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How to Decrease Complications after Distal Pancreatectomy

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Abstract

Postoperative pancreatic fistula (POPF) is the main cause of morbidity after distal pancreatectomy (DP). Its incidence remains high at 10–50 % and may lead to other, severe complications. Mortality after distal pancreatectomy is still low. Several surgical techiques, pharmacological methods and evaluation of risk factors have been studied in the past, but the incidence of POPF remains high.

The aim of this thesis was to find surgical and pharmacological ways to reduce the risk of fistula. A further aim was to examine the effect of centralization on complications and fistula rate in distal pancreatectomies.

The Finnish binding anastomosis technique, where the pancreatic stump is inserted into the jejunal end, sutured with peripancreatic stitches and tightened by a purse-string suture has yielded promising results in pancreaticoduodenectomies. Study I reported the use of this technique on distal pancreatectomies in a randomized trial. This trial compared binding anastomosis to the traditional handsewn closure technique. The study showed that the binding anastomosis technique is not suitable for distal pancreatectomies, nor does it reduce the fistula rate.

Study II was a randomized placebo-controlled trial investigating the effect of hydrocortisone on overall complications and clinically significant POPF after open distal pancreatectomy. The Tampere Pancreas Group has previously shown that hydrocortisone lowers the rate of overall complications after pancreaticoduodenectomy. It was hypothesized that as an anti-inflammatory drug hydrocortisone could reduce the risk of complications by reducing the postoperative inflammation of the pancreatic remnant. Study II showed that perioperative hydrocortisone, continued for two postoperative days, may help to reduce overall complications after open distal pancreatectomy. The incidence of clinically significant POPF was significantly lowered with hydrocortisone treatment, 5.9% vs. 42.9%. No adverse effects were seen.

Centralization of pancreatic surgery has proceeded in Finland and its benefits have recently been shown in pancreaticoduodenectomies. Study III analysed the effect of

hospital and operation volume on major postoperative complications and POPF after distal pancreatectomy during the period 2012–2014. This study showed that the rates of POPF and major postoperative complications were similar in high and low-volume centres. However, management of complications differed and reoperations were performed ten times more often in low-volume centres.

In conclusion, this thesis shows that the incidence of POPF after distal pancreatectomy is still high and that reducing it is challenging. Many surgical techniques have failed to reduce the rate of POPF, as did binding anastomosis. However, by administering perioperative hydrocortisone the incidence of complications and postoperative pancreatic fistula after open distal pancreatectomy were reduced. Hospital volume had no effect on postoperative complications or fistulas, but for optimal treatment of complications the centralizing of distal pancreatectomies is also crucial. Reoperations were needed ten times more often in low-volume centres. In light of the results of this thesis the use of perioperative hydrocortisone treatment and centralizing operations to high-volume centres to reduce the rate of postoperative pancreatic fistula after open distal pancreatectomies and to improve their treatment is to be recommended.

Tiivistelmä

Haimafisteli eli haimanesteen vuoto haiman katkaisupinnasta on yleisin komplikaatio haiman hännän poistoleikkauksen jälkeen. Haimafistelin ilmaantuvuus on korkea 10–50 % ja se voi johtaa muihin, vakaviinkin komplikaatioihin. Kuolleisuus haiman hännän poistoleikkauksen jälkeen on kuitenkin matala. Haimafistelin ehkäisemiseksi on yritetty kehittää uusia leikkaustekniikoita lähinnä haiman katkaisumenetelmän suhteen ja haimanesteen vuotoa on yritetty vähentää erilaisilla lääkeaineilla. Fisteliin johtavia riskitekijöitä on tutkittu laajasti, mutta ongelmaan ei ole löytynyt ratkaisua ja fistelin ilmaantuvuus on säilynyt korkeana.

Tämän väitöskirjan tavoitteena oli etsiä keinoja haiman hännän (ja rungon) poistoleikkauksen jälkeisten fisteleiden vähentämiseksi leikkausmenetelmällä ja lääkeaineella. Lisäksi tavoitteena oli selvittää haiman hännän poistoleikkausten keskittämisen vaikutusta leikkauksen jälkeisiin komplikaatioihin ja fisteleihin.

Upotussauma, jossa haiman katkaisupinta upotetaan ohutsuolen sisään, toimii haiman pään poistoleikkauksessa. Ensimmäisessä osatyössä haiman katkaisupinta upotettiin ohutsuolen sisään vastaavalla upotusmenetelmällä haiman hännän poistoleikkauksessa satunnaistetussa tutkimuksessa. Tutkimuksessa verrattiin upotusmenetelmää perinteiseen katkaisupinnan sulkuun. Tulokset osoittivat, että upotustekniikka ei sovellu haiman hännän poistoleikkauksiin, eikä se vähentänyt myöskään fistelien määrää.

Toinen osatyö oli satunnaistettu lume-kontrolloitu kaksoissokkotutkimus, jossa selvitettiin leikkauksenaikaisen hydrokortisonihoidon vaikutusta haiman hännän poistoleikkauksen jälkeisiin komplikaatioihin ja fisteleiden ilmaantuvuuteen. Haiman pään poistoleikkauspotilailla hydrokortisonin on aiemmin osoitettu vähentävän merkittäviä komplikaatioita. Toisen osatyön oletuksena oli, että hydrokortisoni voisi anti-inflammatorisena lääkeaineena vähentää komplikaatioita vähentämällä leikkauksen jälkeistä tulehdusreaktiota haimassa. Hydrokortisonilla oli suotuisa vaikutus leikkauksen jälkeisiin kokonaiskomplikaatioihin. Kliinisesti merkittävien fisteleiden ilmaantuvuuteen hydrokortisonihoito vaikutti alentavasti, 5,9 % vs. 42,9 %. Haittavaikutuksia ei ilmaantunut.

Suomessa haimakirurgian keskittäminen on edennyt vähitellen ja sen edut on osoitettu haiman pään poistoleikkauksessa. Kolmannessa osatyössä selvitettiin sairaalan leikkausmäärien vaikutusta haiman hännän poistoleikkauksen jälkeisiin kokonaiskomplikaatioihin sekä fisteleihin Suomessa vuosina 2012–2014. Tämä tutkimus osoitti, että keskittäminen on järkevää myös haiman hännän poistoleikkausten suhteen. Korkeat leikkausmäärät eivät vaikuttaneet kokonaiskomplikaatioiden tai fisteleiden ilmaantuvuuteen, mutta komplikaatioiden hoidossa oli selkeä ero. Matalan leikkausmäärän yksiköissä tehtiin komplikaatioiden vuoksi kymmenen kertaa enemmän uusintaleikkauksia kuin korkean leikkausmäärän yksiköissä.

Yhteenvetona voidaan todeta, että haimafistelin ilmaantuvuus on korkea ja siihen vaikuttaminen on haastavaa. Toistaiseksi minkään kirurgisen katkaisupinnan sulkumenetelmän ei ole todettu vähentävän fisteleitä. Haiman upottaminen ohutsuoleen ei myöskään tuonut ratkaisua ongelmaan. Leikkauksen aikaisella hydrokortisonihoidolla kuitenkin saavutettiin selkeä vähenemä haimafisteleissä. Sairaalakohtaisilla leikkausmäärillä ei todettu vaikutusta komplikaatioiden tai fisteleiden ilmaantuvuuteen, mutta komplikaatioiden asiantuntevan hoidon vuoksi haiman hännän poistoleikkaustenkin keskittämisen todettiin olevan tärkeää. Näin vältetään tarpeettomat uusintaleikkaukset, joita matalan leikkausmäärien sairaaloissa tehtiin kymmenen kertaa enemmän kuin korkean leikkausmäärän sairaaloissa. Haiman hännän poistoleikkauksen jälkeisten fisteleiden vähentämiseksi ja hoidon optimoimiseksi voidaan väitöskirjatutkimuksen tulosten perusteella suositella hydrokortisonihoidon käyttöä ja leikkausten keskittämistä suuren leikkausmäärän sairaaloihin.

List of Original Publications

This thesis is based on the following original publications, which are referred in the text by their Roman numerals I–III.

I   Antila A, Sand J, Nordback I, Räty S, Laukkarinen J. 2014, Is Roux-Y binding pancreaticojejunal anastomosis feasible for patients undergoing left pancreatectomy? Results from a prospective randomized trial. Biomed Res Int, 2014:508714.

II   Antila A, Siiki A, Sand J, Laukkarinen J. 2019. Perioperative hydrocortisone treatment reduces postoperative pancreatic fistula rate after open distal pancreatectomy. A randomized placebo-controlled trial. Pancreatology, 19(5):786–792.

III   Antila A, Ahola R, Sand J, Laukkarinen J. 2019. Management of postoperative complications may favor the centralization of distal pancreatectomies. Nationwide data on pancreatic distal resections in Finland 2012–2014. Pancreatology, 19(1):26–30.

Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body mass index
CCI	Comprehensive complication index
CD	Clavien-Dindo
CP	Central pancreatectomy
CR-POPF	Clinically relevant postoperative pancreatic fistula
CT	Computed tomography
DFA1	First postoperative day drain fluid amylase
DGE	Delayed gastric emptying
DM	Diabetes mellitus
DP	Distal pancreatectomy
ERAS	Enhanced recovery after surgery
ERCP	Endoscopic retrograde cholangiopancreaticography
EUS	Endoscopic ultrasound
FBPJ	Finnish binding pancreaticojejunal anastomosis
HC	Hydrocortisone
HVC	High-volume centre
ICU	Intensive Care Unit
IPMN	Intraductal papillary mucinous neoplasm
ISGPS	International Study Group on Pancreatic Surgery
ISGPF	International Study Group on Pancreatic Fistula
LOS	Length of hospital stay

LDP	Laparoscopic distal pancreatectomy
LVC	Low-volume centre
MCN	Mucinous cystic neoplasm
MDCT	Multidetector computed tomography
MIDP	Minimally invasive distal pancreatectomy
MRI	Magnetic resonance imaging
MVC	Medium-volume centre
NET	Neuroendocrine tumour
NGT	Nasogastric tube
ODP	Open distal pancreatectomy
PCN	Pancreatic cystic neoplasm
PD	Pancreaticoduodenectomy
PDAC	Pancreatic ductal adenocarcinoma
PFU	Prospective follow-up
PGA	Polyglycolic acid
PJ	Pancreaticojejunal anastomosis
POD	Postoperative day
POPF	Postoperative pancreatic fistula
PPH	Postpancreatectomy haemorrhage
RCT	Randomized controlled trial
RDP	Robotic distal pancreatectomy
RPT	Prospective randomized group
SCN	Serous cystic neoplasm
SPN	Solid pseudopapillary neoplasmn
TP	Total pancreatectomy
US	Ultrasonic dissector

x

Contents

1 Introduction

Distal pancreatectomy (DP) accounts for about 20% of all pancreas resections. Mortality has diminished close to zero mainly because of surgical techniques and improved perioperative care. Morbidity remains high at approximately 20–50% (Bruns et al., 2009). Postoperative pancreatic fistula (POPF) is the most common complication after DP, the incidence ranging from 15 to 50% (Knaebel et al., 2005). POPF can lead to other, severe complications and may prolong hospital stay and increase the costs (Reeh et al., 2011).

Fistula prevention has been a challenge in recent years. The risk factors for fistula have been studied extensively (Allen et al., 2014, Kleeff et al., 2007). Many different surgical techniques for closing the pancreas stump have been investigated and compared (Kollar et al., 2016). Some pharmacological methods have also been proposed. Nevertheless, the fistula rate has not diminished and novel techiques and treatments are needed to solve this problem.

In pancreaticoduodenectomy (PD) postoperative pancreatic inflammation has been shown to predispose to POPF (Uemura et al., 2012, Bannone et al., 2018). Hydrocortisone, as an anti-inflammatory drug, has reportedly reduced major complications after PD (Laaninen et al., 2016). Moreover, centralizing PD has led to improved quality and safety (Ahola et al., 2017).

This thesis focuses on improving the outcome of distal pancreatectomy by proposing novel ideas for reducing fistula and investigating the effect of centralization on distal pancreatectomy.

2   Review of the Literature

2.1   Anatomy and physiology of the pancreas

The pancreas is a retroperitoneal organ located behind the stomach and transverse colon. The pancreas has five parts: the uncinate process, head, neck, body and tail. The superior mesenteric artery and vein go behind the neck and the tail is usually attached to the hilum of the spleen. The splenic vein goes underneath the pancreas and the splenic artery above it (Drake, T, Vogl, W. & Mitchell, A., 2005).

The pancreas has an exocrine and endocrine function. The exocrine pancreas composes about 98% of the pancreas and consists of acinar and ductal cells. The acinar cells secrete digestive entzymes (trypsin, amylase, lipase, chymotrypsin, nucleases, elastase, cholesterolesterase and colipase) and the ductal cells produce electrolytes and bicarbonate, which neutralize gastric acid. Most enzymes are secreted in inactive form, activated in the duodenum due to active trypsin and enteropeptidases (Bardeesy, DePinho, 2002). Pancreatic juice is secreted into the main pancreatic duct (duct of Wirsung) through smaller ducts. The main pancreatic duct enters the duodenum through the major papilla of the duodenum (papilla of Vater). The pancreatic duct joins the common bile duct and forms the papilla of Vater before entering the duodenum. The papilla of Vater is surrounded by smooth muscle, making a sphincter to the papilla (sphincter of Oddi), which controls the secretion of pancreatic juice into the duodenum. The exocrine function is regulated by gastrointestinal hormones (secretin, gastrin and cholecystokinin) and the parasymphatetic nervous system.

The endocrine part of the pancreas consists of islets of Langerhans and constitutes only 1–2% of the pancreas. Alpha cells secrete glucagon, beta cells produce insulin, delta cells somatostatin and PP cells secrete pancreatic polypeptide into the bloodstream. Insulin and glucacon regulate the blood glucose level, somatostatin decreases insulin, glucagon and pancreatic polypeptide secretion and also inhibits the exocrine function.

2.2 Distal pancreatectomy

2.2.1 Indications

Indications for distal pancreatectomy (DP) include malignant, premalignant or benign lesions in the pancreatic body or tail. Chronic inflammation or trauma may also necessitate DP. The abdomen is nowadays imaged more frequently and lesions are increasingly detected in the tail of the pancreas.

Malignant tumours in the tail of the pancreas usually attain a large size before causing any symptoms and have often reached an advanced stage by diagnosis. The most common symptoms are pain, weight loss and recent diabetes. However, no obstructive symptoms in the biliary or gastrict tract occur in tumours in the pancreatic tail. Ductal adenocarcinoma is found in 15% of cases in the body and tail of the pancreas. Other malignant diseases may also metastase to the pancreas, especially renal carcinomas.

Pancreatic cystic neoplasms (PCN) include intraductal papillary neoplasm (IPMN), serous cystic neoplasm (SCN) and mucinous cystic neoplasm (MCN). Three types of IPMNs have been identified; branch duct type, main duct type and mixed type, all being premalignant conditions. IPMNs are intraductal mucin-producing neoplasms and cause dilatation of the pancreatic duct. Frequency of malignancy is highest in main duct IPMN, close to 80% and significantly lower, 20%, in branch duct IPMN (Salvia et al., 2004, Rodriguez et al., 2007). Surgical resection is recommended for all main duct IPMNs and for branch duct IPMNs having worrisome features such as rapid growth, size >40 mm, mural nodules, symptoms, elevated serum CA19-9 tumour marker level and main duct dilatation >5mm. Mixed type IPMN should be managed similarly to main duct IPMN and the risk of malignancy is comparable to that in main duct type. Symptoms include pancreatitis, abdominal pain, back pain, nausea, vomiting and weight loss. Pancreatic insufficiency, including steatorrhoea, diabetes mellitus and jaundice may occur in later stages (C. Shi, Hruban, 2012). SCNs are always benign and do not require surgery unless the diagnosis is uncertain or significant symptoms are present (Jais et al., 2016). MCNs are usually found in the tail of the pancreas and appear in women. They have malignant potential and are usually resected. Small MCNs without worrisome features may even be observed. Nevertheless, accurate preoperative diagnosis is sometimes difficult to achieve by imaging (Nilsson et al., 2016, Keane et al., 2018). In addition, solid pseudopapillary neoplasm (SPN) is a rare tumour in the pancreas requiring resection (Del Chiaro, Verbeke et al., 2013, European Study Group on Cystic Tumours of the Pancreas, 2018).

Neuroendocrine tumours may also be found in the pancreatic tail. Non-functional and functional tumours have been observed. Surgery should be considered in all functional and also in non-functional tumours, except for the smallest perceptible (Sallinen et al., 2017).

2.2.2 Preoperative imaging and endoscopy

Imaging of the pancreas is crucial in evaluating pancreatic neoplasms. Ultrasound, multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) are the most used tools to achieve diagnosis. MDCT has 86% sensitivity in diagnosing pancreatic masses, but only 55% for tumours less than 3 cm in diameter (Sahani et al., 2008). Most pancreatic masses are hypoattenuating and seen in the venous phase, while neuroendocrine tumours are often hypervascular and seen in the arterial phase. MDCT cannot detect small tumours, small hepatic metastases or peritoneal seeding. Magnetic resonance imaging (MRI), especially with magnetic resonance cholangiopancreatography, outperforms CT in yielding more information on the pancreatic and biliary ducts and evaluates the ductal communication present in branch-duct IPMN (Xu, Sethi, 2016). MRI can also detect smaller tumours and metastases better than CT and gives information on possible mural nodules on cysts, which often require surgery. Endoscopic ultrasound (EUS) can detect and stage small tumours (0.2 cm) and allows biopsy of lesions. Its sensitivity in detecting pancreatic cancer is 94–100%. The availability of EUS is limited and also entails a long learning curve to achieve good results (de la Santa, L G et al., 2014). EUS is useful for identifying worrisome features in PCN and in distinguishing features requiring surgery. However, EUS is recommended in addition to other imaging (European Study Group on Cystic Tumours of the Pancreas, 2018).

ERCP is used in cases of biliary stricture requiring drainage and makes it possible to image the shape of a stricture in the biliary duct or pancreatic duct and also to take brush cytology or biopsies from strictures. Peroral pancreatoscopy using SpyGlass-DStm (Boston Scientific, Natick MA, USA) can be used to investigate IPMNs, allowing visualizing the pancreatic duct epithelium and direct biopsies (Nagayoshi et al., 2014, Ohtsuka et al., 2018). Main duct IPMN can be treated by partial pancreatectomy if no high-grade dysplasia or invasive carcinoma is present on the surgical margins. With pancreatoscopy, the main duct can be visualized pre- or perioperatively to determine the adequate transection line and also to visualize the possible skip lesions in remnant pancreas (Arnelo et al., 2014).

2.2.3 Surgical techniques

Distal pancreatectomy was first performed by Billroth in 1884. The pancreatic tail is removed left of the superior mesenteric and portal vein from subcostal or midline laparotomy or minimally invasively through small incisions. The pancreatic body and tail are removed with or without the spleen. In cases of malignancy splenectomy is performed, the short gastric vessels connecting the stomach and splenic hilum, splenic artery and vein are ligated from their origin and the pancreas is divided at the level of the portal vein. The inferior mesenteric vein is preserved if possible (Figure 1). For malignant tumours splenectomy is recommended and in the case of benign lesions the spleen can be saved if technically

possible (Shoup et al., 2002, Lillemoe et al., 1999). Little is known about nodal staging in DP, but according to a recent article, 20 or more lymph nodes should be collected in order to determine the nodal status. Lymph node dissection includes nodes in the splenic hilum, the splenic artery and on the inferior edge of the pancreas (Malleo et al., 2018). The pancreatic stump can be divided and closed in various ways, described later in Chapter 2.6.1. Traditionally postoperative drains are used, but according to recent evidence their routine use should be abandoned (Chapter 2.6.1.6).
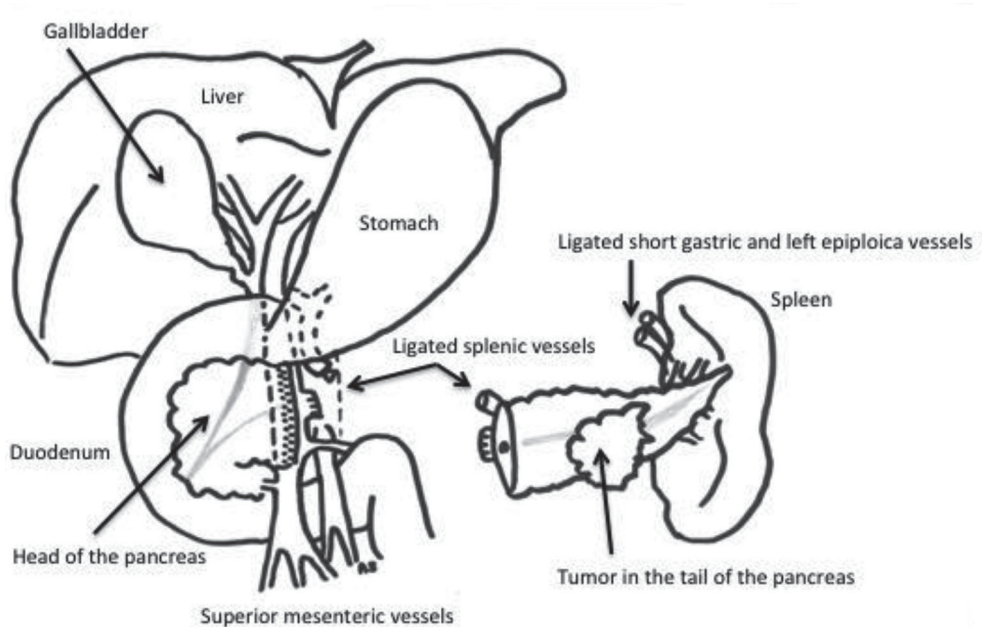
Figure 1.   Distal pancreatectomy and splenectomy

Spleen preserving DP can be performed either by ligating the main vessels or by saving them. When ligating the veins, the risk of spleen infarction and the formation of gastric varices is significantly higher (Partelli et al., 2016, Butturini et al., 2011). The spleen blood supply is normally delivered through the short gastric vessels and the left gastroepiploic vessels in addition to the splenic vessels. Splenic preserving DP ligating the splenic vessels was first introduced by Warshaw (Warshaw, 1988). In that technique the spleen is perfused by the preserved short gastric vessels (Figure 2).
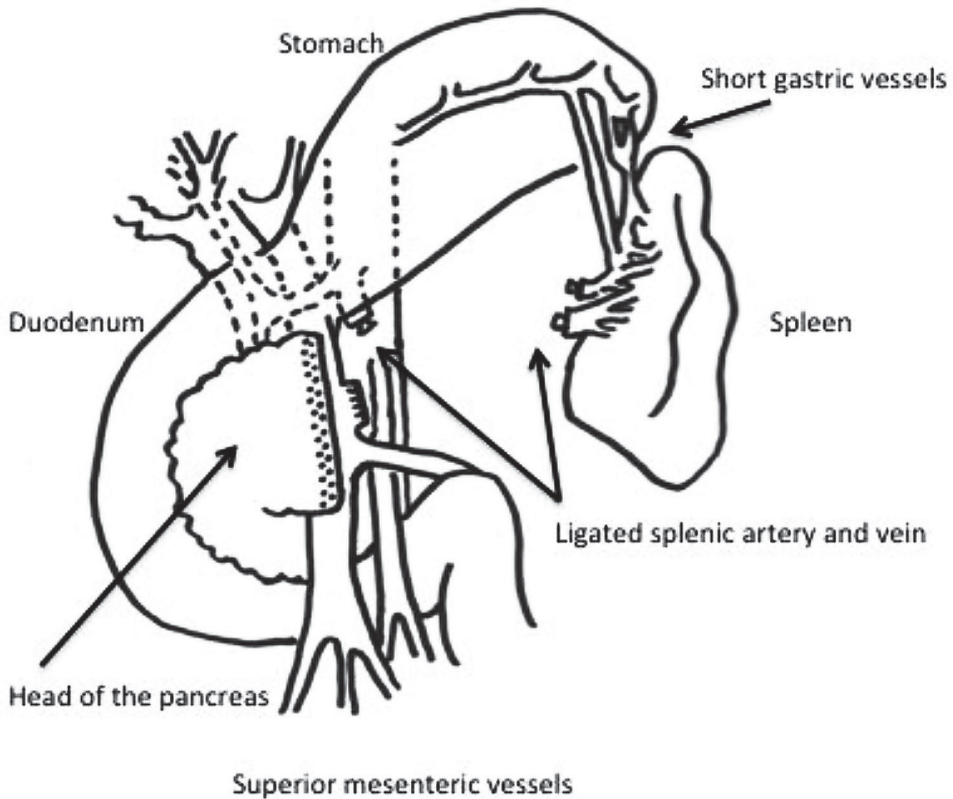
Figure 2.   The Warshaw's technique. Spleen preserving DP by ligating the splenic vessels. The spleen is perfused by preserved short gastric vessels

Spleen preserving DP with conservation of the splenic artery and vein was introduced in 1943 and the technique was elucidated elaborated by Kimura (Kimura et al., 1996) (Figure 3). The technique is safe and easy and can be used for benign and premalignant lesions of the pancreatic tail (Kimura et al., 2007). The Warshaw technique (vessel ligation) affects spleen perfusion more than the vessels preserving technique, but blood circulation recovers in the case of a normal spleen (Sato et al., 2000). Possible postoperative splenic infarction can generally be treated conservatively and splenectomy is seldom needed (N. Shi et al., 2016).
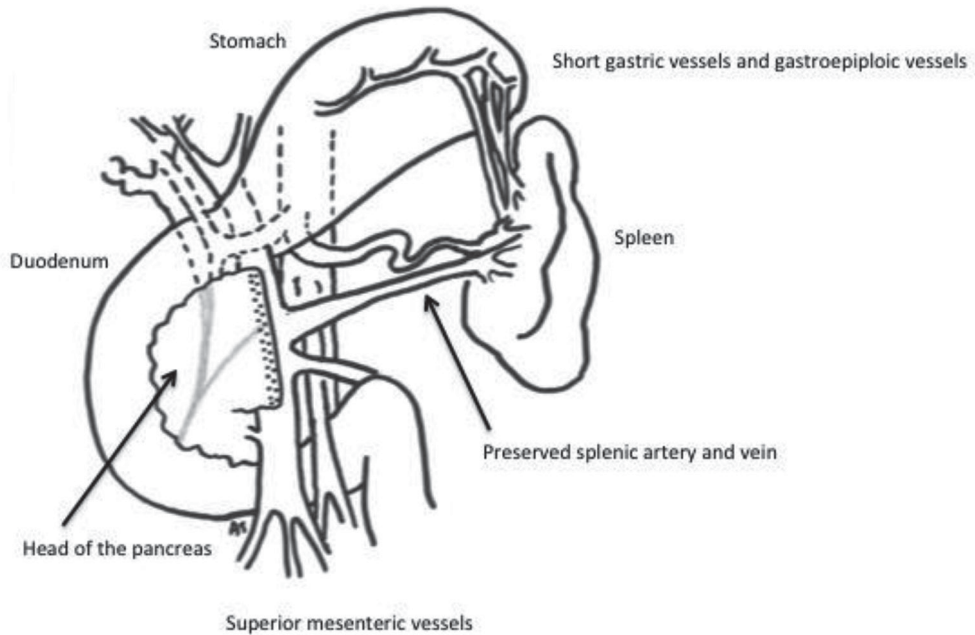
Figure 3.   The Kimura technique. Spleen preserving DP by preserving the splenic vessels

2.2.4 Laparoscopic approach

Laparoscopic surgery has increased in recent years and has become standard for many operations. In laparoscopy the overall blood loss is lower, the patient recovers faster and hospital stay is shorter. However, laparoscopy often increases the operating time. Laparoscopic distal pancreatectomy (LDP) was introduced by Cuschieri in 1996 (Cuschieri, Jakimowicz & van Spreeuwel, 1996) and has become a common method in recent decades. Laparoscopy in DP has been proven to be safe and shortens the length of hospital stay (LOS), speeds up recovery and has become the approach of choice for lesions involving the pancreatic tail (Briggs et al., 2009, Butturini et al., 2011). The first RCT was conducted in the Netherlands, comparing time to functional recovery after minimally invasive and open distal pancreatectomy (LEOPARD trial). The authors reported a two-day reduction in time to functional recovery after minimally invasive distal pancreatectomty (MIDP) compared to open distal pancratectomy (ODP). Neither CR-POPF nor overall complication rate was reduced, but there was less DGE and better quality of life at the same cost (de Rooij et al., 2018).

The LEOPARD trial also showed that MIDP is at least as cost-effective as open DP in terms of time to functional recovery and quality-adjusted life-years. One year after surgery there was no difference in patients' cosmesis and quality of life (van Hilst et al., 2019). Suprisingly, in the LEOPARD trial there were more cases of POPF after MIDP than after

ODP (44% vs. 25%) at one-year follow-up. However, this trial was not powered to show difference in complications. The ongoing DISPACT 2 trial is intended to compare the complication index between ODP and MIDP, and will hopefully serve to clarify the issue (WHO International Clinical Trials Registry Platform).

However, MIDP may not be the optimal choice for centrally located lesions near major blood vessels. Laparoscopy in malignant lesions is controversial and in many institutions patients with malignant lesions undergo an open procedure. According to recent retrospective trials, early and long-term results do not differ between open and laparoscopic DP for pancreatic ductal adenocarcinoma (PDAC) and LDP; LDP is a safe and effective approach to PDAC in terms of postoperative morbidity and oncologic outcome (Sulpice et al., 2015, Bauman et al., 2018, Stauffer et al., 2016, Bjornsson, Sandstrom, 2014). A recent systematic review and meta-analysis involving over 11,000 patients reported comparable survival and R0 resection rate. However, because LDP was more often performed on smaller tumours and the lymph node invasion rate was also lower, the oncologic outcome is not clear (van Hilst, Korrel et al., 2018). One retrospective propensity score-matched cohort study was presented in January 2017 in Annals of Surgery comparing minimally invasive versus open distal pancreatectomy for PDAC. Oncologic safety remains unclear, because lymph node retrieval and the Gerotas fascia resection rate were lower in LDP, but the R0 resection rate was higher in LDP while overall survival was similar (van Hilst et al., 2017). A pan-European, randomized controlled multicentre trial (DIPLOMA Trial) is currently enrolling patients to compare LDP with ODP for pancreatic ductal adenocarcinoma (PDAC) with standardized surgical technique and this trial may yield more information about the oncologic equivalency of ODP and LDP (van Hilst et al., 2017).

Spleen preservation with or without ligation of the splenic vessels can also be performed laparoscopically. Warshaw's technique (ligation of splenic vessels) is laparoscopically faster and associated with reduced intraoperative blood loss (Butturini et al., 2012). After ligating the vessels, there is a risk of postoperative splenic infarction and the formation of perigastric varices due to left-sided portal hypertension. Varices are not associated with bleeding during long-term follow-up (Butturini et al., 2012, Miura et al., 2005). Spleen preservation is still worth trying, also laparoscopically with benign tumours and both techniques are acceptable.

2.2.5 Robotic distal pancreatectomy

Robotic distal pancreatectomy (RDP) was first performed in 2003 by Melvin (Melvin et al., 2003). Robotic operations allow a three-dimensional view, stabilize motion and tremor and have a so-called endo-wrist system to help facilitate motion. According to a recent meta-analysis, RDP is safe and surgically as good as LDP. It increases the rate of spleen preservation and reduces the risk of conversion (Guerrini et al., 2017). Some studies have reported longer operating time with RDP, but slightly shorter LOS and reduced blood

loss (Gavriilidis, Roberts & Sutcliffe, 2019). No difference in morbidity, POPF or blood transfusion has been reported between RDP and LDP (Daouadi et al., 2013). So far, no RCT has been published to confirm the findings between RDP and LDP, but RDP currently seems to be comparable to LDP with higher costs and better view and motion.

2.3 Parenchyma-sparing surgery

Parenchyma-sparing surgery has been proposed for benign or low-grade malignant tumours in the pancreatic isthmus or body. Extended DP or extended PD would be another option to treat lesions in those locations. Extended operations may lead to exocrine and endocrine dysfunction. Postoperative diabetes rates vary from 5% to 14% in patients with normal pancreas after DP (Maeda, Hanazaki, 2011, De Bruijn, Kirstin M. J., van Eijck, Casper H. J., 2015). In chronic pancreatitis the incidence of postoperative diabetes is even higher, up to 40%. Central pancreatectomy (CP) and enucleation are the most common parenchyma-sparing types of surgery. These should be considered especially for young patients to diminish the risk for exocrine or endocrine insufficiency. Indications for parenchyma-sparing surgery include endocrine neoplasms, cystadenomas and solid pseudopapillary neoplasm (SPN).

2.3.1 Central pancreatectomy

In CP, the pancreatic corpus with the tumour is resected and the distal stump is anastomosed to the jejunum or the stomach and the proximal stump is closed by sutures or stapler (Crippa et al., 2010). This leads to two possible sites for POPF to develop. Because the indication for CP is benign or premalign, the pancreas is usually "soft" with nondilated pancreatic duct. CP has higher morbidy rate, up to 60%, but the mortality rate is low. POPF occurred in 30%–60% of patients (Iacono et al., 2013, Xiao et al., 2018). Compared to DP, morbidity and fistula rates are significantly higher, but the incidence of exocrine or endocrine insufficiency is lower (Iacono et al., 2013).

2.3.2 Enucleation

In enucleation the tumour is enucleated carefully from the pancreas tissue and the small vessels are ligated. The pancreatic capsule is closed when possible. The diameter of the tumour must be <2 cm and it must be >3 mm from the main pancreatic duct. Overall morbidity after enucleation is high (>60%), but the rate of severe complications is low. The overall POPF rate is over 50%, but the CR-POPF rate is comparable to DP (Wang et al., 2018, Strobel et al., 2015). Usually no endocrine or exocrine dysfunction appears after

enucleation (Hackert et al., 2011). Enucleation is the best choice for small insulinomas, but preoperative imaging to determine the size and distance to the main pancreatic duct is crucial.

2.4   Postoperative complications after distal pancreatectomy

2.4.1   Morbidity and mortality

Distal pancreatectomy can nowadays be performed with low mortality rate thanks to advances in surgical techniques and perioperative care (Kleeff et al., 2007, Lillemoe et al., 1999). Mortality ranges between 0% and 2% (Fahy et al., 2002, Nathan et al., 2009, McPhee et al., 2007, Sledzianowski et al., 2005) and is lower than for PD. Mortality is higher in men, older patients and patients operated on at the lowest-volume centres, while in high-volume centres it is close to 0% (McPhee et al., 2007).

Despite low mortality, DP has a high morbidity rate, ranging from 22% to 57%, (Sledzianowski et al., 2005, McPhee et al., 2007, Lillemoe et al., 1999, Diener et al., 2011). Pancreatic fistula (defined in Chapter 2.4.2) is the main cause of postoperative morbidity and occurs more frequently after DP than after PD. It often leads to other complications like intra-abdominal abscesses, postoperative pancreatic haemorrhage, delayed gastric emptying, wound infection and sepsis (Knaebel et al., 2005, Kleeff et al., 2007). Perioperative mortality is often due to POPF (Nathan et al., 2009). The pancreatic fistula rate after DP is approximately 30% (Ferrone et al., 2008, Diener et al., 2011). Due to the absence of an extensive reconstruction as in the PD procedure, complications after DP are seldom life-threatening but complications lengthen the hospital stay and may as much as double the costs (Rodriguez et al., 2006, Pratt et al., 2007). In addition, complications may require radiological or endoscopic intervention or even reoperation. Hospital readmissions usually occur in patients who develop POPF or abscesses, the most frequent complications after DP (Marchegiani et al., 2017).

2.4.2   Postoperative pancreatic fistula

POPF is the most common complication after DP and occurs in approximately 30% of patients after DP (Ferrone et al., 2008, Diener et al., 2011). Pancreatic enzymes leak from the cut edge and cause fluid accumulation and even severe infections, sepsis or haemorrhage. Various techniques for closing the pancreatic remnant have been extensively studied in order to decrease the fistula rate, but this problem remains unsolved (Miyasaka et al., 2017). It is more common in DP than in PD and the incidence varies widely depending on the definition used. POPF after PD is usually more severe and more life-threatening than after DP (McMillan et al., 2016).

In order to objectively compare the occurrence of fistulas between different surgical centres, the International Study Group on Pancreatic Fistulae (ISGPF) published in 2005 a definition for the clinical grading of POPF. POPF was defined as any measurable fluid output of an operatively placed drain with amylase more than three times the normal serum value. Grades A, B and C were defined. The definition was updated in 2016 and the former Grade A fistula is no longer defined as a fistula because of the lack of clinical impact. Instead, it has been redefined and is now known as a "biochemical leak" and the term fistula is only used in cases of clinical relevance. In biochemical leak the drain amylase level is >3 times the upper limit of normal serum amylase value. In grade B the drain is present and contains amylase rich fluid > three weeks after the procedure or there is a repositioning of the drain through percutaneous or endoscopic interventional drainage. In Grade B there is a change in the management of the clinical pathway and signs of infection are perceptible. Treatment in the ICU may be needed, but there is no organ failure. In cases of POPF-related haemorrhage angiographic procedures may be needed in Grade B. Grade C entails organ failure, reoperation or the death of a patient. Treatment in the ICU is often needed and LOS is greatly prolonged (Bassi et al., 2005, Bassi et al., 2017).

This new classification improved discrimination between different POPF grades after DP (van Hilst, de Pastena et al., 2018). The earlier classification left more room for different interpretations. Some included the POPF needing interventional drainage for Grade B and some shifted this type of POPF to Grade C. Now it is clear; with interventional drainage the POPF continues to be classified as Grade B, but reoperation classifies it as Grade C, as does any organ failure or death (Figure 4).

To identify patients at high risk for fistula, Fistula Risk Scores have been developed. Risk scores are allocated mainly for PD and have been shown to correlate with fistula development after PD (Callery et al., 2013). The Fistula Risk Score for PD defines four characteristics: soft texture of the pancreas, small diameter of the pancreatic duct, histopathological diagnosis and blood loss greater than 400ml, all of which warrant a score of 10. Patients scoring 7–10 points are at high risk for POPF. For DP, perioperative risk factors have been shown to have poor predictive capability and no real scoring system has so far been proposed (Ecker et al., 2017, McMillan, Vollmer, 2014).

Biochemical leak	⟷	Surgical drainage < 21 days No change in clinical pathway
Grade B Pancreatic Fistula	⟷	Surgical drainage > 21 days Change in management of clinical pathway Percutaneus or endoscopic drainage Angiography for POPF-related bleeding Sign of infection without organ failure
Grade C Pancreatic Fistula	⟷	Reoperation Organ failure Death
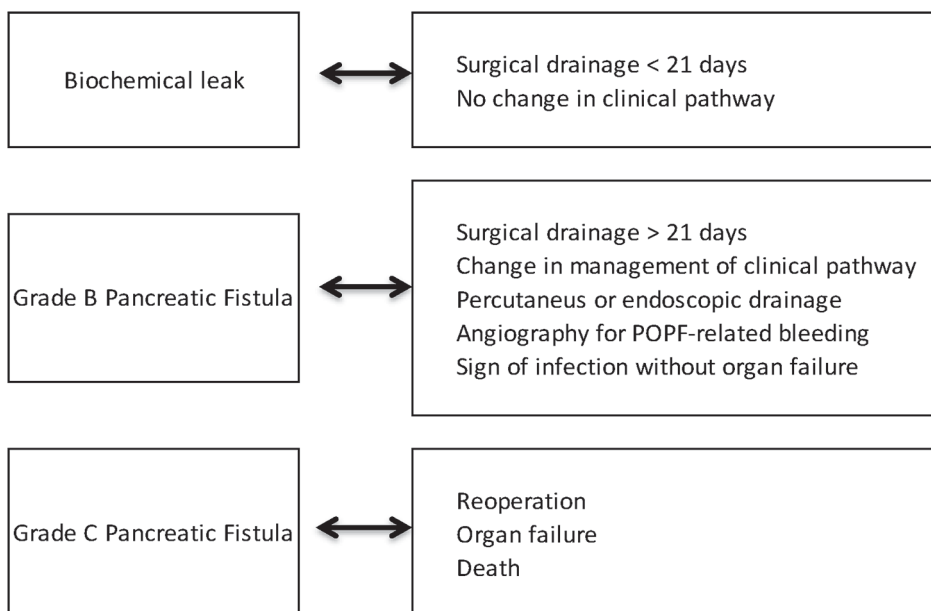
Figure 4.   ISGPS 2016 postoperative pancreatic fistula definition

2.4.3 Postpancreatectomy haemorrhage

Postoperative pancreatic haemorrhage (PPH) is a rare and severe complication after pancreatic surgery. It occurs in 4–17% of patients after PD, in 2–3% after DP (Lermite et al., 2013, Sledzianowski et al., 2005) and is associated with a high mortality rate of 35% (Roulin et al., 2011). Bleeding sites after DP are the pancreatic stump, tributaries of the splenic artery, splenic hilus or tributaries of the splenic vein stump or resection site (Wente, Veit et al., 2007).

The International Study Group of Pancreatic Surgery (ISGPS) proposed a definition for PPH with Grades A, B and C. These are defined by four parameters: time of onset, severity, location and clinical impact. The onset is early (<24 h) or late (>24 h) and the location is intra- or extraluminal. Severity may be mild or severe and clinical impact varies. Grade A has no major clinical impact and does not delay the patient's discharge from hospital. In Grade B the bleeding is severe and the patient may need invasive treatment (relaparotomy or embolization) and LOS is prolonged. Grade C is always life-threatening and the blood loss is severe (Wente et al., 2007).

2.4.4 Delayed gastric emptying

Delayed gastric emptying (DGE) is the most common complication after pancreatic surgery, especially after pancreaticoduodenectomy (PD), but also occurs after DP (Wente, Bassi et al., 2007). The aetiology of DGE is uncertain, but it is often associated with other intra-abdominal complications (pancreatic fistula, fluid collection) or resection of the duodenum, which causes a decrease in plasma motilin levels (Kunstman et al., 2012). It has also been reported that DGE is often caused by postoperative pancreatic inflammation (Raty et al., 2006). It usually resolves by itself, but delays discharge from hospital, causes discomfort and increases costs. DGE also occurs after DP, but with lower frequency and is seldom reported. According to different studies, it occurs in 5–25% and is often associated with pancreatic fistula (Glowka et al., 2016, Seeliger et al., 2010, Kleeff et al., 2007).

The International Study Group of Pancreatic Surgery (ISGPS) also published a definition for DGE in 2007 defining DGE into three grades according to the duration of the nasogastric tube (NGT), solid food toleration, vomiting and need for prokinetics. Grade A does not usually change clinical management, but NGT is needed or repositioned between postoperative days (POD) 4 and 7 but solid foods intake resumes before POD 14. In Grade B the NGT is present for POD 8–14, or reinserted after POD 7. The patient can ingest solid food before POD 21. Grade B prolongs hospital stay and causes discomfort. Grade C is present when the NGT is still in place or has been repositioned after POD 14 or if the patient cannot take solid food by 21 POD. Grade C is often associated with other complications and patients need nutritional supplementation (Wente et al., 2007, Park et al., 2009).

2.4.5 Clavien-Dindo classification

Overall complications are often reported according to the Clavien-Dindo classification (CD), which was introduced in 1992. This classification is simple to use and enables international comparison of overall morbidity rates (Dindo, Demartines & Clavien, 2004). The therapy needed to treat the complication determines the complication grade. This classification is also suitable for pancreatic surgery (DeOliveira et al., 2006). Complications are divided into five grades. Grade III complications require invasive treatment, such as surgical, endoscopic or radiological interventions. The complications in Grades I and II require only minor deviations from the normal postoperative pathway. Grade I includes treatment with antiemetics, antipyretics, electrolytes or diuretics and wound infections opened at the bedside. Grade II patients need antibiotics, blood transfusion or parenteral nutrition. If the complication is life-threatening and requires ICU treatment, the grading is IV. Grade V means mortality.

2.4.6 Comprehensive complication index

In the Clavien-Dindo classification (CD), only the most severe complication is reported and this determines the grade. As a limitation, CD may underestimate the impact of multiple and less severe complications. In 2013 Slankamenac et al. introduced the comprehensive complication index (CCI), which classifies every postoperative complication occurring after an intervention. The CCI is based on the Clavien-Dindo classification; a summation of all complications, it reflects the overall morbidity better. The CCI is a complex formula, but can be calculated easily using an online CCI calculator based on CD graded complications, scores ranging from 0 to 100 (Slankamenac et al., 2013, Slankamenac et al., 2014, Ray et al., 2019).

2.5 Risk factors for complications after distal pancreatectomy

The risk factors for complications after DP can be divided into patient, surgery and hospital related factors (Figure 5). These risk factors have been widely studied and many methods have been tested to exert influence where feasible. The findings of different studies are to some extent contradictory, especially regarding patient related risk factors.

Patient related risk factors	Surgery related risk factors	Hospital related risk factors
BMI Comorbidities Smoking Age Gender Albumin/nutrition level Pancreatic texture Main duct diameter Pathology	Operative time Blood loss Splenectomy Closure mechanism Drainage Laparoscopy Pharmacology	Hospital volume Patient care Multidisciplinary team

Figure 5. Risk factors for complications after DP

2.5.1 Patient related risk factors

2.5.1.1 Pancreatic texture

Soft (normal) pancreas has been shown to increase the risk of POPF while firm (fibrotic) texture lowers the POPF rate after PD and DP (Ridolfini et al., 2007, Lin et al., 2004, Fahy et al., 2002, Ansorge et al., 2012). A recent review and meta-analysis showed a correlation between soft pancreas and POPF (Peng et al., 2017). Soft pancreas is associated with a threefold increased risk of POPF compared to firm pancreas (Pratt, Callery & Vollmer, 2008). Thick pancreas (diameter over 12 mm) is likewise a risk for POPF after stapler closure and another closing method should be used in thick pancreas (Okano et al., 2013, Mendoza et al., 2016, Kawai et al., 2013). Soft and normal pancreas is rich in acinar cells and has a narrow main pancreatic duct, while in fibrotic pancreas the main duct is dilated and the pancreas consists of fibrosis (Laaninen et al., 2012). A duct diameter smaller than 3 mm is a risk factor for POPF after PD (Muscari et al., 2006). However, contradictory results have been reported. Martin et al. recently reported that pancreatic duct size and gland texture are associated with pancreatic fistula after PD but not after DP (Martin et al., 2018). This finding may be explained by the different mechanisms of fistula formation in PD and DP. In DP the leak could be explained by increased pressure in the pancreatic duct caused by the sphincter of Oddi (Hashimoto, Traverso, 2012, Hackert et al., 2017). Main duct dilatation is caused by chronic pancreatitis or obstruction due to a tumour in the head of the pancreas. Main duct IPMN also causes widening of the main pancreatic duct. In DP the tumour is in the tail and does not obstruct the duct at the cut edge, so in terms of DP, the pancreas is usually soft and the main duct narrow (except in chronic pancreatitis), which is the reason for the POPF rate being higher in DP than in PD. Large volume of the pancreatic remnant and the transection site may also effect fistula formation; POPF has been shown to occur more often when the tail has been transsected (Sell et al., 2015, Frozanpor et al., 2010, Pannegeon et al., 2006).

The Tampere Pancreas Group has previously shown that acinar-rich cut edge (>40%) increases and fibrosis decreases the risk for postoperative complications after PD (Laaninen et al., 2012). Also, when the pancreas is fibrotic (acinar cell <40%), no complications occur after PD (Laaninen et al., 2016). In the case of DP, the texture of the pancreas is mainly normal and POPF occurs frequently.

Preoperative imaging has also been used to identify patients at risk of POPF. Frozanbor showed that increased pancreatic remnant volume measured on 3D CT increases the development of POPF (Frozanpor et al., 2010). Preoperative MRI and CT can also be used to measure pancreatic fat, fibrosis, thickness and cross-sectional area; cross-sectional area >377 mm² significantly increases the risk for POPF (Chang et al., 2017). Thick pancreas is one of the risk factors for POPF formation and stapler closure in particular may predispose to risk of POPF (Eguchi et al., 2011).

2.5.1.2   Body Mass Index

Obesity is associated with increased incidence of POPF after DP according to some but not all studies (Sledzianowski et al., 2005, Ferrone et al., 2008). High BMI has been shown to increase the risk for POPF and bleeding, but not to affect the short or long-term outcome after PD (Del Chiaro, Rangelova et al., 2013). In terms of laparoscopic distal pancreatectomy obesity causes longer operating time and greater blood loss, but has no significant influence on postoperative outcome (Sahakyan et al., 2016). High BMI correlates with other risk factors such as soft and fatty pancreatic parenchyma, which explains the risk (Mathur et al., 2007). Poor nutritional status (Sierzega et al., 2007) and hypoalbuminemia <3.5 g/dl have also been associated with higher POPF rate, 19.6% vs. 12.9% (Ecker et al., 2017). It is important to optimize the patient's nutritional status preoperatively.

2.5.1.3   Comorbidities and smoking

Smoking has been shown to increase the risk for POPF, and the effect of smoking on impaired wound healing is also well known (Krueger, Rohrich, 2001, Nathan et al., 2009). Preoperative diabetes may even protect against POPF according to a few studies (Nathan et al., 2009, Mathur et al., 2007), probably due to fibrosis of the pancreas in diabetic patients.

2.5.1.4   Other factors (age, gender)

There are many studies about age as a risk factor for morbidity or POPF. In most studies, age has not been an independent risk factor but a few studies have reported a correlation. It has been shown that patients younger than 65 years are almost three times more likely to develop CR-POPF (Yoshioka et al., 2010, Ecker et al., 2017). Conversely, increased risk of POPF has been found in older patients (Peng et al., 2017, Kleeff et al., 2007). Male gender has been shown in some studies to increase the risk for complications (Ferrone et al., 2008).

2.5.2 Surgery related risk factors

2.5.2.1   Operating time and blood loss

Operating time and blood loss are independent risk factors for morbidity (especially POPF) after DP (Hashimoto, Traverso, 2012), which has also been shown in a meta-analysis (Peng et al., 2017). Blood loss >225 ml, visceral obesity and open passive drainage were recently shown to be independent predictive factors for CR-POPF after DP in a retrospective single-institution analysis of 208 DP (32 CR-POPF) (Vanbrugghe et al., 2018).

2.5.2.2   Spleen preservation

Some studies have shown that splenectomy is associated with a higher risk for POPF (Shoup et al., 2002, Goh et al., 2008). The reason may be the ischaemia caused to the pancreatic stump by splenic vessel ligation or increased operative blood loss, which may also affect morbidity. Kleef et al. reported a higher fistula rate in splenectomized patients, but in an earlier study by Lillemoe et al. no difference was seen (Kleeff et al., 2007, Lillemoe et al., 1999). Recent studies have also found no difference between DP with and without splenectomy (Peng et al., 2017, Ridolfini et al., 2007). A recent meta-analysis of seven studies showed that spleen preservation had no impact on CR-POPF (Tieftrunk et al., 2018). Spleen preservation in DP for benign or low-grade malignant disease has also been shown to be safe and to reduce the occurrence of perioperative infection complications, severe complications and LOS when compared to DP with splenectomy (Pendola et al., 2017, Shoup et al., 2002).

2.5.3 Hospital related risk factors

2.5.3.1   Hospital volume

DP is not defined as equally high-risk surgery as PD. Mortality is close to zero even though morbidity rates are high. An association between high hospital volume and lower postoperative mortality has been shown in PD (Birkmeyer et al., 2003, Ahola et al., 2017). Differences in mortality between high and low-volume hospitals are not explained by fewer complications but by failure to rescue the patient from mortality following complications. Failure-to-rescue rates are significantly higher in very low-volume centres compared with high-volume centres (Ghaferi, Birkmeyer & Dimick, 2011). The mortality risk is also attributable to patient characteristics, such as age and comorbidity (LaPar et al., 2012). There are only a few reports making a distinction between the outcomes of pancreatic resections; usually the studies discuss pancreatic resections in general, or only PD. In a study in the United States 1998–2003, where the DP subgroup was analysed separately, mortality was 5.1% in LVC compared to 0.43% in HVC in DP (McPhee et al., 2007).

2.5.3.2   Detection of complications

Distal pancreatectomy patients are at high risk for complications. DP complications are rarely life-threatening, but they do increase LOS and costs and also suffering to patients. Detection and treatment of complications after pancreatic surgery often need CT imaging and interventional radiology services around-the-clock. The decision on how to treat the complication often requires a multidisciplinary approach. A reasonable volume of pancreatic surgery is needed to achieve and sustain experienced perioperative management.

The ward staff also needs to be trained to recognize worrisome signs of complications and experienced surgeons need to be readily available. Most postoperative complications can nowadays be treated conservatively or with minimally invasive approaches instead of open surgery. In LVCs modern treatment may be limited.

2.6 Methods aiming to prevent complications after distal pancreatectomy

2.6.1 Surgical techniques

2.6.1.1 Conventional technique

Closure of the pancreatic stump is thought to be the most important step in DP to decrease the risk of POPF. Traditionally the pancreas is divided with a scalpel and the cut edge can be shaped in fish-mouth style in order to close the anterior and posterior capsule even in thicker pancreas. The pancreatic stump is closed with interrupted mattress sutures. Hand-sewn closure is the oldest technique and suitable for all textures. The fistula rate after suture closure has been reported to be unsatisfactory at approximately 30–35%, but the classification of fistulas in older studies is not amenable to comparison (Nathan et al., 2009, Ferrone et al., 2008). The main pancreatic duct should be ligated separately, failure to ligate may double the risk of fistula development (Bilimoria et al., 2003, Yoshioka et al., 2010, Pannegeon et al., 2006).

2.6.1.2 Stapler closure of the pancreatic stump

Stapler and suture closure are the main ways to close the pancreas remnant. Stapler closure was first reported in 1979 and has become a common method, mainly because of the increase in laparoscopic procedures. Staplers can also be used in open procedures; this is safe, easy, fast and ensures good haemostasis, even though thick pancreas continues to be a risk factor in stapler closure (Kawai et al., 2013, Okano et al., 2013). Stapler closure has been compared with other closure methods in many studies and POPF rates are lower with staplers, but not significantly in all (Probst et al., 2015, Knaebel et al., 2005, Zhang et al., 2015, Zhou et al., 2010, Frozanpor et al., 2010, Ban et al., 2012). Only one multicentre randomized trial has been reported comparing stapler closure with other methods, the DISPACT trial. This was a European multicentre trial with 450 patients divided into suture or stapler groups. No difference found in the incidence of POPF, the fistula rates in the groups being almost identical at 36 % vs. 37 % (Diener et al., 2011). On the other hand, stapler closure has also been reported to be associated with higher fistula rate (Kleeff et al., 2007).

The stapler device can be reinforced, for example, with Seamguard bioabsorbable membrane or mesh or the stapler line can be oversewn. Seamguard is composed of polyglycolic acid and trimethylene carbonate. Some studies, including one RCT, found that reinforcing

the staple line with some form of mesh reduced the incidence of POPF (Jimenez, Mavanur & Macaulay, 2007, Thaker et al., 2007, Yamamoto et al., 2009, Hamilton et al., 2012). In the RCT, Seamguard mesh reinforcing to the stapler line decreased CR-POPF from 24% to 1.9%, but BMI in the reinforced stapler group was significantly lower (Hamilton et al., 2012). However, contrasting results have also been reported, some with an increased incidence (Guzman et al., 2009, Ferrone et al., 2008, Ceppa et al., 2015). To conclude on the results from the meta-analyses and multicentre prospective non-randomized studies, no significant difference in CR-POPF was found between stapler closure with or without reinforcement. Both may safely be used in DP (Kawai et al., 2017, Jensen et al., 2013). A multicentre, randomized trial recently also showed no difference in CR-POPF between reinforced staplers and bare staplers, the respective fistula rates being 16.3% and 27.1% (Kondo et al., 2019).

Adding sutures to the stapler line does not improve the results (Zhang et al., 2015, Goh et al., 2008, Bilimoria et al., 2003). Tripple-row staples may be preferable to double-row staplers in the prevention of POPF (Sugimoto et al., 2013). Stapler closure is not superior to hand-sewn closure but devices may improve in the future in terms of closure mechanism, reinforcement techniques and suitability for use on thick pancreas. Stapler closure of a thick pancreas may increase the risk of POPF (Kawai et al., 2013).

2.6.1.3   Pancreatic transection devices

Many devices can be used for transection of the pancreas. These are so-called non-closure techniques. A retrospective study showed that bipolar scissors, which cut and coagulate simultaneously, decreased the risk of POPF after DP from 36% to 10% compared to hand-sewn suture closing (Kawai, Tani & Yamaue, 2008). Ultrasonically activated scalpel (Harmonic scalpel; Ethicon Endo-Surgery, Johnson & Johnson) likewise decreased the POPF rate from 30% to 0% (Sugo et al., 2001) and from 25.8% to 3.7% in one RCT comparing ultrasonic dissection (US) with conventional dissection (Suzuki et al., 1999). After transsecting the pancreas with US, the main pancreatic duct was ligated separately. US transsection and reinforced stapler (RS) was compared recently in two retrospective matched cohort studies. Rate of CR-POPF was 40% in the US group and 12% in the RS group (Pulvirenti et al., 2019). Saline-coupled radiofrequency dissector (TissueLink; Salient Surgical Technologies, Denver, NH, USA) was used to cut the pancreas in a retrospective study and achieved a 10% POPF rate vs. 36% in the traditional closure group (Blansfield et al., 2012). LigaSure (Covidien/Medtronic, Dublin, Ireland) sealing device has so far only been tested on an animal model with 0% POPF rate (Hartwig et al., 2010) but thickness and fibrosis of the human pancreas may enhance the result with this technique, which has not so far been studied in humans.

2.6.1.4   Pancreatoenteric anastomosis

Pancreatojejunostomy (PJ) and pancreatogastrostomy have also been performed in an attempt to reduce the risk of POPF after DP (Okada et al., 2014, Klein et al., 2012, Kleeff et al., 2007). Many of these studies compare enteric anastomosis to stapler closure with no effect on POPF rate. A recent Japanese RCT comparing pancreaticojejunostomy and stapler closure likewise reported no significant difference in POPF. PJ may, however, be preferable to stapler closure in thick pancreas (Kawai et al., 2016). By contrast, differences in favour of pancreaticojejunostomy have been found, especially when comparing anastomotic closure to hand-sewn closure (Zhang et al., 2015, Wagner et al., 2007, Meniconi et al., 2013, Yanagimoto et al., 2014). Zero fistula rates after pancreaticojejunostomy have been reported, the numbers of patients in those studies, however, were small (Meniconi et al., 2013, Wagner et al., 2007). Pancreatigogastrostomy did not reduce CR-POPF compared with hand-sewn closure in a recent RCT (Uemura et al., 2017). It is to be hoped that two ongoing RCTs in Japan investigating anastomotic closures and POPF will clarify the efficacy of this method. The Finnish binding anastomosis technique, where the pancreatic stump is inserted into the jejunal end, sutured with peripancreatic stitches and tightened by a purse-string suture has yielded promising results and is routinely used in PDs performed in Tampere University Hospital (Nordback et al., 2008).

2.6.1.5   Stump coverage

Covering the resection margin with autologous tissue, absorbable fibrin sealant (Tachosil®) or fibrin glue has been reported in some studies to lower the incidence of POPF (Hassenpflug et al., 2012, Walters et al., 2011, Kleeff et al., 2007, Suzuki et al., 1995). Absorbable fibrin sealant (Tachosil®) has been studied in several RCTs in recent years, but no significant reduction in POPF has been seen (Park et al., 2016, Sa Cunha et al., 2015, Montorsi et al., 2012, Huttner et al., 2016, Gong et al., 2018).

Fibrin glue can be added to the closure line of the pancreas and adding it to the suture line reportedly decreased the fistula rate from 40% in the control group to 15.4% (Suzuki et al., 1995). Pancreas stump coverage with falciform ligament or serosal patch from the jejunal loop or stomach has shown an improvement in fistula rate and also reduced LOS and costs (Hassenpflug et al., 2012), but the RTC (DISCOVER) by the same research group to investigate the use of teres ligament patch failed to show a significant decrease in clinically relevant fistula formation (22.4 vs. 32.9%). Ligament Teres patch still showed a significant decrease in readmission (13.1 vs. 31.5%) and reoperation (1.3 vs. 13%) rates (Hassenpflug et al., 2016). An earlier RCT adding falciform ligament patch and fibrin glue to a sutured or stapled line did not reduce the rate or the severity of POPF (Carter et al., 2013).

In mesh reinforcement the mesh is wrapped around the pancreatic stump after DP. Polyglycolic acid (PGA) mesh is composed of a bioabsorbable recombinant membrane made of a synthetic polymer with cellulose-like structure. In a nonrandomized retrospective

study it was used in DP to prevent fistula and the POPF rate was low, at 4%, compared to controls at 27% (Ochiai et al., 2010). In 2017 a RCT was published on PGA mesh wrapped over the cut edge and the rate of POPF was significantly lower in the PGA group than in the control group (11.4% vs. 28.3%) (Jang et al., 2017).

2.6.1.6 Postoperative drains

Postoperative drains are traditionally used in pancreatic surgery for monitoring the fluid postoperatively, but their advantage has recently been questioned. In the case of fistula, the drain creates a controlled fistula and decreases the incidence of fluid accumulation. Retrospective studies on both DP and PD patients have been presented. In PD, the absence of a drain has been shown to increase mortality (Van Buren et al., 2014) even though a recent RCT concluded that routine drainage after PD is unnecessary in terms of mortality, morbidity or reinterventions (Witzigmann et al., 2016). Another RCT reported that in patients at low risk for POPF (drain amylase level <5000 U/L), intra-abdominal drains can be safely removed on the POD 3 after standard PD or DP (Bassi et al., 2010). For DP only, a few non-RCT and retrospective studies have been presented reporting no difference in complications with or without drainage and also one RCT (Behrman et al., 2015, Paulus, Zarzaur & Behrman, 2012). According a recent RCT there were no differences in Grade 2 or higher complications or in clinically relevant fistula rate with or without intraperitoneal drainage after DP, but the incidence of intra-abdominal fluid collections was higher in the no-drain group, most of whom needed no intervention (6% needed percutaneous drainage) (Van Buren et al., 2017). Nevertheless, prophylactic drains probably reduce the severity of POPF and also the reoperation rate. (Ecker et al., 2017.) On the other hand, drains may even prolong the fistula or contaminate sterile self-curing collections, thereby making them clinically relevant.

Even though routine drainage has not been shown to afford much advantage, drains are commonly used in clinical practice (Maggino, Malleo, Salvia et al., 2019). A recent observational study reported a drainage rate after DP of 84.4%, which is in line with earlier reports in the literature (Seykora et al., 2019, Behrman et al., 2015, El Khoury et al., 2018). In that study only 15.2% of drains were removed on or before the third postoperative day. Early drain removal was shown to have better outcomes than late removal and it moreover reduced the development of POPF. Drain amylase level on the first postoperative day (DFA1) was the best predictor of POPF. They also identified an optimal cut-off for drain fluid amylase value on DFA1, namely >2000 U/L (Maggino, Malleo, Bassi et al., 2019). DFA1 has been shown to predict POPF in other studies (Vass et al., 2018).

Type of drain used has also recently been discussed. Passive open gravity drains and closed-suction drains have been compared. According to a recent RCT, drain type does affect the POPF or complication rate in pancreatic resections (Cecka et al., 2018). A prospective, observational study compared these two drain types and no difference was found in PD or DP (Marchegiani et al., 2018). However, in a recent retrospective analysis

of a single institution open passive drainage was found to be an independent risk factor for POPF after DP in addition to visceral obesity and blood loss >225 ml (Vanbrugghe et al., 2018).

2.6.1.7   Pancreatic stenting

Pancreatic stents can be placed pre- or peroperatively using endoscopic retrograde cholangio-pancreaticography (ERCP) or intraoperatively during surgery by placing the stent from the pancreatic main duct into the duodenum before closure of the stump. The idea is to drain the pancreatic juice to the duodenum via the papilla of Vater and to decompress the main pancreatic duct. Many meta-analyses have reported good results and low POPF rates (Abe et al., 2008, Rieder et al., 2010, Hashimoto, Traverso, 2012, Oida et al., 2011, Fischer et al., 2008). So far only one RCT has been published in Sweden and in that trial prophylactic pancreatic stenting did not reduce POPF or other complications after DP (Frozanpor et al., 2012). There were differences in these studies, however; in the RCT the stent was placed at the time of pancreatic resection and in earlier studies one week before DP.

2.6.2 Pharmacological methods

Somatostatin analogues (octreotide, pasireotide) have long been used in pancreas resection to prevent and to treat POPF. This treatment has an inhibitory effect on the exocrine function of the pancreas. In a Cochrane review octreotide did not affect clinically relevant POPF, but studies mainly consisted of PD patients (Gurusamy et al., 2012). According to another meta-analysis, octreotide reduced postoperative complications, but readmission, LOS, mortality, reoperation and clinically relevant POPF rate remained the same (Koti et al., 2010). No RCT including only DP patients has been presented. Several retrospective analyses have been reported, some favouring the use of octreotide and some finding no difference (Lorenz et al., 2007, Ridolfini et al., 2007). In 2014 Allen (Allen et al., 2014) published an RCT where pasireotide reduced the risk of POPF in DP from 23% to 7%. They analysed both DP and PD and found significant differences in both groups. The cost analysis in that RCT also showed that POPF doubled the costs and routine use of pasireotide did not increase the overall costs (Ma et al., 2017). Conversely, in a recently published article comparing pasireotide to historical controls pasireotide did not prevent POPF after DP or PD, the fistula rate was 17% compared 15.5% among the historical controls. No difference was found in the subgroups (DP or PD), the rate being 15.2% in DP and 17.9% in PD (Elliott et al., 2018). This was not an RCT, but the finding renders the effect of pasireotides debatable. Similar findings were also reported in another recent article where pasireotide did not decrease CR-POPF after pancreatic surgery (PD and DP), nor did it reduce length of hospital stay or postoperative complications (Young et al., 2018). Pasireotide is an expensive drug and also causes dose-limiting nausea as a side effect, 17%

and 38% in the studies mentioned above. Another RCT is needed to ascertain the true effect of pasireotides after pancreatic resection. Tampere Pancreas Group has previously shown that perioperative hydrocortisone reduces the incidence of major complications after PD (Laaninen et al., 2016). It is cheap and has no side effects according to that study.

Another interesting drug is botulinum toxin, which is a smooth muscle relaxant. It can be injected endoscopically into the Spincter of Oddi to prevent POPF by relaxing the muscle. Hackert et al. published a prospective clinical trial of botulinum injection six days before DP and it seemed to be safe and efficient. No CR-POPF was found in the botulinum toxin group compared to controls (33%) (Hackert et al., 2017). These results are promising and will be validated in a multicentre RCT in Germany.

Narcotic pain medicators may also cause dysfunction in the Sphincter of Oddi. Morphine, commonly used for postoperative pain, causes contraction of the Sphincter of Oddi. This may predispose to the development of POPF by increasing the pancreatic duct pressure, when the flow of pancreatic juices into the duodenum decreases and the healing of the stump is disrupted. Dose-dependent postoperative narcotic use has been shown to be associated with the development of CR-POPF after DP (Hashimoto, Traverso, 2012, Kowalsky et al., 2018). The use of opioids in patients after DP should be limited.

2.6.3 Patient care

Patient care during and after surgery is crucial for the morbidity rate and treatment of complications has attracted more attention in recent years. Postoperative care should be standardized and ward staff trained to detect deviations from the normal postoperative pathway. Routine management of postoperative pain, ICU admission criteria and routine use of drains and drain removal criteria should be noted. Intraoperative fluid therapy also needs to be observed and standardized, because it was recently been shown that liberal fluid balance is associated with increased rate of CD>IIIB after DP and PD (50 vs. 27.1%, p=0.03) (Andrianello et al., 2018). It has been shown in a retrospective analysis that the implementation of new departmental guidelines for distal pancreatectomy is closely associated with low frequency of intra-abdominal abcesses and major (Clavien-Dindo III-IV) complications (Yui et al., 2014). In case of complications, access to and availability of an ICU should be fast and easy. In low-volume centres (LVC) operations are performed so seldom that the nurses or doctors on the ward have difficulties in establishing a routine in postoperative care and in detecting and managing complications.

Critical pathway protocols or fast-track protocols are good for improving quality and lowering costs. They provide a structured roadmap for postoperative care from the preoperative stage until discharge and should be in use in every high-volume centre (HVC) and high-quality centre. With protocols postoperative hospital stay and costs can be reduced, maintaining or improving outcomes without increasing readmissions in DP (Kennedy et al., 2009, Pecorelli et al., 2017). An enhanced recovery after surgery (ERAS)

programme has also been introduced in pancreatic surgery, but its benefits are not yet clear (Lassen et al., 2012, Kagedan et al., 2015). It seems to be safe and may reduce the incidence of minor complications, promote recovery and shorten LOS in high-risk pancreas surgery in general, even though it may not affect the rate of POPF (Ji et al., 2018, Morgan et al., 2016). In LDP the enhanced recovery programme also improves outcomes by reducing LOS, saving on costs and restoring the patient's normal gut function significantly faster (Richardson et al., 2015).

2.6.4 Centralization of pancreatic surgery

PD has been shown to carry lower mortality and morbidity and also better oncological outcome in high-volume centres (Ahola et al., 2017, Hata et al., 2016). Centralization of pancreatic surgery has proceeded in many countries, including Finland, in the last few years. So far, centralization of DPs to high-volume centres does not seem to occur and there are only few studies concerning only DPs in terms of postoperative complications and mortality and hospital volume. Most studies include all types of pancreatic resections, PD, DP and TP. Yet there are differences in mortality and morbidity among these different procedures. Postoperative mortality after DP is significantly lower than after PD and after TP there are no fistula related complications (McPhee et al., 2007). Few studies report separately on DP; no significant difference has been seen in the frequency of postoperative complications in DP analysed by hospital volume in the United States (Rosales-Velderrain et al., 2012). A difference in mortality has still been reported in DP, being 5.1% in LVCs and 0.43% in HVCs in the United States in the period 1998–2003 (McPhee et al., 2007).

2.6.5 Can we decrease complications after distal pancreatectomy?

Mortality after DP is low these days, due to advantages in surgical techniques and improved perioperative care. Yet morbidity remains high. Many of the surgical methods mentioned above have been tried out to improve morbidity, especially POPF rate after DP. There are many promising methods and encouraging results in small series, which often lack of significance in RCTs. So far no method has been proven to be better than others, and, due to inconsistent results, no consensus has been reached. More innovations are needed in this field.

Our hospital has succeeded among PD patients in creating well functioning anastomosis, to lower the POPF rate after PD (Nordback et al., 2008). It is not known whether such anastomosis could also lower the fistula rate in DP patients.

The failure of numerous surgical methods to reduce the fistula rate compels us to seek other than surgical methods. Various drugs have been tried and pasireotide has recently yielded promising results (Allen et al., 2014). In a recent study on PD, perioperative

hydrocortisone reduced the complication rate, but its usefulness in DP is not known (Laaninen et al., 2016).

Morbidity and mortality have been shown to be reduced in PD after centralization procedures to HVCs (Hata et al., 2016). The effect of centralization on DP has not been established.

The question remains if it is possible to improve outcomes after DP by means of novel surgical or medical methods or by centralizing operations or by combination of all of these.

3 Aims of the Study

The aim of this thesis was to investigate the postoperative complications of distal pancreatectomy, various strategies to improve the outcome and to innovate new ones. The specific aims were:

I   To investigate whether the Finnish binding anastomosis used in PD is also suitable for use in DP and its effect on POPF rate.

II To investigate whether perioperative hydrocortisone treatment reduces the POPF rate and overall complications after open DP.

III To study the national data on DP in Finland in terms of hospital volume and complication rate.

4 Patients and Methods

4.1 Study I

In Study I patients scheduled for elective DP in Tampere University Hospital 2009–2013 were considered for recruitment. Preoperative CT scan and tumour location were used as the recruitment criteria. In Finnish binding pancreaticojejunal anastomosis (FBPJ) the transection line of the pancreas must be left of the portal vein in order to mobilize the pancreas 2–3 cm before inserting it into the jejunal limb. Tumours in the pancreatic body were eligible for randomization. FBPJ is in use in PD in Tampere University Hospital and has been shown to reduce the risk for POPF after PD. When the distal pancreas was removed, and if still eligible, the patients were randomized to either the FBPJ or the hand-sewn group. Patients eligible for FBPJ were defined as the prospective randomised group (RPT arm). In addition, all other DP patients were included in the prospective follow-up (PFU arm).

Out of 47 DPs, only 16 patients met the randomization criteria and were randomized to either the FBPJ or the conventional hand-sewn group. In two patients FBPJ was technically impossible and they received a hand-sewn closure. In addition, one patient had an inoperable disease. FBPJ anastomosis was technically possible in only five patients and hand-sewn closure in ten patients in the RPT arm. Hand-sewn closure was also made in 11 patients in the non-RPT arm. A further 20 patients not included in the study in the prospective follow-up arm also received hand-sewn closure. Thus, a total of 41 patients had a hand-sewn closure (Figure 6).
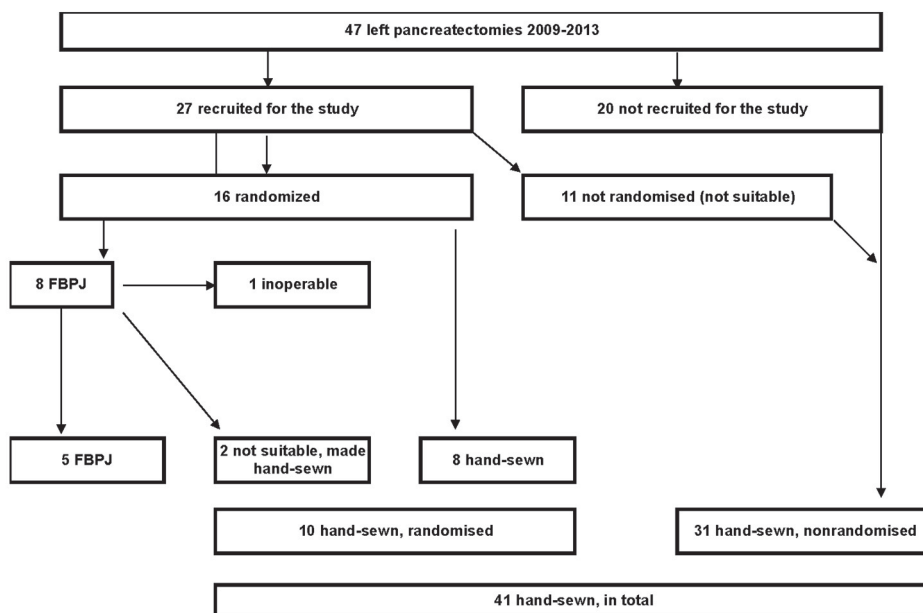
Figure 6.   Flow chart of the study patients in Study I

Out of 47 DPs, 27 were recruited and only 16 of these met the randomization criteria. Finally, among the randomized patients, only five received an FBPJ and eight patients a hand-sewn closure.

Perioperatively all patients received prophylactic antibiotics (rocephalin 2 g ceftriaxone; Roche, Espoo, Finland and metronidatzole 500 mg, metronidatzole, Braun, Germany). Patients randomized for FBPJ received pancreaticojejunal anastomosis (Figure 7). The pancreatic remnant was inserted 2–3 cm inside the jejunal limb using peripancreatic sutures (4-0 Maxon, Covidien, USA) after which the purse-string suture (4-0 PDS, Ethicon, USA) was tightened and the roux-Y anastomosis completed. In the hand-sewn group the pancreas was divided with a scalpel, the pancreatic main duct was closed and the stump was oversewn with 4-0 Maxon. A non-suction drain was placed near the anastomosis in both groups.

Postoperatively, according to standard protocol, drain amylase concentrations were measured on the third postoperative day and daily after that if the drain was still in place. Postoperative complications (fistulas, bleeding, abscesses, wound infections), LOS and mortality were defined. POPF was defined according to the international criteria at that time. Primary endpoints were feasibility of FBPJ technique in DP and the effect of FBPJ on fistula incidence.
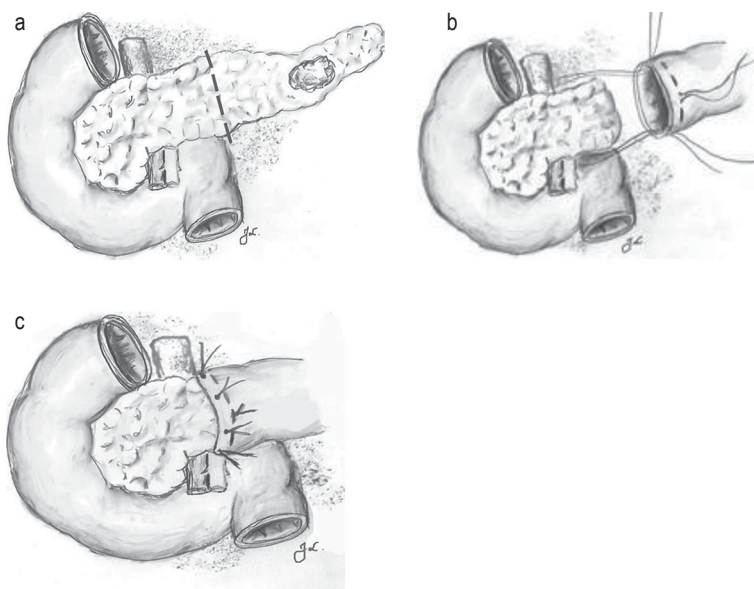
Figure 7.   FBPJ after distal pancreatectomy

The transsection line needs to be clearly to the left of the portal vein (a). After mobilizing the pancreatic stump 2–3 cm, it is inserted inside the jejunal loop with the aid of anchoring sutures (b). The purse-string applied in the jejunum is tightened (c) (Antila et al., 2014).

4.2   Study II

In study II, 47 patients were assessed for eligibility and 40 were randomized between November 2013 and January 2017 at Tampere University Hospital in Finland. Exclusion criteria were ongoing cortisone treatment, ceftriaxone allergy or chronic pancreatitis. Patients were randomized to two groups before surgery: the hydrocortisone or the placebo group. PD patients were also included in the study as a separate group using the same study protocol.

Out of 40 randomized patients, five had an advanced, inoperable disease and three underwent a different procedure (PD, total pancreatectomy and pseudocysto-jejunostomy) and were excluded from the study. Finally, 31 patients continued through the study after randomization; 14 were randomized to the placebo group and 17 to the hydrocortisone group (Figure 8).
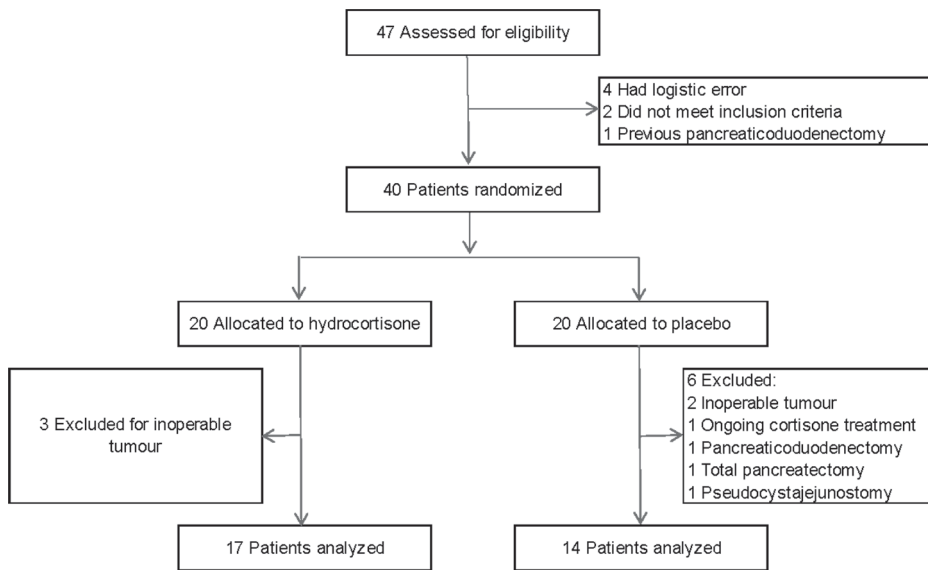
Figure 8.   The Flow chart of Study II

Seventeen patients were randomized to the hydrocortisone group and fourteen to the placebo group (Antila et al., 2019).

All operations were open procedures with hand-sewn closure of the pancreatic stump. The pancreas was cut using a scalpel, the main duct was sutured separately and the cut edge was oversewn with interrupted 4-0 Maxon (Covidien, USA) sutures. The percentage of acini cells in the pancreatic transection line was analysed by the pathologist perioperatively. Patients received routine antibiotic prophylaxis of ceftriaxone 2 g (Rocephalin; Roche, Basel, Switzerland) and metronidatzole 500 mg (Metronidatzole; Braun, Melsungen, Germany) intravenously and either HC 100 mg or placebo intravenously depending on the randomisation. HC treatment continued for risk patients with 100 mg/placebo three times a day until the third postoperative day. Ceftriaxone 2 g i.v was also continued.

The randomisation list was compiled by a biostatistician and randomization was made preoperatively. The HC solution consisted of hydrocortisone sodium succinate (Solu-Cortef; Pfizer Manufacturing, Puurs, Belgium) in 0.9% sodium chloride solution (Natriumklorid Braun, 9 mg/mL; B. Braun Melsungen, Melsungen, Germany). Infusion bags were filled with 100 mg hydrocortisone in 2 ml of sodium succinate added into 100 ml of 0.9% sodium chloride solution. The placebo solution was made up by adding 2 ml of 0.9% sodium chloride solution into 100 ml of 0.9% sodium chloride solution.

PPH, DGE and POPH were defined according to international classifications (Bassi et al., 2005, Wente et al., 2007, Wente et al., 2007). The original ISGPF classification for POPF grading was used in the analysis. Grade B and C POPF were defined as clinically

significant POPFs. Clavien-Dindo classification was used to score complications (Dindo et al., 2004). The primary endpoint was major complications and the secondary endpoint CR-POPF.

4.3   Study III

All patients who underwent DP between 2012 and 2014 were identified from the Care Register for Social Welfare and Heath Care and the Nordic Classification of Surgical Procedures using codes (ICD10 codes JLC10 and JLC11). Overall 194 patients were obtained. Patient data on medical history, postoperative complications, POPF, 90-day mortality, reoperations and hospital stay were recorded from the patient records. Data regarding the operation details were also studied. Emergency operations and patients with no records were excluded. POPFs were graded according to the new ISGPF classification (Bassi et al., 2017) and postoperative complications according to the Clavien-Dindo classification. Grades III-V were considered major complications. Operating centres were grouped as high-volume centres (HVC); >10 DPs, medium-volume centres (MVC); 4–9 DPs and low-volume centres (LVC) fewer than 4 DP annually.

4.4   Statistics

For Study I, the power calculation was made by estimating that FBPJ would reduce the POPF rate by 50%. If the patients with hand-sewn closure had twice as many clinically relevant POPFs compared to FBPJ, (30% vs. 15%), we would need 26 patients in each group to be able to show a statistically significant difference with power $\pi=0.80$ (α 0.05). We estimated that about one third of the patients would not meet the recruitment criteria based on CT, and that about 10% of the recruited patients would not meet the randomization criteria according to the findings during surgery. Thus for 52 randomized patients we would need 58 recruited patients, and for those we would need a population of 78 distal pancreatectomies.

Study II was designed to include both PD and DP patients, but planned to be published separately (Laaninen et al., 2016). The interim analysis of PD patients showed that HC treatment reduced the fistula rate after PD to almost nil. For the study on DP patients for power calculation we used the estimate that HC would decrease the incidence of POPF to one seventh. We estimated that 36 consecutive patients scheduled for open distal resection would need to be randomised to show a statistically significant difference (alpha 0.05, 80% power). Finally, 40 patients were randomised to allow for 10% dropout.

In Study III, the statistical analysis was performed using IBM SPSS statistical software. Fisher's exact test for cross-tabulated variables and Mann-Whitney test for quantitative

variables were used to calculate the significance between the two groups. P≤0.05 was considered statistically significant.

4.5 Ethics

All studies were conducted in accordance with the Helsinki Declaration. The protocols for Studies I and II were approved by the ethics committee of Tampere University Hospital. Study I was registered at clinical.trials.com, NCT02113046 and Study II, NCT01460615. Study III was granted ethical approval by the Regional Ethics Committee of Pirkanmaa, Finland (ETL code R12241). The data collection for Study III was approved by the National Institute for Heath and Welfare in Finland.

5   Results

5.1   Roux-Y binding pancreaticojejunal anastomosis and distal pancreatectomy

In Study I, out of 47 DPs, only 16 patients met the randomization criteria and were randomized to either FBPJ or the conventional hand-sewn group. Finally, FBPJ anastomosis was technically possible in only five patients and hand-sewn closure in ten patients in the RPT arm. In total 41 patients had a hand-sewn closure.

Interim analysis was made when 47 consecutive patients had undergone DP and the study was discontinued mainly because the patients seemed not to be eligible for FBPJ anastomosis.

The main endpoints were feasibility of FBPJ in DP and POPF rate. Only 13/47 (27%) patients were eligible for FBPJ and in addition the POPF rate was high in these FBPJ patients. Of the randomized patients 60% in the FBPJ group and 12.5% in the hand-sewn group developed POPF. Thirty-day mortality was zero and no reoperations were needed in either group. Patient demographics and postoperative complications are shown in Table 1. The incidence of POPF in the different groups is shown in Table 2. Final histopathogical diagnoses did not differ between groups.

Table 1.   Patient demographics and postoperative complications in Study 1 (Antila et al., 2014)

Characteristics	FBPJ		Hand-sewn rand		Hand-sewn all	
N	5		8		41	
Age	67	(55–74)	60		66	(26–85)
Gender M/F	1/4		0,33		15/26	
BMI (mean)	28,2		27,2		26	
Smoking	1 (20%)		0		7	(17%)
Alcohol abuse	0		1	(12.5%)	5	(12.1%)
DM	0		2	(25%)	5	(12.1%)
Cardiac disease	0		1	(12.5%)	3	(7.3%)
Hypertension	2	(40%)	2	(25%)	20	(48.7%)
Wound infection	0		0		4	(9.7%)
PPH	0		0		0	
Abscess	3	(60%)	0		9	(21.9%)
Pancreatitis	0		1	(12.5%)	2	(4.9%)
Trypsinogen posit	1	(20%)	1	(12.5%)	10	(24.3%)
Length of stay (d)	10	(7–15)	7	(6–9)	7	(6–32)
Readmission	1	(20%)	1	(12.5%)	4	(10%)
Operating time (mins)	170	(136–300)	162	(115–200)	170	(90–305)
Blood loss (ml)	750	(300–2350)	750	(300–1300)	750	(100–3600)
Mortality	0		0		0	

Table 2. Incidence of POPF in the different groups in Study I

	FBPJ n=5, randomised	Hand-sewn n=8, randomised	All hand-sewn n=41, non-randomsed
Pancreatic fistula			
Grade A	0	0	0
Grade B	60% (3)	13% (1)	37% (15)
Grade C	0	0	0

5.2   Prevention of complications through hydrocortisone

In Study II, pre- and perioperative characteristics were otherwise identical in the HC and placebo groups, but patients' ages in the HC group were significantly higher (Table 3). The final histopathological diagnoses did not differ between groups; 10 IPMN, 5 adenocarcinomas, 4 NET, 3 MCN, 3 SCN, 1 metastasis from renal cancer, 1 solid pseudopapillary neoplasm, 1 pseudocyst, 1 lymph node, accessory spleen and 1 mesothelial cyst (Table 4).

Table 3.   Pre- and perioperative characteristics in hydrocortisone and placebo group patients in Study II (Antila et al., 2019)

	Hydrocortisone (n=17)	Placebo (n=14)	p value
Age yrs, median (range)	73 (41–82)	61 (39–76)	0.045
Male	7 (41%)	4 (29%)	0.707
BMI, kg/m^2	27 (22–35)	29 (21–39)	0.164
COPD	1 (6%)	2 (14%)	0.576
Diabetes	7 (41%)	5 (36%)	1
ASA class I–II III	 6 (35%) 11 (65%)	 7 (50%) 7 (50%)	0.481
Operating time min, median (range)	158 (103–391)	159 (108–224)	0.942
Blood loss mL, median (range)	550 (120–2300)	700 (50–1400)	0.975
Main pancreatic duct diameter < 3 mm ≥ 3 mm	 16 (94%) 1 (6%)	 13 (93%) 1 (75)	1
Splenectomy	12 (70,6%)	6 (42.9%)	0.157
Acini>40% in the transsection line	17 (100%)	14 (100%)	1
Soft pancreas texture	17 (100%)	14 (100%)	1

Table 4.   Final histopathological diagnosis in the groups in Study II (Antila et al., 2019)

	Hydrocortisone	Placebo	P value
Histopathological diagnosis			0.578
Pancreatic ductal adenocarcinoma	4 (23%)	1 (7%)	
NET	2 (12%)	2 (13%)	
Cystic tumour	9 (53%)	8 (57%)	
Other	2 (12%)	3 (21%)	

The primary endpoint was major complications graded by Clavien-Dindo scoring (Clavien-Dindo III–V). No significant differences between the HC and placebo groups were found 5.9% (1/17) and 21.4% (3/14) respectively (p=0.304). Hospital stay and readmission rate were similar and 90-day mortality was zero in both groups.

The rate of Grade B or C POPF was significantly reduced by HC treatment compared to the placebo group (5.9% vs. 42.9%, p=0.028). In the HC group there was only one Grade C fistula. This patient was treated with both percutaneous and endoscopic drainage. In the placebo group, patients 42.9% (6/14) developed clinically significant fistula. These included four Grade B fistulas and two Grade C fistulas. One Grade C fistula resulted in the patient's death on day 96 post-operatively. This patient was treated with both percutaneous and endoscopic drainage and relaparotomy. Bowel necrosis was seen at laparotomy, caused

by prolonged infection inducing reduced blood circulation in the atherosclerotic vessels. Postoperative complications are shown in Table 5.

The incidence of biochemical leak (former POPF Grade A) was six in the HC group and one in the placebo group (ns). These fistulas did not affect the patients' clinical pathways.

Table 5.   Postoperative complications in the groups in Study II (Antila et al., 2019)

	Hydrocortisone (n=17)	Placebo (n=14)	P value
Pancreatic fistula			
Grade B	0	4 (28.6)	1.00
Grade C	1 (5.9%)	2 (14.2%)	0.028
Overall (B+C)	1 (5.9%)	6 (42.9%)	
Delayed gastric emptying	1 (5.9%)	0	1.00
Intra-abdominal fluid collection	2 (11.8%)	3 (21%)	0.636
Wound infection	1 (5.9%)	3 (21%)	0.304
Intra-abdominal haemorrhage	0	0	
Pneumonia	1 (5.9%)	2 (14.3%)	0.576
Spleen necrosis	1 (5.9%)	1 (7.1%)	1.00
Lymphatic leak	2 (11.8%)	1 (7.1%)	1.00
CT verified pancreatitis	1 (5.9%)	1 (7.1%)	1.00
Urine trypsinogen positive ≥ 2 days	4 (23.5%)	5 (35.7%)	0.693
Pulmonary embolism	1 (5.9%)	0	1.00
Clavien-Dindo			
I	4 (23.5%)	4 (28.6%)	
II	6 (35.3%)	5 (35.7%)	
III	1 (5.9%)	2 (14.3%)	
IV	0	0	
V	0	1 (7.1%)	
Clinically significant (III–V)	1 (5.9%)	3 (21.4%)	0.304
Reoperation	0	1 (7.1%)	0.452
Total hospital stay (days, range)	8 (2-23)	7 (6-38)	0.625
Readmission	3 (17.6%)	3 (21.4%)	1.00
90-day mortality	0	0	

5.3   National data on pancreatic distal resections in Finland 2012–2014

A total of 194 DPs were performed nationwide in Finland during the period 2012–2014 in 18 different hospitals. These included 2 HVCs, 6 MCVs and 10 LVCs. Eighty-one patients were operated on in HVCs (42%), 84 in MVCs (43%) and 29 in LVCs (15%). Patient demographics or perioperative data were similar between the hospital volume groups (Table 6). The final histopathological diagnoses are shown in Table 7.

Table 6.   Pre- and perioperative characteristics in the groups in Study III (Antila et al., 2019)

	High-Volume centre n=81	Medium-volume centre n=84	Low-volume centre n=29	
Age , median, years (range)	62 (0.3–80)	65 (21–80)	67 (41–85)	
Sex ratio (F/M)	45/36	60/24	17/12	
BMI	26,1 (16–40)	23.6 (19–40)	28.4 (23–36)	
Diabetes	20 (24.7%)	10 (14.1%)	8 (29.6%)	
Laparoscopic procedure	23 (28.4%)	23 (27.4%)	1 (3.4%)	p=0.008
Combined resection of other organs	9 (11.1%)	17 (20.2%)	4 (13.8%)	
Hand-sewn closure of the pancreatic	25 (30.9%)	20 (23.8%)	11 (37.9%)	
Stapler closure of pancreatic stump	54 (66.7%)	64 (76.2%)	16 (55.2%)	
Splenectomy	42 (51.9%)	58 (69.0%)	16 (55.2%)	
Blood loss (ml)	850 (150–5300)	590 (0–16000)	500 (300–2500)	
Operating time (min)	167 (115–317)	200 (114–377)	180 (120–258)	
Number of hospitals	2	6	10	

Table 7.   Final histopathological diagnoses in all patients in Study III (Antila et al., 2019)

	All patients n=194
Adenocarcinoma	40 (20%)
Neuroendocrine carcinoma	7 (4%)
Intraductal papillary mucinous carcinoma	2 (1%)
Gastrointestinal stromal carcinoma	1 (1%)
Renal metastasis	6 (3%)
Colon carcinoma	1 (1%)
Neuroendocrine tumour	43 (33%)
Mucinous cystic neoplasm	23 (12%)
Intraductal papillary mucinous neoplasm	17 (9%)
Serous cystic neoplasm	20 (10%)
Solid pseudopapillary neoplasm	3 (2%)
Chronic pancreatitis	7 (4%)
Pseudocyst	7 (4%)
Gastrointestinal stromal tumour	1 (1%)
Cyst	5 (3%)
Fibrosis	1 (1%)
Spleen accessorius	7(4%)
Haemangioma	1(1%)
Nesidioblastosis	1(1%)

The rate of clinically relevant POPF did not differ between the volume groups. In all patients the POPF (B/C) rate was 17.2%. In HVCs CR-POPF occurred in 21%, in MVCs in 10.7% and in LVCs in 17.2%. However, Grade C POPF was found more often in LVCs, the rate being 1.2% in HVCs, 0% in MCVs and 6.9% in LVCs, p=0.030. There were no differences in the incidence of intra-abdominal fluid collection postoperatively.

Clavien-Dindo Grade III–V complications likewise showed no differences; 16.0% of HVC patients, 18.1% of MVC patients, 20.7% of LVC patients. Furthermore, we found no difference in LOS or readmission rates between the different volume groups. Ninety-day mortality was zero in all groups. Reoperations were performed significantly more often in LVCs, on 10.3% of patients (3/29), and in HVCs and MVCs on 1.2% (1/81) and 1.1% (1/84) respectively, p=0.025. Postoperative complications in the groups are shown in Table 8.

In all open procedures the clinically relevant fistula rate was 17.2% and in the laparoscopic procedures 12.8% (ns). More laparoscopic procedures were performed in HVCs and MVCs than in LVCs (28%, 26% and 3% respectively, p=0.008). Stapler closure and hand-sewn closure had similar fistula rates, 17% and 17.0%. In all malignant cases the fistula rate was 14.2%.

Table 8. Postoperative complications in the groups in Study III (Antila et al., 2019)

% (n)	High-volume centre n=81	Medium-volume centre n=84	Low-volume centre n=29	
Pancreatic Fistula				
Grade B	19.8% (16)	10.7% (9)	10.3% (3)	
Grade C	1.2% (1)	0.0% (0)	6.9% (2)	P=0.030
Grade B/C	21.0% (17)	10.7% (9)	17.2% (5)	
PPH	4.9% (4)	4.8% (4)	6.9% (2)	
DGE	3.7% (3)	10.7% (9)	20.7% (6)	P=0.018
Intra-abdominal collection	28.4% (23)	25.0% (21)	20.7% (6)	
Interventional drain	13.6% (11)	11.9% (10)	10.3% (3)	
Pancreatic stent	2.5% (2)	2.4% (2)	6.9% (2)	
CT verified pancreatitis	3.7% (3)	2.4% (2)	0.0% (0)	
Lympha leak	1.2% (1)	1.2% (1)	0.0% (0)	
Wound infection	9.9% (8)	3.6% (3)	10.3% (3)	
Pneumonia	12.3% (10)	6.0% (5)	10.3% (3)	
Pulmonary embolism	3.7% (3)	0.0% (0)	5.0% (1)	
Clavien-Dindo III–V	16.0% (13)	18.1% (15)	20.7% (6)	
Reoperation	1.2% (1)	1.2% (1)	10.3% (3)	p=0.025
Total hospital stay, median (range)	7 (3–25)	8 (3-30)	8 (5–40)	
Readmission	16.3% (13)	13.1% (11)	24.1% (7)	
90-day mortality	0.0% (0)	2.4% (2)	0.0% (0)	

6 Discussion

Pancreatic surgery has been prone to complications, pancreatic fistula being the most feared. In distal pancreatectomy much effort has been made to reduce the rate of pancreatic fistula in terms of different closure mechanisms or medical therapy. This thesis focuses on the feasibility of a new anastomosis techique in DP and the effect of perioperative hydrocortisone treatment on postoperative complications. In addition, the benefits of centralization of DPs are demonstated.

Technically distal pancreatectomy differs from PD in lack of reconstructive anastomosis. However, in distal pancreatectomy the pancreatic cut line can also be anastomosized to the jejunum. Tampere binding anastomosis is now a routine procedure in PD in Tampere, Finland and provides low fistula rates in PD. It was therefore hoped also to achieve some improvement in the fistula rate after DP. Unfortunately, Tampere binding anastomosis was not suitable for DP, and this was the major finding in Study I. It was suitable for only a small number of patients and, according to our small study, it does not seem to reduce the POPF rate. Tampere binding anastomosis requires mobilization of the pancreatic stump by 2–3 cm, in order to insert it inside the jejunal loop and this is how it differs from other anastomosis used in DP and reported in the literature. Earlier retrospective non-randomized studies on PJ of the pancreatic stump showed no POPF (Kleeff et al., 2007, Wagner et al., 2007, Meniconi et al., 2013), but a Japanese RCT reported no reduction in POPF between stapler and PJ groups (Kawai et al., 2016). PJ end-to-side anastomosis was made in duct-to-mucosa fashion in RCT and in earlier retrospective studies PJ was made in a capsule-to-seromuscular fashion after ligating the main pancreatic duct. In our study the anastomosis differs markedly from both techniques mentioned and the techniques in these different studies cannot really be compared. Pancreaticogastrostomy did not reduce the CR-POPF either in recent RTC, making pancreatic anastomosis not beneficial (Uemura et al., 2017). Tampere binding anastomosis works in PD, where the pancreatic juice goes downstream, but the mechanism for fistulae after DP is apparently different and low pressure in the duodenum is probably needed to allow the healing of either PJ anastomosis

or the cut edge. Also, opening the GI tract while performing anastomosis may turn fluid collections contaminated with GI tract microbes. Furthermore, in the case of a fistula, the intestine also leaks and makes the fistula more severe

In Study II, among patients receiving hydrocortisone, the incidence of clinically significant POPF (Grades B and C), was 5.9%. In the HC group there was only one Grade C fistula among 17 patients (5.9%). The POPF rate with HC is comparable to that with another recently studied drug, pasireotide, which reduced the incidence of clinically relevant pancreatic fistula to as low as 7% after DP (Allen et al., 2014). The Tampere Pancreas Group has recently demonstrated that perioperative hydrocortisone treatment reduces CR-POPF after PD (11% vs. 27%) (Laaninen et al., 2016). With pasireotide, the CR-POPF rate was 10% in PD patients (Allen et al., 2014). This makes the effect of hydrocortisone and pasireotide similar among pancreatic resections, PD and DP. Two retrospective studies on the effect of pasireotide have been published since Allen's study, with no effect on fistula rate after DP and PD (Elliott et al., 2018, Young et al., 2018). To the best of my knowledge, so far no other studies on hydrocortisone for prevention of fistula after pancreatic surgery have been published.

In Study II, the incidence of biochemical leak (formerly Grade A POPF) was similar between the groups, but HC clearly reduced the risk of clinically relevant fistula (Grade B+C) (5.9% vs. 42.9%). It is debatable HC treatment has any effect on initial fistula formation or inflammation, but it seems obvious that the biochemical leak does not advance to a clinically relevant state (B and C) due to the HC treatment. HC treatment may decrease the inflammation process on the pancreatic stump and still allow the juice to run downstream into the duodenum, as hoped. In any case Grade A fistulas do not alter the clinical pathway and are nowadays defined as biochemical leak rather than true POPF.

With HC treatment, the CD III–V rate was 5.9% in DP, compared to 21% in the placebo group. Thus HC treatment seems also to have a lowering effect on major complications even though difference did not reach statistical significance in Study II. The small number of patients in each group may explain why no significant difference was seen. In the study on PD, hydrocortisone significantly reduced the major complications (CD III–V) compared to the placebo group, 18 % vs. 41% (Laaninen et al., 2016). HC therefore seems also to reduce major complications after open pancreatic surgery in general.

Furthermore, pasireotide causes significant dose-limited nausea as a side effect (17% in the study by Allen and 38% in the recent study by Elliott) and significant cardiac disease excludes patients from taking it in the first place (Allen et al., 2014, Elliott et al., 2018). During HC treatment there were no adverse effects or dropouts due side effects. Another advantage of hydrocortisone over pasireotide is the price; HC is cheap, whereas pasireotide is expensive,

Hydrocortisone is an old drug with anti-inflammatory effects. Our hypothesis is that POPF and other complications occur after postoperative pancreatic inflammation. By intervening in the inflammation cascade with HC after DP or PD, some effect on POPF

or other complications could be anticipated. Postoperative pancreatitis has recently been shown to be associated with increased incidence of POPF (Bannone et al., 2018). The exact mechanism of cortisone is not fully understood; it may be both local and systematic. Tampere Pancreas Group currently aims to identify the mechanisms by which hydrocortisone works on acinar and stellate cells in our pancreas laboratory with several ongoing studies.

Study III reported nationwide results from DPs performed in Finland in the period 2012–2014. PDs have been transferred to higher-volume centres in recent years and this centralization has reduced postoperative mortality and morbidity and also improved long-term survival after pancreatoduodenectomy (PD) (Ahola et al., 2017, Gooiker et al., 2011). In the case of distal pancratectomy, the rate of POPF and the Clavien-Dindo III–V complication were similar in high and low-volume centres, but the management of complications detected differed between centres with different surgical volumes. Reoperations were performed ten times more often in the low-volume centres in Finland. Proper management of complications often requires a multidisciplinary approach, which is often unavailable in LVC units. Reasonable volumes are needed to achieve and sustain experienced perioperative management. In Finland, with a population 5.4 million, 18 different hospitals were performing DP in 2012–2014. There were hospitals in which DP was performed very rarely and which lacked experienced postoperative observation. By checking the reoperations performed in LVCs we could speculate that they were all unnecessary and could have been avoided by the use of conservative or minimally invasive approaches. In low-volume centres CT-imaging facilities and options for modern treatment may be limited. The reoperation rate in most studies is around 0–5% in LDP and ODP (Marchegiani et al., 2017). The study showed that only the reoperation rates of HVCs are comparable with international results. Thus Finland can only come up to the international standard by centralizing operations to high volume centres.

Perioperative care in general needs improvement and it is essential for patients to regain full functional capacity. ERAS is a standardized and multidisciplinary model of perioperative treatment and can also be applied to pancreatic surgery (Pecorelli et al., 2017). In order to introduce the ERAS model, the hospital needs a reasonable number of patients, which also favours centralizing DP to HVCs. In Finland, according to the current statement by the medical authorities, all surgery for pancreatic cancer should be centralized to the country's five university hospitals.

Study III also showed underutilization of laparoscopic approach in Finland in DP. LDP was performed on 24% of the whole study group, most often in HVCs (28%) and MVCs (26%) and on only 3% in LVCs. MIDP should be increased in Finland to improve outcomes. Laparoscopic DP is associated with significantly less overall morbidity than open technique (Venkat et al., 2012). Laparoscopy shortens postoperative recovery by accelerating the normal gut functions (Mehrabi et al., 2015). So far there is only one RCT on MIDP vs. ODP showing that MIDP reduces time to functional recovery compared to ODP. The overall complication rate was similar in spite of less delayed gastric emptying and

better quality of life with MIDP (de Rooij et al., 2018). For cancer, oncologic equivalency has not been shown in any RCT and many European pancreatic surgeons still consider ODP a better choice for the treatment of cancer (de Rooij et al., 2016). ERAS is safe to implement in LDP and saves costs (Richardson et al., 2015). Open surgery is recommended for malignancies. In Study III, in 21% of DP: s the histopathological diagnosis was adenocarsinoma. In addition, some other diagnosis groups included patients with suspicion of malignancy. This means that approximately 70% of all DPs could have been performed laparoscopically. Since only 24% of DPs in 2012–2014 were performed laparoscopically, there is much room for improvement in this regard – even in high-volume centres.

A weakness of the randomized Studies I and II is definitely the small number of patients. It was challenging in Study I to find patients suitable for anastomosis, which was the reason for its early discontinuation. The only conclusion which can really be drawn from that Study is that binding anastomosis is not suitable for DP, mainly due to the location of the transection site. Transsection in DP is mainly done at the portal vein level, which makes binding anastomosis technically unfeasible. In Study II, the small study group and the open surgical technique are limitations. When the study was planned, LDP was not routine in our institution as it is now, and later we wanted to keep the study group homogenous. Nevertheless, the use of HC can be recommended in both ODP and LDP. In the nationwide Study III, CR-POPF incidence among all patients was very good, 16%, but the study population was heterogeneous with respect to the fistula reducing methods used. Pasireotide, HC, staplers and pancreaticojejunal anastomosis were used among patients, which also reflects clinical practice worldwide.

Many researchers in recent years have tried to solve the POPF problem after DP by innovating new surgical methods, but without success. All the different methods seem equally bad at improving the POPF rate and the stump could probably be closed in various ways with the same outcome. The risk factors for POPF are obesity, soft pancreas or gender and these cannot be affected. Their role in fistula formation has also been contested in many studies. The mechanism for POPF formation may be totally different in DP than in PD. Since studies of different closure mechanisms of the pancreatic stump have not given the answer, recent studies have focused on decreasing the pressure at the Sphincter of Oddi. The leak may be a result of obstruction by the Sphincter of Oddi, which increases the intraductal pressure in the main pancreatic duct and leads to leak. Early drain removal or no drain at all may be a way to decrease fistula related problems and this merits consideration. Fistulas still occur, but by early drain removal we might leave them in biochemical leak state. Long retention of the drain probably just turns them into clinically relevant ones. This and many other perioperative care measures are subject to variation even within hospitals due to a lack of perioperative protocols. In addition to standardized perioperative care, by increasing the use of laparoscopy we might help patients recover better than by developing new closure methods. From a pharmacological perspective, hydrocortisone seems promising in decreasing the POPF rate and morbidity in pancreatic surgery. It is

speculated that the pancreatic juice may flow better into the duodenum because the inflammation in the pancreas decreases.

In conclusion, by centralizing surgery to high-volume centres, by increasing the use of laparoscopy in distal pancreatectomies and by using standardized, multidisciplinary perioperative protocols, we could probably improve patient recovery and morbidity after DP, even without being able to lower the actual POPF rate. We should concentrate more on dealing with the fistulas rather than identifying and preventing them. Nevertheless, innovations, especially for decreasing intraductal pressure, are still needed and some promising methods are already emerging. In pancreatic surgery, what matters is the whole organization, the way of detecting and healing unavoidable complications, rather than the individual surgeon's skills or a single surgical method or medical therapy.

7 Conclusions

The conclusions of this thesis are:

I   Tampere binding pancreaticojejunal anastomosis is not suitable for most cases of distal pancreatectomy, nor does it seem to decrease POPF.

II Hydrocortisone treatment reduces the incidence of clinically significant fistula after open distal pancreatectomy. HC may also have a favourable effect on overall complications after open DP.

III According to a nationwide register, POPF and overall complication rates were similar in different volume hospitals in Finland during the period 2012–1014. However, the management of complications may favour the centralization of pancreatic resections to HVCs, which was seen in the high reoperation rate in LVCs.

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Original Publications

Clinical Study

Is Roux-Y Binding Pancreaticojejunal Anastomosis Feasible for Patients Undergoing Left Pancreatectomy? Results from a Prospective Randomized Trial

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Background. After pancreaticoduodenectomy, the Finnish binding pancreaticojejunal anastomosis (FBPJ) seems to reduce the risk for pancreatic fistula (POPF). Our aim was to investigate whether FBPJ is feasible and prevents the risk for POPF even after left pancreatectomy (LP). *Patients and Methods*. 47 consecutive patients underwent LP. 27 patients were recruited on the basis of CT and, of these, 16 patients were randomized on the basis of findings during surgery (transection line must be left of portal vein, as 2-3 cm pancreatic mobilization is required for FBPJ) to receive either Roux-Y FBPJ or hand-sewn closure of the pancreatic remnant. *Results*. Only 34% (16/47) of the patients met the randomization criteria. Clinically significant POPF rate was higher in FBPJ group (60%) compared to thand-sewn closure group (13%; $P < 0.05$). POPF rate in FBPJ group was higher even when compared to all patients with hand-sewn closure (60% versus 37%; $P < 0.05$). Overall, FBPJ was technically feasible for only 28% of patients. *Conclusion*. FBPJ cannot be recommended for the routine closure of the pancreatic remnant after LP, as it was not technically achievable in 72% of the cases. Moreover, the technique does not seem to reduce the risk for POPF compared to the hand-sewn closure.

1. Introduction

Left pancreatectomy (LP) is used to treat benign and malignant lesions in the body and tail of the pancreas or after abdominal trauma. The postoperative morbidity rate remains high, 30–50% [1, 2], and this is mainly due to pancreatic fistula (POPF) resulting from leakage of pancreatic enzymes from the transsection line of the pancreas. In addition to being the most common and clinically relevant complication, POPF is often associated with other complications such as intra-abdominal abscess, delayed gastric emptying (DGE), postpancreatectomy haemorrhage (PPH), wound infection, respiratory complications, and sepsis [1]. The risk for POPF after distal pancreatectomy remains an unsolved problem despite efforts to improve the surgical resection and closure techniques of the pancreatic remnant. These include hand-sewn suture techniques, stapled closure techniques, pancreatic transsection using various energy devices, pancreaticoenteric anastomosis techniques, application of meshes,

sealing with fibrin sealants, pancreatic stent placement, and administration on octreotide [3–9]. A recent retrospective cost analysis showed that patients with pancreatic fistula double the cost and dramatically increase health care resource utilization [2, 10].

Previously we have shown that after pancreaticoduodenectomy the novel Finnish binding (purse-string) pancreaticojejunal anastomosis (FBPJ) technique reduces the risk for POPF [11]. The aim of this study was to investigate whether FBPJ is a feasible technique after distal pancreatectomy and whether it prevents the risk for POPF after distal pancreatectomy.

2. Patients and Methods

A prospective, randomized trial was designed to include patients with the type of distal pancreatic resection that is technically possible with FBPJ (RPT arm). In addition, all

pancreatic distal resections were included in the prospective follow-up (PFU arm).

2.1. Surgical Technique.
In FBPJ, the pancreatic remnant was inserted 2-3 cm inside the jejunal limb with the aid of seven peripancreatic sutures (4-0 Maxon, Covidien, USA) after which the purse-string suture (4-0 PDS, Ethicon, USA) was tightened and a roux-Y entero-enteroanastomosis was performed (Figure 1). In the hand-sewn closure group, the main pancreatic duct was closed by suturing, followed by oversewing the pancreatic stump with 4-0 Maxon. A Penrose drain was placed near the anastomosis in all patients. A schematic drawing of the FBPJ is shown in Figure 1.

2.2. Recruitment Criteria for the RPT Arm.
FBPJ is technically achievable only when the transection line of pancreas is clearly to the left of the portal vein because the pancreatic remnant needs to be mobilized 2-3 cm to be able to insert it into the jejunal limb. All patients were studied preoperatively by contrast-enhanced computer tomography scan (CT). Patients eligible for randomization according to the location of tumour in the CT analysis were recruited for the study. The rest of the patients were included in the prospective follow-up.

2.3. Randomization Criteria for the RPT Arm.
After removing the distal pancreas, the patients still considered eligible for the FBPJ (i.e., transection line to the left of the portal vein) were randomized to receive either FBPJ or traditional hand-sewn closure of the pancreatic stump.

2.4. Patient Care and Follow-Up.
Perioperatively all patients received a single-dose antibiotic prophylaxis IV (ceftriaxone 2 g, Rocephalin, Roche, Finland, and metronidazole 500 mg, metronidazole, Brown, Germany) and routine antithrombotic (enoxaparin 40 mg, Klexane, Sanofi-Aventis, France, or tinzaparin 4500 IU, Innohep, LEO Pharma, France) prophylaxis s.c. Postoperatively the patients were monitored by the standard pancreatic resection protocol of Tampere University Hospital. Abdominal drain output was recorded daily and the amylase concentration was measured from it on the third postoperative day, and thereafter if the drain still remained in place. The drain was removed when the drain amylase output was less than three times the serum upper limit. The urine trypsinogen strip test was used to detect postoperative pancreatitis and was measured daily during the first postoperative week [12]. Patient demographics (age, sex, BMI, and comorbidities) were compared and postoperative complications (fistulas, bleeding, abscesses, and wound infections) and mortality were defined and compared between the groups. POPF was classified into three grades (A, B, and C) depending on the clinical impact according to the ISGPF classification [13].

2.5. Power Analysis.
For the RPT arm, population size was estimated on the basis of the results from our earlier study of FBPJ after pancreaticoduodenectomy [11], where the rate of clinically relevant (grades B-C) POPF was reduced by 50% compared to our historical controls. If the patients with hand-sewn closure had twice as much clinically relevant POPF compared to FBPJ (30% versus 15%), we would need 26 patients in each group to be able to show a statistically significant difference with power $\pi = 0.80$ (α 0.05). We estimated that about one-third of the patients would not meet the recruitment criteria based on CT and that about 10% of the recruited patients would not meet the randomization criteria according to findings during surgery. Thus for 52 randomized patients we would need 58 recruited patients, and for those we would need a population of 78 distal pancreatectomies. We planned to run the interim analysis when 29 patients had been recruited and estimated that about 40 distal pancreatectomies would be needed to achieve this recruited population.

The interim analysis was run in August, 2013. A total of 47 consecutive patients (16 M/31 F) had undergone distal pancreatectomy with the remaining pancreatic head in Tampere University Hospital between October 2009 and July 2013. We were prepared to increase our series but this proved unnecessary after analysing the results of these 47 patients.

The study protocol was approved by the Ethics Committee of Tampere University Hospital. The study was registered with clinical.trials.com NCT02113046.

Statistical analysis was performed using Fisher's exact test, Mann-Whitney U-test, and logistic regression test. $P < 0.05$ was considered statistically significant.

3. Results

Out of the 47 caudal resections, 27 met the recruitment criteria, but only 16 of these met the randomization criteria in the operation (as described in Section 2, the transsection line or the pancreas needed to be clearly to the left of the portal vein for the patient to be randomized). Patients were randomized into FBPJ or hand-sewn group. Out of the 8/16 patients randomised for FBPJ, in two patients, FBPJ was still technically impossible to accomplish and they received a hand-sewn closure. In addition, one had after all an advanced disease, and distal pancreatectomy was not performed. 8/16 were randomized for hand-sewn closure. Thus, of the recruited patients, five received a FBPJ and ten a hand-sewn closure in the RPT arm and 11 in the non-RPT arm. More 20 patients received a hand-sewn closure in the prospective follow-up arm. Thus a total of 41 patients had a hand-sewn closure. The flow chart is shown in Figure 2.

Patients were well comparable for age, sex, and comorbidities. Patient demographics are shown in Table 1. Indications for surgery were malignant tumours in 28 patients, benign tumors in 14 patients, chronic pancreatitis in 1 patient, and pancreatic pseudocyst in 3 patients. The final histopathological diagnoses are shown in Table 2.

The main endpoints of the study were the feasibility of FBPJ in LP patients and the POPF rate. POPF was significantly higher in the FBPJ group, in which 3/5 patients (60%) developed a grade B POPF compared to the hand-sewn group, where 1/8 patients (13%) developed a grade B fistula ($P < 0.05$). In the FBPJ group two patients

TABLE 1: Patient demographics and postoperative complications in the groups (FBPJ: randomized binding pancreaticojejunal group, hand-sewn rand.: randomized hand-sewn group, and hand-sewn all: all patients with hand-sewn anastomosis).

	FBPJ		Hand-sewn rand.		Hand-sewn all	
n	5		8		41	
Age (median and range)	67	(55–74)	60	(26–80)	66	(26–85)
Gender M/F	1/4		2/6		15/26	
BMI (mean)	28.2		27.2		26	
Smoking	1	(20%)	0		7	(17%)
Alcohol abuse (audit > 6)	0		1	(12.5%)	5	(12.1%)
Diabetes	0		2	(25%)	5	(12.1%)
Cardiac disease	0		1	(12.5%)	3	(7.3%)
Hypertension	2	(40%)	2	(25%)	20	(48.7)
Wound infection	0		0		4	(9.7%)
PPH	0		0		0	
Abscess	3	(60%)	0		9	(21.9)
Pancreatitis (CT verified)	0		1	(12.5%)	2	(4.9%)
Trypsinogen strip test positive	1	(20%)	1	(12.5%)	10	(24.3%)
Length of stay (days)	10	(7–15)	7	(6–9)	7	(6–32)
Readmission	1	(20%)	1	(12.5%)	4	10%
Operative time (mins, median, and range)	170	(136–300)	162	(115–200)	170	(90–305)
Blood loss (mL, median, and range)	750	(300–2350)	750	(300–1300)	750	(100–3600)
Mortality	0		0		0	

TABLE 2: Final histopathologic diagnoses (FBPJ: randomised binding pancreaticojejunal group, hand-sewn rand.: randomised hand-sewn group, and hand-sewn all: all patients with hand-sewn anastomosis).

	FBPJ		Hand-sewn rand.		Hand-sewn all	
n	5		8		41	
Adenocarcinoma	2	(40%)	4	(50%)	13	(32%)
Neuroendocrine tumour	3	(60%)	2	(25%)	9	(22%)
Intraductal papillary mucinous neoplasm					4	(10%)
Pseudocyst			1	(12.5%)	3	(7%)
Mucinous cystic neoplasm					2	(5%)
Chr. pancreatitis					1	(2%)
Haemangioma			1	(12.5%)		
Nesidioblastoma					1	(2%)
Kidney ca metastases					1	(2%)
Serous cystadenoma					5	(12%)
None					1	(2%)

had an operatively placed drain removed and needed an interventional radiology placed drain due to subsequent abscess. The third patient had a high amylase output from the operatively placed drain, which was kept in place and removed five weeks postoperatively. In the hand-sewn group the patient who developed a grade B fistula was discharged with the drain but was readmitted and the CT showed pancreatitis and collection of fluid. The operatively placed drain was removed after six weeks, after which no additional drainage was needed. Fistula rates are shown in Figure 2.

The fistula rate in the FBPJ group was significantly higher, not only compared to the RPT hand-sewn group (POPF gr B 60% versus 13%; $P < 0.05$) but also compared to all hand-sewn closures (POPF gr B 60% versus 37%; $P < 0.05$).

In addition to the high fistula rate, only 13/47 (27%) of patients were eligible for FBPJ according to our interim analysis, so we decided to discontinue the study at this point.

30-day mortality was zero. There was no postoperative haemorrhage. No reoperation was needed in either group. Among the prospective follow-up hand-sewn patients, four patients had a wound infection, one patient had a lymphatic leak, and two patients had pancreatitis. Urine trypsinogen strip test was positive on two or more days in one patient in FBPJ (20%) and in ten patients in all hand-sewn groups (24%; NS) suggesting postoperative pancreatitis. Blood loss during surgery, length of hospital stay, and readmission rate to hospital were comparable between the groups. All these characteristics are shown in Table 1.
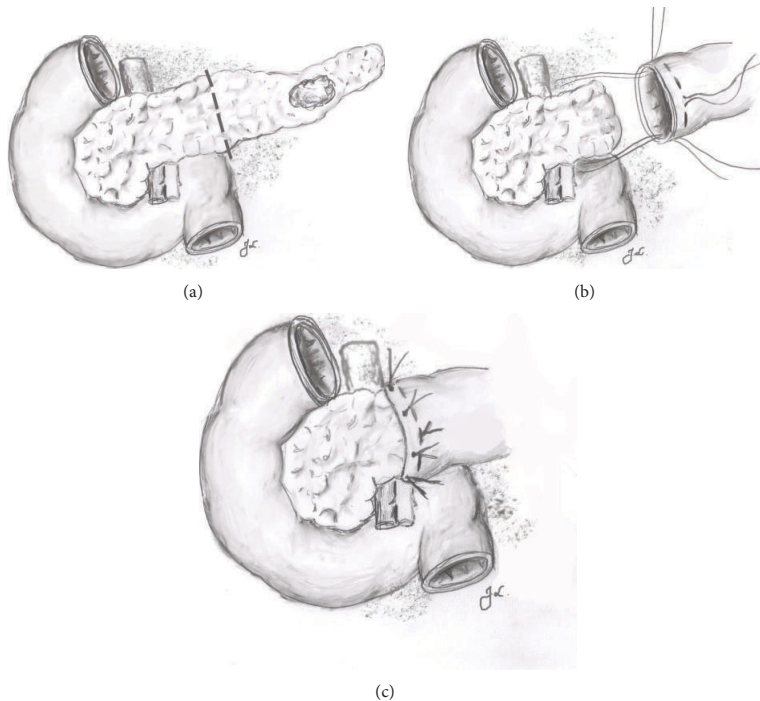
(a)

(b)

(c)

FIGURE 1: Schematic drawing of the binding (purse-string) pancreaticojejunal anastomosis (FBPJ) after left pancreatectomy. The transsection line needs to be clearly to the left of the portal vein (a). The pancreatic remnant is mobilized 2-3 cm and it is inserted inside the jejunal loop with the aid of anchoring sutures (b). The purse string applied in the jejunum is tightened to secure the anastomosis (c).

4. Discussion

POPF remains the most common complication after distal pancreatectomy with an incidence between 20 and 40% [3, 14, 15] and many surgical techniques for resection and closure of the pancreatic remnant have been studied without major success [3–5, 7, 9, 14, 16–19]. We have previously shown that the novel FBPJ technique reduces the risk for pancreatic fistula after pancreaticoduodenectomy [11], and within this study we investigated whether the FBPJ technique was feasible even for LP. We concluded that FBPJ cannot be recommended for a routine for pancreatic remnant closure after LP, as it is not technically achievable in most of the cases and does not seem to reduce the risk for POPF compared to the hand-sewn closure.

Stapler and suture closure are the two most common strategies for managing the pancreatic remnant. In the DISPACT trial [3], which included 450 patients, two groups of patients were randomized to either stapler or hand-sewn closure of the pancreatic remnant with no difference found in POPF incidence. The meta-analysis likewise revealed no significant differences between suture and stapler closure [4]. Several other methods have also been tried [16]. Recently the use of saline-coupled radiofrequency dissector in stump closure reduced the POPF rate, but further prospective

studies are needed [5]. Pancreaticojejunostomies (PJ) have also been performed to reduce the fistula rate and the findings have been encouraging [6, 8]. In 2007 Wagner et al. [6] found a zero POPF rate Roux-en-Y end-to-side PJ after suture closure versus 20% in suture closure only. In their study, POPF was not classified into three grades according to the ISGPF definition and the number of patients was only 23 versus 20 in either group. In 2013 Meniconi et al. [8] reported a retrospective analysis where the fistula rate was also zero in PJ and 29% in the hand-sewn group. In the PJ group the main pancreatic duct was closed, after which the pancreatic remnant was invaginated into a jejunal loop. This was a nonrandomized retrospective study on a small group of patients (24 versus 12). We have shown previously that after pancreaticoduodenectomy the novel FBPJ technique reduces the risk for pancreatic fistula [11].

In this study we wanted to investigate whether FBPJ can also be used in distal pancreatectomy and whether it reduces the risk of pancreatic fistulae. FBPJ is technically achievable only when the transsection line of the pancreas is clearly to the left of the portal vein because the pancreatic remnant needs to be mobilized 2-3 cm before it can be inserted inside the jejunal loop. This is the reason why only 27 out of 47 patients who received an LP resection were recruited. We estimated the suitable patients based on the location
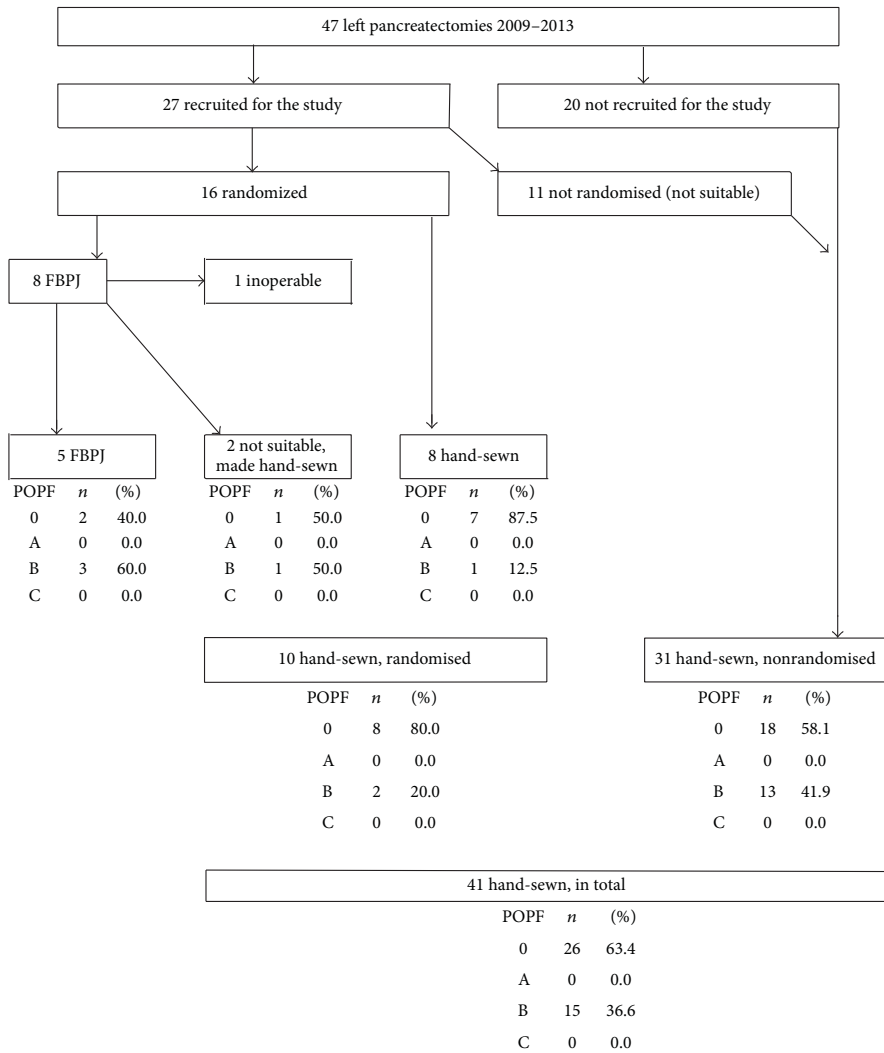
FIGURE 2: Flow chart of the study patients and POPF rate in each group. Out of 47 consecutive patients, 27 were recruited and only 16 of these met the randomization criteria. Finally, only 5 patients received a FBPJ (POPF 60%) and 8 patients a hand-sewn closure (POPF 12.5%) from the randomized patients. The POPF rate was 36.6% in all hand-sewn closure patients.

of the tumour preoperatively with the help of contrast-enhanced CT scan. Randomization was done intraoperatively and only 16 patients out of the total 46 met the randomization criteria, and of these one had an inoperable tumour and in two the FBPJ was impossible to perform. In most of the distal pancreatectomies it is not technically possible to mobilize the pancreatic remnant 2-3 cm in order to insert it inside the jejunal loop. The FBPJ would therefore have been technically feasible for only 28% (13/47) of patients. In the other studies where PJ was performed with good results [6, 8] the pancreatic remnant was invaginated instead of

being inserted inside the jejunal loop. The anastomosis was made by capsule-to-seromuscular single layer sutures when the pancreatic remnant did not need to be mobilized as in our FBPJ technique. This may explain why it was possible to perform PJ on all patients in those studies.

FBPJ did not decrease the number of pancreatic fistulae in this small study. On the contrary, it seemed to increase the cases of POPF. In addition, FBPJ anastomosis is feasible in only a minority of patients, which is why we discontinued the study after performing the interim analysis. The number of patients who received FBPJ was small, but, as most patients

did not seem to be eligible for this kind of anastomosis, it was challenging to achieve a large enough patient population in the FBPJ group to show the differences in the fistula forming.

In conclusion, the FBPJ technique, which reduces the POPF rate after pancreaticoduodenectomy, is suitable only for selected patients with LP and thus it cannot be recommended for routine use in the closure of the pancreatic remnant. In addition, according to this study it does not seem to reduce the risk of POPF.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

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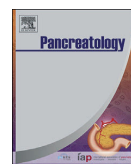
Perioperative hydrocortisone treatment reduces postoperative pancreatic fistula rate after open distal pancreatectomy. A randomized placebo-controlled trial

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ABSTRACT

Background: Postoperative pancreatic fistula (POPF) is the most common complication after distal pancreatectomy (DP). In a recent RCT on pancreaticoduodenectomy (PD), perioperative hydrocortisone (HC) treatment reduced Clavien-Dindo (C-D) III-V complications. The aim of this study was to investigate whether perioperative HC treatment reduces the overall complications and clinically significant POPF after distal pancreatectomy (DP).
Methods: Fourty consecutive patients undergoing DP were randomized to receive intravenous HC 100mg/placebo every eight hours until the second postoperative day. Thirty-one patients were completed with DP and received HC/placebo every 8 h for two days postoperatively. The primary endpoint was overall complications (C-D III-V) and the secondary endpoint was the development of clinically significant POPF.
Results: Pancreatic duct diameter, operative time and blood loss were similar in the groups. Ninety-day mortality was zero. With HC treatment the rates of C-D III-V complications tended to be lower compared to the placebo group (5.9% vs 21.4%, p = 0.034). The rate of grade B/C POPF was significantly reduced with HC treatment compared to the placebo group (5.9% vs. 42.9%, p = 0.028).
Conclusion: Perioperative HC treatment may have a favourable effect on overall major complications after open DP. HC treatment reduces the incidence of clinically significant POPF after open DP.
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Introduction

Post-operative pancreatic fistula (POPF) is the most common complication after DP, and the incidence remains high ranging 16–50% [1,2]. POPF is often associated with other complications, including wound infection, intra-abdominal abscess, delayed gastric emptying (DGE), postpancreatectomy haemorrhage (PPH), wound infection or sepsis [3,4]. Many surgical strategies have been studied to decrease fistula formation after DP [5–9] as well as endoscopic pancreatic duct decompression [10,11] and pharmaceutical measures [12].

We have shown in a recent RCT that perioperative hydrocortisone (HC) treatment reduces major complications (Clavien-Dindo III-V) after pancreaticoduodenectomy (PD) in high-risk patients with "soft", acinar-cell rich pancreas. HC treatment also tended to reduce the rate of clinically relevant POPF, but the difference was not statistically significant in this patient population alone (11% vs 27%; p = 0.118) [13].

The aim of this study was to investigate whether perioperative HC treatment reduces major complications (Clavien-Dindo III-V) and prevents the risk of POPF after open DP.

Methods

We conducted a prospective, single-centre, randomized trial at Tampere University Hospital, Finland. The RCT was conducted according to the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Tampere University Hospital. The study was designed simultaneously with another study on HC treatment in PD patients, reported recently in Annals of Surgery

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[13] and conducted partly parallel with this study. The Clinical Trial number is NCT01460615. The study was duly monitored and approved by the Finnish Medicines Agency (FIMEA).

Patients

Eligibility criteria included consecutive adult patients scheduled for elective, open DP for a disease of the pancreatic body or tail. Patients with ongoing cortisone treatment, ceftriaxone allergy or chronic pancreatitis were excluded. It was intented to include only patients with soft high-isk pancreas in the study. The patients gave their written and oral informed consent before randomization.

Randomization

The randomization list was made at the beginning of the study by a biostatistician. After providing written informed consent, patients were randomized before surgery to either the HC or the placebo group. The research nurse delivered the externally similar HC/placebo bags to the surgical ward on the morning of the procedure according to the randomization number. The HC solution contained hydrocortisone sodium succinate (Solu-Cortef; Pfizer Manufacturing, Puurs, Belgium) in 0.9% sodium chloride solution (Natriumklorid Braun, 9 mg/mL; B. Braun Melsungen, Melsungen, Germany) Infusion bags were filled with 100 mg hydrocortisone in 2 ml of sodium succinate added into 100 ml of 0.9% sodium chloride solution. The placebo solution was made up by adding 2 ml of 0.9% sodium chloride solution into 100 ml of 0.9% sodium chloride solution.

Intervention

All operations were open procedures with a standard technique performed by experienced surgeons. No laparoscopic procedures were included in the study to standardize the operation. No octreotide or pasireotide were used. Pancreatic parenchyma was divided with a scalpel. Bleeding was controlled with Prolene 5—0 (Ethicon, USA) suturing. During the operation the percentage of acini cells in the pancreatic transection line was analysed by the pathologist [14]. Pancreas texture type was also estimated to be either soft or hard. Pancreatic duct diameter was measured by probing. All patients underwent standard hand-sewn closure of the stump. The main pancreatic duct was closed separately by suturing, followed by oversewing of the pancreatic stump with interrupted 4-0 Maxon (Covidien, USA) sutures. A Penrose drain was placed beside the stump.

At the induction of anaesthesia, all patients received a routine antibiotic prophylaxis of ceftriaxone 2 g (Rocephalin; Roche, Basel, Switzerland) and metronidazole 500 mg (Metronidatzole; Brown, Melsungen, Germany) intravenously and either HC 100 mg or placebo intravenously depending on the randomization. Patients needing other resections than DP were excluded from the study. The patients who continued in the study received HC 100 mg/placebo every eight hours until the second postoperative day (total of 9 doses). Ceftriaxone 2 g i.v. was also continued until the second postoperative day.

Postoperatively the patients were followed-up according to the standard pancreatic resection protocol of Tampere University Hospital. Abdominal drain output was measured and recorded daily. Amylase concentration was measured on the third postoperative day from the drain and repeatedly thereafter if the drain was still in place. The drain was removed when the amylase levels were less than three times the serum upper limit and the fluid was clear. Patients' age, sex, BMI and comorbities were recorded. Postoperative complications; fistulas, bleeding, wound infections,

general infections, abscesses and 90-day mortality were recorded prospectively and compared between the groups.

Endpoints and definitions

The primary endpoint was the development of overall complications and the secondary endpoint was the development of clinically relevant POPF. The study was conducted before the new ISGPF classification, and thus the original ISGPF classification was used for POPF grading in the analysis. Grade B and C POPF were defined as clinically significant POPFs [15]. The overall postoperative complications were graded by Clavien-Dindo scoring [16]. Overall morbidity was defined as Grades II-V, and major complications as Grades III-V according to the Clavien-Dindo classification. Postoperative hospital stay was defined as primary hospital stay after the surgery. Overall hospital stay also included the days after readmission. Mortality was recorded as death within 90 days of surgery.

Statistical analysis

The study was designed simultaneously with another RCT on HC treatment in high-risk PD patients [13]. At that time, it was estimated that HC treatment on high-risk PD-patients lowered the overall complication and fistula rate after PD to one seventh, which was used for the power calculation. Calculations were made prior to the randomized trial. We estimated that 36 consecutive patients scheduled for open distal resection would need to be randomized to show a statistically significant difference (alpha 0.05, 80% power). Due to the estimation of a 10% dropout, 40 patients were randomized.

The statistical analysis was performed using SPSS statistical software. Fisher's exact test for cross-tabulated variables and Mann-Whitney test for quantitative variables were used to calculate the significance between the two groups.

Results

Over the study period of 27 months, 47 patients were scheduled to undergo an open DP for benign or malignant disease. Of these, seven were excluded before randomization: 4 for logistic reasons, 2 did not meet the inclusion criteria and one had a previous PD. The remaining 40 patients were randomized preoperatively. Of these, one was observed to be on ongoing cortisone treatment only after inclusion for randomization, and was excluded from the study prior to surgery. During surgery, five patients were diagnosed with advanced, inoperable disease and three patients went through a different procedure (PD, total pancreatectomy and pseudocystojejunostomy) and were excluded from the study. The remaining 31 patients continued through the study after randomization. Of these, 14 were randomized to the placebo group and 17 to the hydrocortisone group. The flowchart is shown in Fig. 1.

No significant differences in the pre- or perioperative characteristics were found between the hydrocortisone and placebo groups, except that the median age was slightly higher in the HC group, p = 0.045. Patient characteristics are shown in Table 1 and the final histopathological diagnoses are seen in Table 2. No difference in previous diseases or drug usage was observed and no octreotide or pasireotide was used for the patients. The percentage of acinar cells at the transsection line analysed intraoperatively from the frozen section was over 40% in all patients. Pancreas texture was also defined as soft for all patients during the operation. Pancreatic duct diameters were similar between the groups, 94% in the HC group and 93% in the placebo group being <3 mm. Operative time was similar in the groups, as was blood loss. The
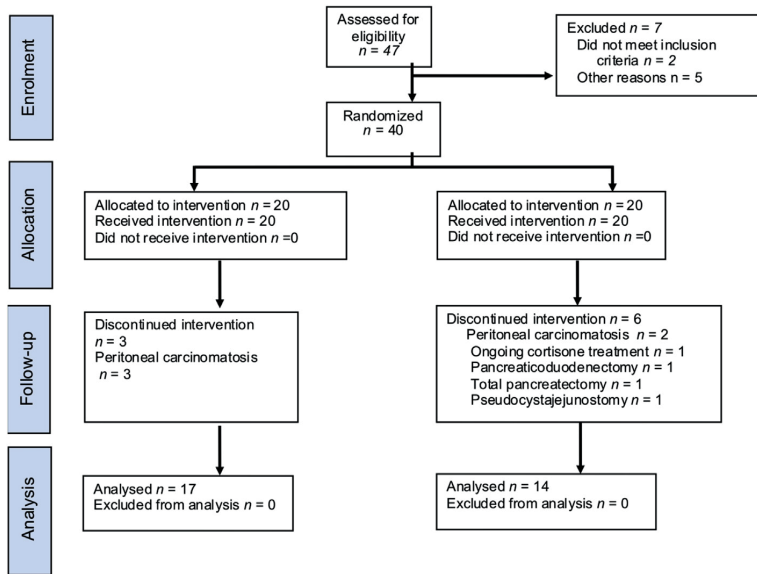
Fig. 1. CONSORT flow diagram for the trial.

Table 1
Pre- and perioperative characteristics of the HC group and the placebo group.

	Hydrocortisone (n = 17)	Placebo (n = 14)	p value
Age yrs, median (range)	73 (41—82)	61 (39—76)	0.045
Male	7 (41%)	4 (29%)	0.707
BMI, kg/m2	27 (22—35)	29 (21—39)	0.164
COPD	1 (6%)	2 (14%)	0.576
Diabetes	7 (41%)	5 (36%)	1.00
ASA class			
I-II	6 (35%)	7 (50%)	0.481
III	11 (65%)	7 (50%)	
Operative time min, median (range)	158 (103—391)	159 (108—224)	0.942
Operative blood loss mL, median (range)	550 (120—2300)	700 (50—1400)	0.975
Main pancreatic duct diameter			
<3 mm	16 (94%)	13 (93%)	1.00
≥3 mm	1 (6%)	1 (7%)	
Splenectomy	12 (71%)	6 (43%)	0.157
Acini >40% in the transsection line	17 (100%)	14 (100%)	1.00
Soft pancreas texture	17 (100%)	14 (100%)	1.00

Table 2
Final histopathological diagnoses in the groups.

	HC	Placebo	P value
Histopathological diagnosis			0.578
Pancreatic ductal adenocarcinoma	4 (23%)	1 (7%)	
NET	2 (12%)	2 (13%)	
Cystic tumour	9 (53%)	8 (57%)	
Other	2 (12%)	3 (21%)	

surgical technique was similar for all patients, the pancreas was cut with a scalpel and the duct was closed and the cut edge was hand sewn. Splenectomy was performed on 70% (12/17) in the HC group and on 42% (6/14) in the placebo group, p = 0.157. These parameters are shown in Table 1.

Primary endpoint

The overall morbidity was 48.4% (15/31), defined as complications graded Grade II or higher on the Clavien-Dindo classification [16]. In the HC group the overall morbidity was 41% (7/17 patients) and in the placebo group 57% (8/14). Major complications (Clavien III-V) occurred in 12.9% (4/31) of all patients. There were no statistically significant differences between the groups, 5.9% (1/17) and 21.4% (3/14) in the HC and placebo group respectively (p = 0.304) The details of complications and their management are presented in Table 3.

Secondary endpoint

The secondary endpoint of this study, the incidence of clinically significant POPF (grades B and C), was 22.6% (7/31) among all patients. In the HC group there was only one Grade C fistula among 17 patients (5.9%). This patient developed sepsis, and needed both percutaneous drainage and endoscopic retrogradic pancreaticography (ERP) to treat the POPF. She also developed a pulmonary embolism.

Table 3
Postoperative complications in the groups. The overall fistula rate was significantly lower in the hydrocortisone group (6% vs 43%). Hydrocortisone also seems to have a favourable effect on major complications (Clavien-Dindo III-V).

	Hydrocortisone (n = 17)	Placebo (n = 14)	P value
Pancreatic fistula			
Overall (B + C)	1 (6%)	6 (43%)	0.028
Grade B	0	4 (29%)	
Grade C	1 (6%)	2 (14%)	
Delayed gastric emptying	1 (6%)	1 (7%)	1.00
Intra-abdominal fluid collection	2 (12%)	3 (21%)	0.636
Wound infection	1 (6%)	3 (21%)	0.304
Intra-abdominal haemorrhage	0	0	
Pneumonia	1 (6%)	2 (14%)	0.576
Spleen necrosis	1 (6%)	1 (7%)	1.00
Lymphatic leak	2 (12%)	1 (7%)	1.00
CT verified pancreatitis	1 (6%)	1 (7%)	1.00
Urine trypsinogen positive $\geq$ 2 days	4 (24%)	5 (36%)	0.693
Pulmonary embolism	1 (6%)	0	1.00
Clavien-Dindo			
I	4 (24%)	4 (29%)	
II	6 (35%)	5 (36%)	
III	1 (6%)	2 (14%)	
IV	0	0	
V	0	1 (7.1%)	
Clinically significant (III–V)	1 (6%)	3 (21%)	0.304
Reoperation	0	1 (7.1%)	0.452
Total hospital stay (days, range)	8 (2–23)	7 (6–38)	0.625
Readmission	3 (18%)	3 (21%)	1.00
90-day mortality	0	0	

In total, 6/14 (42.9%) clinically significant fistulas developed in the placebo group. Four of these were Grade B fistulas. They were treated with original, intra-operatively placed drain and medical interventions. One Grade C fistula required percutaneous drainage followed by ERP and a pancreatic stent. Another Grade C fistula resulted in the patient's death on day 96 post-operatively. He was readmitted for infected collection of fluid and treated with a percutaneous radiologic drain and an endoscopic stent for collection. Finally the patient developed an intestinal necrosis seen in laparotomy due atherosclerosis and attributed to prolonged infection. With HC treatment the rate of clinically relevant POPF (5.9% vs 42.9%, p = 0.0281) was significantly lower compared to that in the placebo group. Fig. 2.

The incidence of former grade A POPF, also called a biochemical leak, was 22.6% (7/31) among all patients: 6 in the HC group and 1 in the placebo group (ns). These fistulas had no impact on the treatment of the patient. Thus, the overall incidence of any POPF was 45.2%: 22.5% grade A, 12.9% grade B and 9.6% grade C. The overall incidence of any POPF was similar in the two groups, but, interestingly, six out of the seven clinically relevant grade B–C fistulas were seen in the placebo group, whereas in the HC group almost only grade A fistulas were seen.

HC treatment was well tolerated and no adverse events occurred. The rates of wound infections and other infections were similar in the HC and placebo groups. Length of primary or total hospital stay did not differ between the groups with 8 (3–23) vs. 7 (6–38) days' total stay and 7 (6–14) and 8 (3–16) days' primary stay.
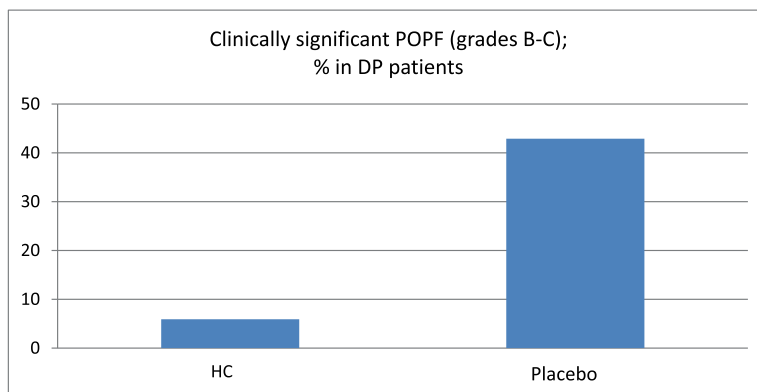

Fig. 2. Hydrocortisone treatment significantly reduced the rate of clinically significant POPF (5.9% vs 42.9%, p = 0.0281.

The readmission rates were similar: 17.6% and 21.4% respectively in the HC and placebo groups. Of these, in the HC group one patient had a spleen necrosis diagnosed on the twelfth postoperative day and one patient had an intra-abdominal haematoma diagnosed on the 24th postoperative day. Both were completely healed with no need for invasive procedures.

In both groups 90-day mortality was zero.

Discussion

Postoperative pancreatic fistula remains the most common complication after DP. In our recent randomized trial we showed that perioperative HC treatment reduces Clavien-Dindo 3—5 complications after PD, and also the clinically relevant POPF rate tended to be lower (11% vs. 27%). The present study was run partly concomitant with the PD RCT with the same protocol. Our main finding was that HC treatment significantly reduced the risk of POPF after DP from 43% to 5.9%. A tendency for fewer overall Clavien-Dindo III-V complications in the HC group was also seen.

Many recent RCTs have tried to lower the fistula rate after DP. The multicentre randomized DISPACT trial in 2011 found no difference between the stapler and hand-sewn group in the incidence of pancreatic fistula: 32% vs. 28% [5]. However, some meta-analyses have reported reduction in fistula rates after stapler closure [1,17]. Resection with a stapler reinforced with absorbable materials has been shown to reduce POPF, the B and C fistula rate being 1.9% among patients with mesh reinforcement vs. 20% of the patients without mesh in the stapler line [6]. The Tachocil patch has been shown in two RCTs not to lower the incidence of POPF [18]. However, adding a seromuscular patch to the staple line significantly decreased morbidity, but the clinically different POPF rate was similar [19]. Teres ligament patch reduced the complications after DP, but the clinically relevant fistula rate was not reduced [20]. Pancreaticojejunal anastomosis and pancreaticogastrostomy of the pancreatic stump have also been used without a significant decrease in fistula rate [9,21,22]. Preoperative endoscopic pancreatic stenting was studied in one prospective single-institution RCT in Sweden and did not reduce PF after DP [10]. Inducing relaxation of the Sphincter of Oddi by endoscopic botulinum toxin injection is promising according to one non-randomized trial having a B/C fistula rate of 0% vs. 33% and an RCT to clarify the effect is ongoing in Germany [11].

On the pharmaceutical side, octreotide and pasireotide have been investigated. Octreotide has showed a reduction in overall fistula rate after pancreas surgery, but no difference was found in clinically relevant POPF [23]. Somatostatin analogue pasireotide significantly reduced the incidence of clinically relevant pancreatic fistula in a recent RCT to as low as 7% [12].

In this study HC treatment reduced the clinically relevant B/C fistula rate to 5.9%, which is equivalent to the low fistula rates reported in the studies before [5,6]. For instance, pasireotide treatment reduced the B/C fistula rate from 23% to 7% in patients undergoing DP [12]. Difference was found only on clinically relevant POPF, not among Grade C fistulas only. The overall incidence of clinically relevant POPF in the placebo group of this study was 42%, within the range reported in earlier studies with open DP [10,12,20,24]. In our series less than 10% of the patients had corpus tail resections, without difference between the groups. This partly explains the fistula rate, as tail resections have been reported to carry a higher incidence of POPF compared to corpus + tail resections [25].

Severe complications (Clavien-Dindo III-V) tended to occur less often in the HC group than in the placebo group (5.9% and 21.4; ns; p = 0.30 respectively). Furthermore, the rate of severe complications in the HC group (5.9%) was less than half of the rate of severe

complications reported in a recent RCT comparing PJ and stapler closure 11.3% vs. 13.1% [21].

The prevalence of splenectomy was 71% in the HC group and 43% in the placebo group (ns). No association to the POPF or overall complications was seen in the splenectomized patients or in the patients where the spleen was saved. There was one spleen necrosis detected in both groups, both of these healed conservatively and were graded as Clavien-Dindo grade II complications. The rates of wound infections and other infections as well as the readmission rates were similar in the HC and placebo groups. There was one death on the 96th day in the placebo group, which was not included in 90-day mortality since it did not occur during the initial admission: The patient was readmitted and died of bowel necrosis caused by prolonged infection and atherosclerosis.

This study was performed partly simultaneously with the RCT on PD with the same HC/placebo protocol [13], but designed to be presented separately, mainly because of the different POPF and complication profiles of PD and DP. By separating these studies, we give valuable information to the field on these two different operations. If the results are combined, the overall incidence of clinically significant POPF is 8.9% in the HC group and 27.1% in the placebo group (p = 0.032). Thus HC seems to be effective in reducing clinically significant fistula overall in open pancreatic resections. As comparing these two studies, the effect of HC treatment on fistula rate seems to be higher after DP than after PD. The mechanism of fistula formation after DP is somewhat different compared to that after PD. Presumably after both operations, HC decreases inflammation and oedema in the pancreatic tissue. One may speculate that in the DP operation this effect is enough to create a lower pressure inside the pancreatic duct, enabling a better flow towards duodenum, thus preventing the formation of a fistula. In PD operation the prevention of fistula may be more complex, as also a good healing of the pancreatico-jejunal anastomosis is needed to prevent a fistula.

High frequency of acinar cells (>40%) in the cut edge of the pancreas increases the risk of postoperative complications and is an objective method to recognize the soft, nonfibrotic pancreas [14]. In our hospital acinar cells in PD and DP are nowadays counted routinely by a pathologist perioperatively from a frozen section to identify patients at risk of complications. In general, the majority of DP patients are at high risk of complications and have an acinar-rich cut edge and thus a high incidence of POPF. Unlike with the pancreatic head tumors, distally located tumors do not occlude pancreatic flow in the remaining pancreas, and thus in the remaining pancreas less fibrosis and more acinar cells as well as a normal pancreatic duct are present. Also on the present study all patients had an acinar-rich high-risk soft pancreas with a non-dilated duct, and thus the tumour pathology did not seem have an effect on the individuals' risk to develop a POPF.

The HC dose we used was identical to that used in the other RCT in PD patients. Also in this study the peri-operative use of 100 mg of hydrocortisone three times a day was confirmed safe [13]. Similarly, a study using it to prevent atrial fibrillation in cardiac surgery found it safe without any increase in adverse effects such as wound infection or stomach ulcers [26]. HC treatment in our study was also well tolerated, and no adverse events occurred. With pasireotide the most common adverse events were dose-limiting nausea (17%) and hyperglycaemia [12].

We hypothesize that POPF and other complications occur after postoperative pancreatic inflammation. Earlier we have reported that a large proportion of acinar cells at the transection line of the pancreas indicate a significant risk for complications. We have also demonstrated that the inflammation cascade at the transection line of the pancreas begins early and that the peak activation of inflammation markers (NF-kB and MCP-1) can be seen within 4 h of

surgical trauma. Recently it was shown that postoperative acute pancreatitis is associated with increased occurrence of POPF and overall morbidity after PD [27] In this study the activation was significantly higher in acinar cell rich pancreata than in fibrotic pancreata [14]. These findings led us to hypothesize that postoperative inflammation increases complications, and that we might be able to reduce the complications with corticosteroid treatment. In our pancreas laboratory we are currently performing mechanistic studies on the effect of hydrocortisone on experimental acute pancreatitis, but at the moment it is too early to speculate with the mechanisms. We assume that the favourable effect of HC is not only "local", but also systematic. Cortisone has been used in experimental acute pancreatitis in animal models [28,29] and also in the treatment of autoimmune pancreatitis [30]. Interestingly, corticosteroids have not been shown to reduce post-ERCP pancreatitis [31] nor to reduce trypsinogen leak after PD [13]. However, the aetiology of the inflammation process due to surgical trauma may differ from that arising in ERCP, which should be a subject for further research.

The strength of this study was that all patients were high-risk patients, having a soft pancreas and narrow pancreatic duct. This was confirmed by analysing the acini in the transection line, considered more objective and not based on the surgeons' subjective estimates of gland texture. All patients had a standardized, similar open tail resection (to standardize the pancreatic trauma). The small number of patients in each group was the main weakness of this study. Likewise the fact that we included only open procedures. At the moment we are using the HC treatment as a routine even for laparoscopic distal resections. Thus we would recommend the use for laparoscopic operations also, even though this has not been shown in a study. However, larger studies are needed to confirm our findings.

HC treatment seems to be a safe, inexpensive and well-tolerated pharmaceutical method in preventing POPF after DP. Among drugs so far only pasireotide has been shown to have a significant effect on POPF after DP, a similar effect on lowering the fistula and complication rate than HC, but seems to have some adverse events. The cost-effectiveness of pasireotide has also been studied and did not increase the overall cost of pancreatic resection [32], but might save costs within the health care system [33]. Nevertheless, the costs using pasireotide are considerably higher than the cost of inexpensive HC treatment, which necessitates further comparative studies with cost-analysis.

For future studies it would also be important to validate the system to confirm a "soft" high-risk pancreas. Acinar cell count is an easy and objective intraoperative method to identify patients at high risk for POPF [14]. This method is routinely used in our hospital among PD and DP patients as is perioperative HC treatment for patients deemed to have a high risk for complications. On the other hand, HC treatment is discontinued after the initial dose if the intra-operative acinar cell analysis renders the patient low-risk for POPF.

In conclusion, perioperative HC treatment reduces the incidence of clinically significant fistula after open distal pancreatectomy. The frequency of POPF after HC treatment is low also when compared to other means of POPF prevention studied earlier. Overall in open pancreatic surgery (PD and DP), HC seems to be effective in reducing clinically significant fistula and may have a favourable effect also on overall complications.

Acknowledgements

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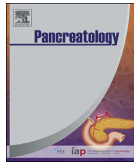
Management of postoperative complications may favour the centralization of distal pancreatectomies. Nationwide data on pancreatic distal resections in Finland 2012–2014

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ABSTRACT

Background: Centralization of pancreatic surgery has proceeded in the last few years in many countries. However, information on the effect of hospital volume specifically on distal pancreatic resections (DP) is lacking.
Aim: To investigate the effect of hospital volume on postoperative complications in DP patients in Finland.
Methods: All DP performed in Finland during the period 2012–2014 were analyzed, information having been retrieved from the appropriate national registers. Hospital volumes, postoperative pancreatic fistulae (POPF) and overall complications were graded. High volume centre (HVC) was defined as performing > 10 DPs, median volume centre (MVC) 4–9 DPs and low volume centre (LVC) fewer than 4 DP annually.
Results: A total of 194 DPs were performed at 18 different hospitals. Of these 42% (81) were performed in HVCs (2 hospitals), 43% (84) in MVCs (6 hospitals) and the remaining 15% (29) in LVCs (10 hospitals). Patient demographics did not differ between the hospital volume groups. The overall rate of clinically relevant POPF, Clavien-Dindo grade 3–5 complications, and 90-day mortality showed no significant differences between the different hospital volumes. Grade C POPF was found more often in LVCs, being 1.2% in HVCs, 0% in MCVs and 6.9% in LVCs, p = 0.030. More reoperations were performed in LVCs (10.3%) than in HVCs (1.2%) or MVCs (1.2%); p = 0.025.
Conclusions: Even though the rate of postoperative complications after DP is not affected by hospital volume, reoperations were performed ten times more often in the low-volume centres. Optimal management of postoperative complications may favour centralization not only of PD, but also of DP.
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Introduction

Centralization of treatment of pancreatic surgery reduces postoperative mortality and morbidity and also improves long-term survival after pancreatoduodenectomy (PD) [1–4]. Compared to PD, postoperative pancreatic fistulas (POPF) are even more common – though less life-threatening - after distal pancreatectomy (DP) and overall morbidity also remains high [5–7]. The effect of hospital volume on complications after DP has

not been widely studied [8]. The aim of this study was to analyze whether hospital volume affects the rate of POPF and overall morbidity after DP according to a nationwide database.

Methods

All patients undergoing DP in the period 2012–2014 were identified from the Finnish Operation and Treatment Register (HILMO) using Nordic Classification of Surgical Procedures codes (ICD10 codes JLC10 and JLC11). All patient records were collected and examined manually. Emergency operations and patients with no data available were excluded.

Postoperative complications, POPF, mortality, reoperations and

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hospital stay were registered. Data on the course of the surgery was also gathered. Complications were graded according to the Clavien-Dindo classification and grades 3—5 were considered major complications [9]. Postoperative pancreatic fistulas were graded according to the new ISGPF classification [10,11]. In grade B fistula the drain is left in place for over 3 weeks or repositioned through percutaneous or endoscopic procedures. Grade C fistula requires either reoperation or leads to organ failure or death of the patient. The final histopathological diagnoses were also gathered.

The hospital DP volumes were calculated and the hospitals were categorized according to operation volume. For this study, high-volume centres (HVC) were defined as those performing 10 or more distal pancreatectomies per year Median-volume centres (MVC) accomplished 4—9 DPs and low-volume centres (LVC) less than 4 DPs per year.

Ethical approval for the study was granted by the Regional Ethics Committee of Pirkanmaa, Finland (ETL code R12241).

Statistical analysis

Fisher's exact test and ×2 test were used as appropriate to calculate statistical differences. Statistical analysis was performed with IBS SPSS statistics software. P ≤ 0.05 was considered statistically significant.

Results

One hundred and ninety-four DPs were performed in Finland between 2012 and 2014 in 18 different hospitals. There were two HVCs, 6 MVCs, and 10 LVCs. Of DPs 85% (165) were performed in HVCs and MVCs (41% in HCVs and 44% in MVCs) and 15% (29) in LVCs. In total 81 DP/3 yr were performed in HVCs, 84 in MVCs and 29 in LVCs.

Patient demographics or perioperative data did not differ between the centres (Table 1). Combined splenectomy (median 60%, range 51—69%) and resection of other organs (16%, range 11—20%) were performed without differences between the centres. Blood loss (median 700 ml, range 10—16000 ml) and operative time (median 187min, range 114—317min) were also similar regardless of hospital volume. For pancreatic stump closure stapler was used in 69% of patients, and the methods did not differ between the groups. There were more laparoscopic procedures in HVCs and MVCs than in LVCs (28%, 27% and 3% respectively, p = 0.008).

The proportion of malignant diseases was similar between the centres. The final histopathological diagnoses are shown in Table 2.

The overall rate for POPF (B/C) rate was 17.2% in all patients. POPF occurred in 21% in HVCs, 10.7% in MVCs and 17.2% in LVCs.

Table 2
Final histopathological diagnoses: all patients.

Adenocarcinoma	40 (21%)
Neuroendocrine carcinoma	7(3,6%)
Intraductal papillary mucinous carcinoma	2(1%)
Gastrointestinal stromal carcinoma	1 (0,5%)
Kidney metastasis	6 (3%)
Colon carcinoma	1 (0,5%)
Neuroendocrine tumour	43 (22,%)
Mucinous cystic nesplasm	23(11,9%)
Intraductal papillary mucinous neoplasm	17 (8,8%)
Serous cystic neoplasm	20 (10%)
Solid pseudopapillary neoplasm	3 (1,5%)
Chronic pancreatitis	7 (3,6%)
Pseudocyst	7 (3,6%)
Gastrointestinal stromal tumour	1 (0,5%)
Cyst	5 (2,6%)
Fibrosis	1 (0,5%)
Spleen accessorius	7(3,6%)
Hemangioma	1(0,5%)
Nesidioblastooma	1(0,5%)

Grade C POPF was found more often in LVCs, the rate being 1.2% in HVCs, 0% in MCVs and 6.9% in LVCs, p = 0.030. The rate of intra-abdominal collections was similar; they occurred respectively in 28%, 25%, and 20.7% in HVCs, MVCs and LVCs. Interventional drain or pancreatic stent was used similarly in the centres to drain a collection in the postoperative treatment of POPF. Delayed gastric emptying (DGE) was found to be more common in LVCs (20.7%) than in HVCs/MVCs (3.7%/10.7%; p = 0.018). However, no difference was found in other complications such as postoperative pancreatitis, lymphatic leak, post-pancreatic hemorrhage (PPH), wound infection, pneumonia or pulmonary embolism (Table 3).

Clavien-Dindo 3—5 complications occurred in 16.0% of HVC patients, in MVCs in 18.1% of patients, and in LVCs in 20.7% of patients. In LVCs the rate for major complications tended to be higher, but this was not statistically significant (p = 0.81). Ninety-day mortality was 0% in HVCs and in the LVC group and 2.4% in MVCs.

Significantly more reoperations were performed in LVCs, on 10.3% of patients (3/29), than in HVCs and MVCs: 1.2% (1/82) and 1.2% (1/87) respectively, p = 0.025. Due to the small number of reoperations, multivariate analysis was not possible. Out of the three re-operated patients in the LVCs, the first patient had POPF, PPH and pneumonia and was treated in the ICU. He underwent reoperation twice; on day 19 due to PPH and intra-abdominal collection (splenectomy and drain repositioned) and on day 49 due to 15 cm wide peripancreatic collection with amylase-rich fluid (drain repositioned). The second patient underwent reoperation on

Table 1
Pre- and perioperative characteristics across the groups.

	High-Volume centre n (DP) = 81	Medium-volume centre n(DP) = 84	Low-volume centre n (DP) = 29	Overall volume n (DP) = 194	
Age, median, years (range)	62 (0.3—80)	65 (21—80)	67 (41—85)	64 (0,3—85)	
Sex ratio (F/M)	45/36	60/24	17/12	122/72	
BMI	26,1 (16—40)	23,6 (19—40)	28,4 (23—36)	26,1 (16—40)	
Diabetes	20 (24,7%)	10 (14,1%)	8 (29,6%)	21,2% (38)	
Laparoscopic procedure	23 (28,4%)	23 (27,4%)	1(3,4%)	47 (24,2%)	p = 0.008
Combined resection of other organs	9 (11,1%)	17 (20,2%)	4 (13,8%)	30 (15,5%)	
Hand -sewn closure of the pancreatic	25 (30,9%)	20 (23,8%)	11 (37,9%)	56 (28,9%)	
Stapler closure of pancreatic stump	54 (66,7%)	64 (76,2%)	16 (55,2%)	134 (69,1%)	
Splenectomy	42 (51,9%)	58 (69,0%)	16 (55,2%)	116 (59,8%)	
Blood loss (ml)	850 (150—5300)	590 (0—16000)	500 (300—2500)	700 (0—16000)	
Oper. time (min)	167 (115—317)	200 (114—377)	180 (120—258)	187 (114—377)	
Number of hospitals	2	6	10	18	

Table 3
Postoperative complications in the groups.

% (n)	High-volume centre n = 81	Medium-volume centre n = 84	Low-volume centre n = 29	
Pancreatic Fistula				
Grade B	19,8% (16)	10,7% (9)	10,3% (3)	
Grade C	1,2% (1)	0,0% (0)	6,9% (2)	P = 0,030
Grade B/C	21,0% (17)	10.7% (9)	17,2% (5)	
PPH	4,9% (4)	4,8% (4)	6,9% (2)	
DGE	3,7% (3)	10,7% (9)	20,7% (6)	P = 0,018
Intra-abdominal collection	28,4% (23)	25,0% (21)	20,7% (6)	
Interventional drain	13,6% (11)	11,9% (10)	10,3% (3)	
Pancreatic stent	2,5% (2)	2,4% (2)	6,9% (2)	
CT verified pancreatitis	3,7% (3)	2,4% (2)	0,0% (0)	
Lympha leak	1,2% (1)	1,2% (1)	0,0% (0)	
Wound-infection	9,9% (8)	3,6% (3)	10,3% (3)	
Pneumonia	12,3% (10)	6,0% (5)	10,3% (3)	
Pulmonary embolism	3,7% (3)	0,0% (0)	5,0% (1)	
Clavien-Dindo III-V	16,0% (13)	18,1% (15)	20,7% (6)	
Reoperation	1,2% (1)	1,2% (1)	10,3% (3)	p = 0,025
Total hospital stay, median (range)	7 (3–25)	8 (3–30)	8 (5–40)	
Readmission	16,3% (13)	13,1% (11)	24,1% (7)	
90-day mortality	0,0% (0)	2,4% (2)	0,0% (0)	

day 8 due to infection and inadequate blood flow to the spleen seen in ultrasound (splenectomy, drain repositioned; produced amylase-rich fluid). The third patient underwent reoperation on day 10 due to DGE (nasogastric tube repositioned, inflammation detected around pancreas with jejunal loops attached). The indications for reoperations in the HVC group were bowel necrosis caused by atherosclerosis and prolonged infection due to POPF, and in the MVC group ureter injury sustained in the primary operation. Clavien-Dindo complication, reoperation and readmission rates are seen in Fig. 1.

There were no differences in total hospital stay, readmission rate or 90-day mortality. These parameters are shown in Table 3. There were two deaths within 90 days postoperatively, both in the MVC group. The first patient died on day 3. This patient had a BMI of 40, and had breathing problems before his death, probably because of a pulmonary embolism. The second patient died on day 12 due to postoperative bleeding. Hemoglobin level was 23 g/l before her death. She also had cholangitis and a choledochal stone had been removed in endoscopic retrograde cholangiography (ERC) 2 days earlier.

In univariate analysis, no single factor significantly affecting the formation of clinically relevant POPF was found. In all open procedures the clinically relevant fistula rate was 17.2% and in the laparoscopic procedures 12.8% (ns). Combined resection of other

organs raised the fistula rate up to 23.3% but without a significant difference between different centre volumes. In stapler closure and in hand sewn closure groups the respective fistula rates were 17% and 17.0% (ns). Malignancy did not protect against fistula formation, the POPF rate being 14,2% in all malignant cases.

Discussion

Ample evidence supports the centralization of PDs [12–16], but it is not known whether it would be beneficial also to centralize DPs. Our aim was to study the effect of hospital volume on the outcome of all DP operations performed nationwide in Finland during the period 2012–2014. We found that the frequencies of clinically relevant POPF and Clavien-Dindo 3–5 complications were not related to hospital volume. However, the management of complications differed significantly, as more reoperations were performed in the LVCs.

The reoperation rate in LVC was 10.3% and included three patients. One might speculate that these were all unnecessary. The first patient with PPH, POPF and intra-abdominal collection, who twice underwent relaparotomy, could have been managed by interventional radiological procedures. The second patient who had an infection and inadequate blood flow to the spleen on ultrasound could have been managed without laparotomy if a CT scan had been performed. The third patient who underwent a laparotomy for DGE could have been managed by watchful waiting, medical treatment, and repeated imaging. Most of the postoperative complications, which in the past may have needed surgery, can today be treated with conservative or minimally invasive approaches. In the low-volume centres the options for modern treatment may be limited.

A laparoscopic approach was taken, most often in HVCs and MVCs. Overall, laparoscopy seems to be underutilized in DPs in Finland, as the overall rate is so low (24%). Laparoscopic DP is associated with significantly less overall morbidity than open technique. Blood loss is smaller and the length of hospital stay is shorter [17]. However, no significant difference in clinically relevant POPF was found. In the LVCs laparoscopic approach was rare which might be explained by the low volume affecting the learning process. Thus, centralizing the procedures to at least MVC/HVC level might be beneficial even in this respect.

The overall clinically relevant POPF rate in our study was 17.2%, which is comparable to what has been reported elsewhere. Post-operative complications occur even in HVCs, and also in this study
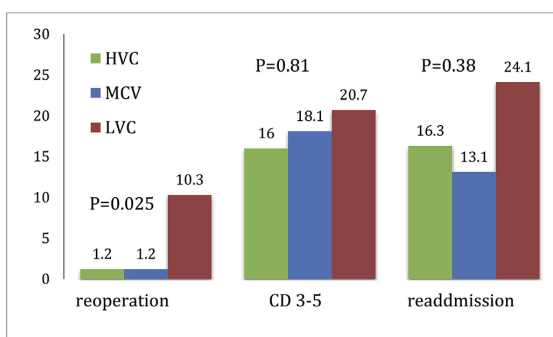

Fig. 1. Reoperation, Clavien-Dindo 3–5 grades and readmission rates seen in different centres. HVC = high volume centre, MVC = median volume centre, LVC = low volume centre).

no significant difference was found either in the incidence of POPF or in Clavien-Dindo 3—5 complications. Nor has a decrease in overall complication rate or POPF rate after DP been reported in HVCs vs. LVCs in the literature. However, only few studies report the rates of complications after DP separately [8]. In our study, DGE seemed to be more common in LVCs, but the patient records may not have all the information reliably listed.

Several studies have reported an association between high hospital volume and lower postoperative mortality in pancreatic surgery [1,2]. It has been shown that higher mortality in low volume centres with high-risk surgery is associated with the hospital's ability to rescue patients from major complications [3,18] The mortality risk is also attributable to patient characteristics, such as age and comorbidity [19]. In this study the deaths occurred in the MVC group and were both sudden and not caused by a treated complication, but one of them was associated with comorbidity, i.e., obesity.

PD has been shown to carry lower mortality and morbidity and also better oncological outcome in high-volume centres [1,20]. So far, centralization of DPs in high-volume centres does not seem to occur, although only few studies have been presented concerning only DPs in terms of postoperative complications and hospital volume [8]. One article which claimed that pancreatic resections can be safely done in MVCs had only 13 DP/11 yrs with a clinically relevant POPF rate in DP of 32% [21]. Factors favoring centralizing DP as well as PD include the overall knowledge of pancreatic surgery and its complications and postoperative care. Treatment and care may require imaging and interventional radiology around-the-clock and the decision-making for treatment also needs a multi-disciplinary approach, which is often lacking in LVC units. Reasonable volumes are needed to achieve and maintain experienced perioperative management. When analysing all patient records from each hospital manually we found no differences between HVCs and LVCs in terms of equipment used in surgery. Time of drain removal varies within centres according to individual surgeon. However, we did find that multidisciplinary teams were used in all tertiary but only in some secondary hospitals (HVCs and MCVs) and in neither of the LVC hospitals. In Finland, where the population is only 5.4 million and both DP and PC volumes are generally small, it would be wise to centralize the know-how in fewer centres in order to achieve the best results.

Risk factors for POPF have been widely studied. A laparoscopic approach has been shown to reduce the overall complications, but not POPF [22]. Many closure methods for pancreatic stump have been developed to reduce the complications, especially POPF. The pancreas can be closed by suturing or staplers, the stump can be covered with various patches or meshes or Tachosil [23]. Pancreatico-jejunal anastomosis and preoperative pancreatic stent have also been used [24,25]. Neither of these has reduced the POPF rate in RCTs. In a recent RCT a ligament Teres patch was shown to significantly decrease reoperation, readmission and reintervention rates without affecting the POPF rate [26]. On the pharmaceutical side, the use of octreotide is controversial. It has no effect on clinically relevant POPF, but it may reduce overall morbidity [27]. Pasireotide has been shown to reduce POPF rate to 7% after DP, in a recent RCT. High BMI has also been shown to increase the morbidity rate [28,29]. The effect of hospital volume in DP only has been poorly reported.

The strength of this study is the nationwide coverage of all DP operations performed in a single country during the study period. The study provides valuable information on nationwide DP volumes and complications rates. This is the first nationwide study on DP in Europe.

The weaknesses of this study include the missing and incomplete data. Patient data was collected retrospectively from 18 different hospitals in Finland and analyzed manually. POPF classification was made according the data found by the authors, so the analysis is consistent throughout the study [11]. Octreotide was not used routinely in any of the hospitals studied, although some surgeons did use it occasionally. It is therefore no included in the analysis. We could find no accurate information on drain removal time and were therefore unable to include this in the data. . Overall, the information is missing randomly and should not affect the results. The hospital volume definition is somewhat arbitrary, as in the literature definitions of volume mostly include both DP and PD. The number of patients in this study is also rather low since DP was performed quite rarely, which is also weakness of the study.

In conclusion, this nationwide register study shows similar POPF and overall complication rates after DPs performed in different volume hospitals in Finland during the period 2012—1014. However, there was a significant difference in the management of postoperative complications, as the reoperation rate was significantly more common in the LVCs. With experienced postoperative management, reoperations could possibly be avoided. This may favour the centralization of pancreatic resections to HVCs — not only for PD, but also for DP.

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