the study enrolment period, a total of 64 patients were considered for DP and subsequently 58 patients were operated on according to the procedure they were allocated to at randomization. No significant differences between the DP and DP+stent groups were observed regarding relevant demographic and background data.

Splenectomy was carried out in the majority of patients (88.9% in the DP and 96.2% in the DP+stent group). Malignant disease was the underlying histopathology in 18 patients (66.7%) in the DP group compared to 16 (61.5%) in the DP+stent group.

ERCP-related complications occurred in three cases. The main pancreatic duct could not be cannulated in two patients, one of whom developed a grade B PF and one who developed mild pancreatitis and a subsequent grade B PF. There was no relationship between stent size and PF risk. DP with stent deployment increased the operating time to 283.3 ± 131.9 minutes from 218.8 ± 94.1 ($p = 0.052$). Stented patients tended to have a longer hospital stay than those with DP alone (19.4 ± 14.4 days vs. 13.4 ± 6.4 days; $p = 0.071$). At the time of follow-up, 6 stents were found to have passed spontaneously. In total, 10 DP (37.0 %) and 13 DP + stent (50.0%) patients developed PF. Clinically significant PF (grades B and C) was observed in 6 DP (22.2%) and 11 (42.3%) DP+stent patients. Neither of these differences reached statistical significance (Table 14). These results did not change on completing a *per protocol* analysis (Table 15). Ten DP+stent (38.5%) and 4 DP (14.8%) patients with clinically significant PF developed intra-abdominal abscesses (OR, 3.59; 95% CI, 0.96–13.50; $p = 0.058$). However, one patient in the DP+stent group who underwent an additional right-sided hemicolectomy had an abscess diagnosed in the area of the ileocolic anastomosis. An additional DP patient developed an intra-abdominal abscess without any signs of PF. No postoperative mortality was recorded and no difference between the groups was seen regarding overall complication rates (Table 14), despite a trend (OR, 3.23; 95% CI, 0.93–11.20; $p = 0.065$) toward more severe Clavien gradings in the DP+stent group.

Variable	DP n (%)	DP+stent n (%)	OR (95% CI)	<i>p</i>
Fistula				
Grade A	4 (14.8)	3 (11.5%)		
Grade B	6 (22.2%)	9 (34.6%)		
Grade C	0	2 (7.7%)		
Significant PF				
No	21(77.8%)	15 (57.7%)	1	
Yes	6 (22.2%)	11 (42.3%)	2.57 (0.78–8.48)	0.122
Clavien grading				
I–II	22 (81.4%)	14 (57.7%)		
IIIa	4 (14.8%)	9 (34.6%)		
IIIb	1 (3.7%)	2 (7.7%)		
IV	0	0		
Significant complication ≥ Clavien IIIa				
No	22 (81.5%)	5 (18.5%)	1	
Yes	5 (18.5%)	11 (42.3%)	3.23 (0.93–11.20)	0.065
Abscess				
No	22 (81.5%)	15 (57.7%)	1	
Yes	5 (18.5%)	11 (42.3%)	3.227 (0.93–11.2)	0.065
Reoperation				
No	26 (96.3%)	23 (88.5%)	1	
Yes	1 (3.7%)	3 (11.5%)	3.39 (0.33–34.91)	0.305
Mortality	0	0		

Table 14. Postoperative outcomes, ITT analysis

Variable	DP n (%)	DP+stent n (%)	OR (95% CI)	<i>p</i>
Significant PF				
No	21 (71.8%)	14 (58.3%)	1	
Yes	6 (22.2%)	10 (41.7%)	2.50(0.74–8.45)	0.140
Severe complication Clavien ≥ IIIa				
No	22 (81.5%)	14 (58.3%)	1	
Yes	5 (18.5%)	10 (41.7%)	3.72(0.89–11.14)	0.076

Table 15. Postoperative Outcomes, *Per Protocol* Analysis.

6.3.1 Comments

This study was designed to test the hypothesis that relieving the pancreatic juice secretory pressure on the stapled gland transection line with a transpapillary pancreatic stent can reduce the PF rate after DP.^{79, 80} After having completed the enrolment of the preplanned and calculated number of patients, we can conclude that pancreatic stenting does not decrease the risk of PF. Only one non-randomized study compared retrospective cohorts of DP patients and suggested that a pancreatic stent clearly decreased the PF risk.⁸¹ In addition, there is circumstantial information which suggests a potential benefit of stent deployment and ‘downstream control’ in patients with established pancreaticocutaneous fistulas.^{82, 83} The potential for an effect of a transpapillary stent is also supported by the obvious mechanical decompression of the intraductal pressure by the stent,⁸⁴ as well as the prophylactic effect of pancreatic stent placement in order to prevent post-ERCP pancreatitis.⁸⁵ Another rationale behind a potentially beneficial effect of such a stent is that smaller amounts of digestive juice may compromise the healing of the pancreatic transection surface. It can be argued that this rationale is not coherent with the lack of a clear-cut effect of pancreatic secretory inhibition (by somatostatin and its analogues) on the PF rate.⁸⁶ Previous studies have, however, not been designed specifically to address PF after DP. An additional complicating factor is the texture of the gland. In the literature covering pancreaticoduodenectomy, the characteristics of the remnant gland, assessed either at the time of the transection of the gland or after a histomorphological description of the transection surface, have been found to predict the subsequent leakage rates.^{30, 87} Although we did not apply a strict intraoperative protocol to assess the texture of the remnant gland, it can be concluded that the vast majority of our patients presented with a gland pathology compatible with a ‘soft gland’ and only 5 patients (2 in DP vs 3 in DP+stent) were eventually found to have chronic pancreatitis. Although the underlying hypothesis for prophylactic stent placement is attractive, it cannot be ruled out that the circumstances may differ fundamentally in a chronic pancreatic fistula situation, as compared to the present human experimental situation. On operative manipulation, compression and application of staple devices and transection of the gland, acute inflammatory responses are triggered within the remaining tissue. In these situations no therapeutic and/or preventive measures have been found to be effective in preventing progress of the disease process or complications from occurring. On the other hand,

stent deployment and duct manipulation may, through similar mechanisms, even be hazardous.⁸⁸ Apparently, pancreatic stenting was followed by numerically more PFs and other related morbidities than seen in our control DP group.

6.4 STUDY IV

182 patients (94 males and 88 females), with a mean age of 65.8 years (range 22–87), were eligible for the study. The underlying diagnoses were malignant disease in 144 patients (79.1%) and benign or premalignant in 38 (20.9%). A preoperative ASA score of II was recorded in 100 patients (54.9%) and of III in 55 (30.2%). In total, 120 patients (65.9%) experienced some postoperative complication (Table 16) and 63 of these had a complication, which was classified as \geq Clavien 3a. The most common surgical complication was a PF, which was observed in 38 patients (20.9%) and 14 of these patients had a grade C fistula. Eight of 24 patients with intra-abdominal abscesses had no apparent pancreatic leakage (no drainage of amylase-containing fluid). The occurrence of a PF increased the mean length of hospital care from 14.3 ± 7.6 to 30 ± 27.7 days (OR 1.067, 95% CI 1.032–1.103, $p \leq 0.001$). 24 patients required reoperation, 11 of them had a Grade C fistula (OR 4.296, 95% CI 1.735–10.634, $p = 0.002$) and among these, seven patients required additional operations. Other indications for reoperations were bile leakage and early postoperative bleeding. Three patients died on the 9th, 10th and 23rd postoperative day, respectively. Two had PF with uncontrollable haemorrhage and one died suddenly due to a massive myocardial infarction without other signs of a postoperative complication. The mean PRV was calculated to be $36.9 \pm 15.5 \text{ cm}^3$ (Figure 6). Duct width was also measured at the level immediately to the left of the superior mesenteric vein and was found to be $4.6 \pm 3.0 \text{ mm}$ (Figure 7). Corresponding values at the 25th, median and 75th percentiles were 24.9, 35.2 and 46.7 cm^3 for PRV and 2.1, 3.9 and 7.1 mm for PDW.

6.4.1 Risk factor analysis

Logistic regression analyses were performed to identify potential determinant variables, including the estimated PRV and the PDW based on categorical variables as delineated in Table 17. PF occurred significantly more often in the patients harboring a large PRV as well as a small PDW at the level of the estimated resection line. With a PRV in the first quartile, i.e. of 24.9 cm^3 , no patient developed a clinically significant PF, i.e.

ISGPF grade B or C. Similarly, with a calculated PDW of 7.1 mm (75th percentile or larger), only one patient developed a PF (Figures 6 and 7). In the multivariate analyses, a large PRV or a small PDW, both significantly and independently increased the risk for PF. With the ambition to bring everything together into a potentially clinically relevant scoring system, according to the 25th, 50th and 75th percentiles, based on gland volume and duct diameter calculations, such an attempt is displayed in Table 19. When the respective gland-duct characteristics are tentatively divided into four groups, based on the sum of scores, three risk categories can be defined (low risk ≤ 1 to a high risk of ≥ 4). Hence, a similar preoperative scoring system could define the risk of PF to be 38.5% if the sum was ≥ 4 compared to 0% if the corresponding figure was ≤ 1 ($p < 0.001$).

Outcome	Number (%)	
Clavien 0	4	(2.2)
Clavien 1	58	(31.9)
Clavien 2	57	(31.3)
Clavien 3a	32	(17.6)
Clavien 3b	15	(8.2)
Clavien 4a	9	(4.9)
Clavien 4b	4	(2.2)
Clavien 5	3	(1.6)
Complication		
Pancreatic fistula (PF)	38	(20.9)
ISGPF A	3	(1.6)
ISGPF B	21	(11.5)
ISGPF C	14	(7.7)
Abscess	24	(13.2) 8 without PF
Intra-abdominal bleeding	13	(7.1) 5 without PF
GI bleeding	6	(3.1) 5 without PF
DGE	16	(8.8) 14 without PF
Bile leakage	8	(4.4) 5 without PF
Lymph leakage	6	(3.3) 6 without PF
Sepsis	4	(2.2) 2 without PF
Pulmonary embolism	3	(1.7) 3 without PF
Reoperation	24	(13.2) 13 without PF

Table 16. Postoperative complications and PF formation after PD.

Variable	No. of PF	Univariate analysis			Multivariate analysis		
		OR	(95% CI)	<i>p</i>	OR	(95% CI)	<i>P</i>
*PRV cm ³							
< 35.2	8/75 (9.4%)	1		0.003	1		0.017
≥ 35.2	27/97 (27.8%)	3.71	1.58-8.71		3.80	1.27-11.40	
*PDW mm							
< 3.9	30/91 (33.3%)	8.459	3.106-23.04	0.001	6.807	2.334-19.850	0.001
≥ 3.9	5/91 (5.5%)	1			1		
-Female	11/88 (11.4%)	0.487	0.226-1.052	0.067	0.516	0.212-1.256	0.145
-Male	22/94 (23.4%)	1					
Malignant	23/144 (16.0%)	0.612	0.256-1.463	0.270	1.003	0.344-2.923	0.656
Benign	9/38 (23.7%)	1	1		1		
R1 resection	11/77 (14.3%)	0.667	0.300-1.480	0.319	0.96	0.338-2.428	0.845
Smoking	5/35 (14.3%)	0.741	0.263-2.085	0.570	0.154	0.523-4.561	0.432
Diabetes	2/26 (7.7%)	0.350	0.078-1.563	0.169	1.956	0.346-11.05	0.443
ASA ≥ 3	9/62 (14.5%)	1.716	0.309-1.659	0.436	1.956	0.519-3.389	0.556
BMI							
20–30	29/152 (19.1%)	1	1		1		
< 20	2/16 (18.8%)	0.648	0.140–3.001	0.648	0.473	0.030–7.502	0.473
> 30	1/14 (7.1%)	0.340	0.043–2.697	0.340	1.124	0.118–10.69	0.919
Age	Continuous	0.973	0.938-1.009	0.146	1.033	0.976-1.093	0.265
Intraop. blood loss	Continuous	1.000	1.000-1.000	0.861	1.000	1.000-1.001	0.319
Operating time	Continuous	1.000	0.999-1.001	0.565	1.000	0.997-1.002	0.762

Table 17. Uni- and multivariate analyses of risk factors for grade B & C pancreatic fistula formation.

* Cut off at median value

*PRV, cm ³	<25 = 0	25-35 = 1	35.1-47 = 2	>47 = 3
*PDW, mm	>7 = 0	4.1-7 = 1	2-4 = 2	<2 = 3
Scoring (PRV + PDW)	Low risk	Intermediate risk		High risk
	0–1 point	2–3 points		≥4 points

Variable	No. clinically significant PF	<i>P</i> value
Low risk	0/49 (0%)	
Intermediate risk	5/55 (14.3%)	≤0.001
High risk	30/78 (38.5%)	≤0.001

Table 18. Pancreatic fistula risk calculation based on preoperative CT/MRI assessments (the 25th, 50th and 75th percentiles) of the pancreatic gland.

* Cut off median value

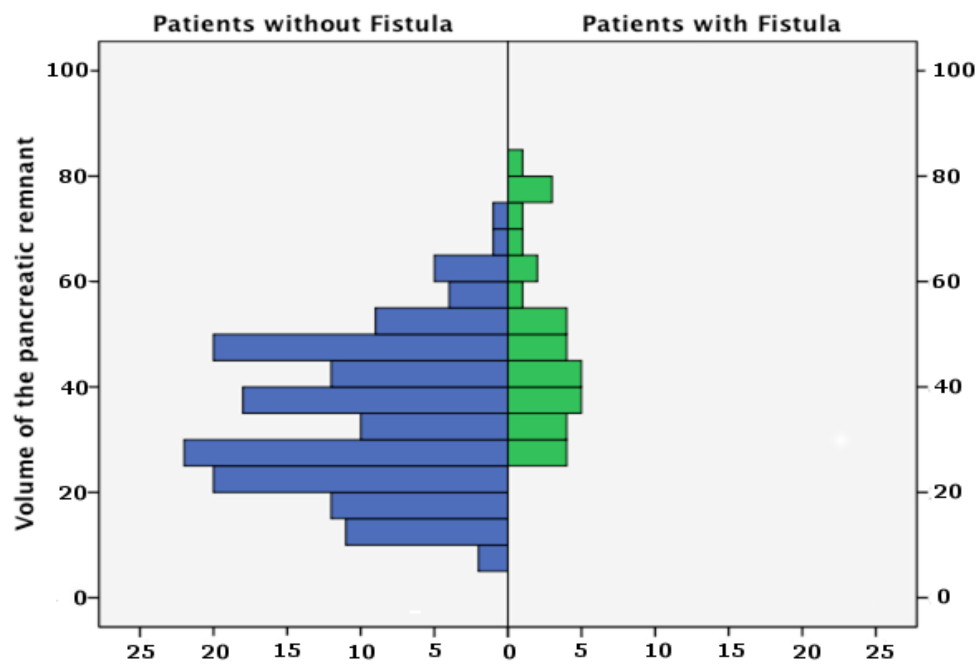


Figure 6. Frequency of PF at different PRVs.

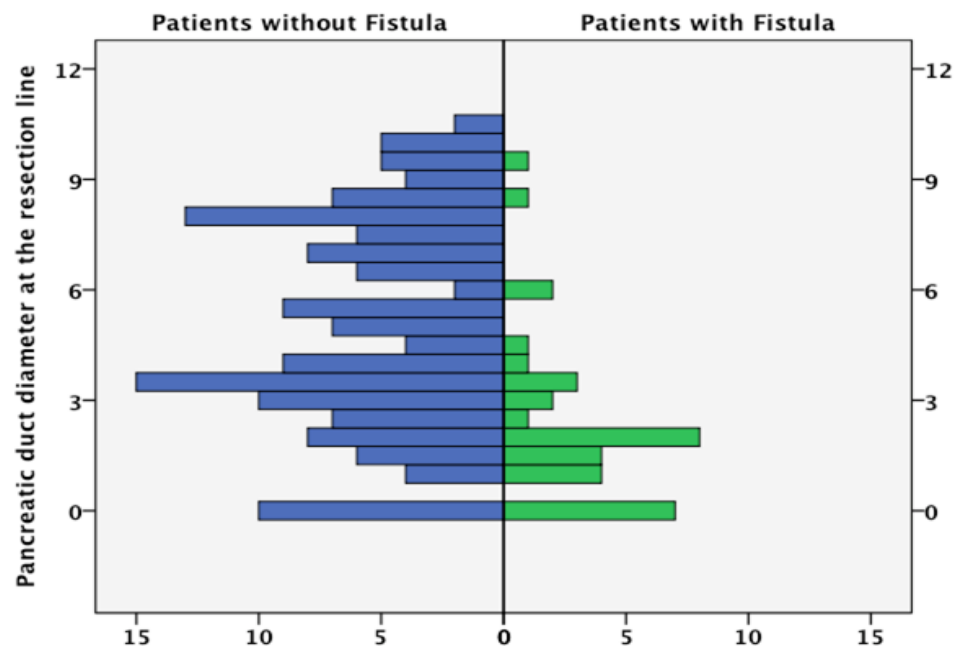


Figure 7. Frequency of PF at different PDWs.

6.4.2 Comments

Obviously, the PF rate and morbidity in general are substantial after PD, as seen in this series as well as in many other recent reports from well-controlled, prospectively collected data sets captured from high-volume centres.⁸⁹ Although complication rates are high, it is also evident that these complications can be managed successfully with a low in-hospital mortality and a decent length of the hospital stay. The critical issue which this study addresses is whether we can define the relevant risk profile of each individual patient and in that case allow preventive preparatory measures to be taken to minimize the risk of PF. On scrutinizing a number of well-defined patient, disease-specific, and radiological criteria, we observed that the PRV and the PDW at the transection line significantly and independently influenced the risk of PF. These risk estimates were apparent in the univariate statistical approaches but, more importantly, also in the multivariate ones. The rationale behind the present findings is basically twofold. First, with an increasing degree of fibrosis of the gland, its volume declines and the duct diameter increases in both relative and absolute terms.⁹⁰ How closely these preoperative assessments are related to the surgeon's intraoperative assessment of the texture of the gland and diameter of the main pancreatic duct will be addressed in detail in a larger patient cohort in order to finally determine the absolute and relative clinical value of the respective scoring approaches. The second precondition is that the larger the gland, the more digestive juice can be produced per unit time to compromise the healing of the pancreaticojejunostomy. It can be argued that this rationale is not corroborated by the lack of clear-cut effects of pancreatic juice secretion inhibition on the healing process. On the other hand, this topic requires a fresh scientific approach based on recently discovered issues relevant to the respective study designs and selection of high-risk study subjects for PF. One limitation of our study relates to the measurements of volumes using CT and MRI images acquired through the use of protocols with different slice thicknesses. However, according to Reiner and co-workers,⁹¹ a good correlation has been reported between preoperative CT/MRI-based measurements of liver resection volume and the intraoperative calculation of the volume of the resective specimens. Moreover, the volume measurements remained within an acceptable range if the thicknesses of the slices were up to 6 mm for CT and 8 mm for MRI. Our CT and MRI protocols were all within those limits. Comparatively few of our patients had both a CT and MRI investigation done within a decent time frame (< 1 month). However, when making a direct comparison between the PRV

estimates we could find an excellent agreement. Another important piece of information emerging from this study was that the original preoperative CT/MRI investigations, performed using different protocols at the primary referring hospitals, could be used to measure PRV and PDW for the prediction of PF after PD. It also has to be recalled that the PRV includes the volume of the pancreatic duct (i.e. non-functioning parenchyma). In patients with an atrophic parenchyma and a dilated duct, the difference between the total volume and the volume minus the dilated duct may be relatively large. However, a malignant obstruction accompanied by an upstream dilatation of the pancreatic duct is most frequently combined with a more predominant parenchymatous atrophy compared to the change in ductal diameter. Again, we tried to apply a pragmatic approach to the problem by defining a composite assessment score incorporating cut-off levels of the respective parameters. From a clinical utility perspective, measurements of the entire remnant volume are achievable, but an additional measurement of the volume from which the duct is deducted would be time-consuming and therefore hard to carry out in daily clinical practice.

7 CONCLUSIONS

I: No significant differences were noted in patient survival nor in stent patency time between cSEMSs and uSEMSs in the palliative treatment of malignant distal biliary obstruction. cSEMSs seemed to be burdened by stent migration as opposed to a potential for tumour ingrowth in the uSEMSs. Otherwise, no differences in complication profiles were observed between the two stent designs.

II: The development of pancreatic fistula after distal pancreatectomy remains a challenge. The technique of closure of the transected surface of the pancreas and the volume of the remaining gland were found to affect the risk of pancreatic fistula.

III: ‘Downstream’ control of the pancreatic duct, through transpapillary stent placement, does not change the risk of PF after DP.

IV: It is possible and relevant to calculate the volume of the pancreatic remnant and the width of the pancreatic duct at the transection line already preoperatively by using CT and MRI. Thereby, prediction of the risk of pancreatic fistula formation after pancreaticoduodenectomy can be achieved.

8 FUTURE PERSPECTIVES

During the process of finalizing a clinically oriented thesis, several ideas have emerged both in the minds of the investigators as well as in the relevant literature. Since this thesis focuses on palliation from hyperbilirubinaemia and jaundice in the palliative management of patients with periampullary cancer, clinical research avenues will pursue some important issues connected to the present study results:

- Regarding palliative stent strategy in patients with distal malignant jaundice, there is a continued great need to further improve stent patency. The goal should be that for the patient undergoing an endoscopic procedure with stent placement, the patency should be maintained for the limited lifetime of the patient. Based on the substantial attempts that have been made so far to optimize stent patency by the introduction of novel seeding and construction material, it can be argued that we have to return to the basic and fundamental questions before significant progress can be anticipated. From that perspective, it is interesting to note that a multicentre trial is in progress comparing stainless steel stents to nitinol, again involving 400 patients. Nanotechnology and other recent advances will eventually provide interesting pathways for the future.
- Preoperative bile duct drainage in patients with moderate jaundice has recently been found to be of no value before surgery with a curative intent. However, with the development of novel therapeutic strategies with neoadjuvant modalities, the need for an optimized stent patency strategy is also evident in these clinical circumstances.
- To overcome the problem of stent migration is not only an issue in this anatomical area. The development of new stent designs is an urgent research area. In this context, it is important to apply lateral thinking since important progress is being made in, e.g. the gastro-esophageal junction area.
- Another question is how to best treat an occluded stent? This demanding scenario will always face the clinician.
- The closer the occlusion is to the biliary bifurcation, the more demanding is the situation to provide relief from jaundice. Should these patients be treated up front through the transhepatic route or is it always worth trying to address the stricture through the papilla?

Regarding pancreatic resection, this represents a surgical intervention burdened by significant morbidity. Control and minimization of PF formation is critical for future therapeutic progress. Clinical research has defined a number of risk factors for the development of PF, i.e. leakage from the pancreaticodigestive anastomosis. Accordingly, a variety of different PF preventive measures have been proposed and subsequently tested, e.g. to stent the remnant duct to bridge and protect the fragile anastomotic area or externalization of the digestive juice from the pancreatic duct by catheter techniques. It seems clear that ‘downstream’ control of the pancreatic duct or bypassing the anastomotic area through stent placement do not change this clinical scenario.

- There is circumstantial information to suggest a potential benefit of stent deployment and ‘downstream control’ in patients with established pancreaticocutaneous fistulas. The potential for an effect of a transpapillary stent is also supported by the obvious mechanical decompression of the intraductal pressure by the stent, as well as the prophylactic effect of pancreatic stent placement to prevent post-ERCP pancreatitis. A trial should therefore be set up to randomize the patients at the time of the diagnosis of a grade B or C PF after DP, to either have a stent or only continued drainage and otherwise conservative therapy.
- Every study focusing on pancreatic leakage and its prevention has to enroll patients who are truly at an increased risk of anastomotic dehiscence. If this is not strictly adhered to, the potential impact of a certain intervention can be diluted to such a degree that a clinically relevant preventive effect is obscured and the controversy is maintained. Hitherto, this has been a problem that has not received the attention it deserves in most studies relevant to a variety of different interventions of a surgical as well as pharmacotherapeutic nature.
- Accordingly, studies addressing issues relevant to the development and progress of e.g. DGE can take the advantage of preoperative risk assessment to offer the patients with a low-risk gland to be enrolled and obtain adequate information and give their informed consent before surgery.

- Similar research protocols have to be developed from a basic platform where the PRV and PDW are given thorough attention when comparing different anastomotic techniques after PD.
- How closely are these preoperative assessments related to the surgeon's intraoperative assessment of the texture of the gland and diameter of the main pancreatic duct?
- Technical improvements in the CT-based technology may allow more accurate assessments of the tissue texture.
- MRI technologies may have advantages which should be further explored.

9 SAMMANFATTNING PÅ SVENSKA (SWEDISH SUMMARY)

Bakgrund: Majoriteten av patienter med bukspottkörtelcancer drabbas av gulsot beroende på obstruktion distalt på gallgången och behöver gallvägsavlastning, företrädesvis genom endoskopisk stentbehandling. Endast 20% av patienter med bukspottkörtelcancer kan genomgå kirurgi med botande syfte. Kirurgin i detta område anses vara riskabel med hög komplikationsfrekvens i första hand beroende på läckage av bukspottkörtelsaft, pankreasfistel (PF). PF kan uppkomma genom läckage från resektionsytan vid borttagning av bukspottkörtelns kropp och svans, distal pankreatektomi (DP) (studie II och III) eller genom anastomosinsufficiens mellan tarm och kvarvarande bukspottkörtel vid resektion av bukspottkörtelns huvud, pankreatoduodenektomi (PD) (studie IV). Detta avhandlingsprojekt berör två viktiga kliniska aspekter. Den första delen jämför öppetstående (dvs den tid som gallvägsavlastningen fungerar) och komplikationsfrekvens då två typer av metallstent jämförs, där den ena typen är ett icke täckt stent och den andra ett liknande stent täckt av en tunn plastfilm på insidan (täckt) (studie I). Nästa del av avhandlingen berör PF. De radiologiska fynden före operation kartläggs och beskrivs med förhoppningen att kunna förutse vilka patienter som har ökad risk för läckage (studie II och IV). I en randomiserad studie utvärderas om förbyggande stentinsättning i bukspottkörtelns gång kan resultera i minskad PF-frekvens efter DP (studie III).

Patientmaterial och metoder: Studie I: 400 patienter med icke operabel cancer med obstruktion av de distala gallvägarna och gulsot randomiseras till att erhålla icke täckt eller täckt metallstent. Överlevnadstid, öppetstående och komplikationsfrekvens utvärderades inom respektive stentgrupp.

Studie II: I denna hypotesgenererande studie genomförd på 51 konsekutiva patienter som genomgått DP, analyserades PF relaterat till patientkaraktistika och radiologiska fynd.

Studie III: 58 patienter rekryterades till en randomiserad studie mellan DP enbart eller DP i kombination med införande av endoskopiskt stent i bukspottkörtelgången (DP+stent), med målsättningen att reducera frekvensen PF i den senare gruppen.

Studie IV: 182 patienter som genomgått PD analyserades med avseende på läckagefrekvens relaterat till patientkaraktistika och radiologiska fynd.

Resultat: Studie I: Median överlevnadstiden var 116 dagar och 174 dagar i täckt respektive icke täckt stent grupperna. Det fanns ingen signifikant skillnad i

öppetstående tid mellan de två stentyperna (154 dagar för täckta och 199 dagar för icke täckta gruppen baserat på 25:e percentilen). Stentmigration drabbade 6 patienter (3,0%) i täckt grupp men inga patienter i den icke täckta gruppen. Denna skillnad var statistiskt säkerställd.

II: Läckage inträffade i 17 fall (33,3%) av de patienter som genomgått DP. PF var vanligare hos de med handsydd förslutning av bukspottkörteln jämfört med där suturmaskin använts (69,2% vs 21,1%). Analys av preoperativa datortomografi bilder indikerade ökad läckagefrekvens hos patienter med stor volym på kvarvarande bukspottkörtel (57,1% vs 20,8%).

III: Läckage inträffade hos 6 patienter i DP-gruppen (22,2%) och 11 (42,3%) av de som genomgått DP+stent. Både operationstid och vårdtid ökade hos de patienter som behandlades med DP+stent.

IV: Läckage inträffade hos 35/182 (19,2%). Stor volym på kvarvarande körtel och smal gång medförde signifikant ökad risk för läckage.

Slutsats: Ett icke täckt metallstent är likvärdigt med täckt stent avseende öppetstående tid, överlevnadstid och komplikationsfrekvens. Preoperativ radiologisk analys av den kvarvarande bukspottkörtelns volym är ett möjligt, och sannolikt kliniskt viktigt instrument för att förutse uppkomsten av PF både vid DP och PD. Förebyggande stent i bukspottskörtelns gång minskar inte frekvensen PF vid DP.

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