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PANCREATIC SURGERY – PERIOPERATIVE PHARMACOTHERAPY IN MITIGATION OF COMPLICATIONS AFTER PARTIAL PANCREATECTOMY AND NOVEL INSIGHTS INTO RARE GROOVE PANCREATITIS

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ACADEMIC DISSERTATION

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“*Alone, it’s just a journey. Now adventures, they must be shared.*”
To Jenni, Aaron, Anna and Aliisa.

ABSTRACT

Background: Pancreatic surgery is major surgery with an abundance of postoperative complications ranging from mild changes in the patient's postoperative care to mortality. A major part of these complications is due to the postoperative pancreatic fistula (POPF), which leads to postoperative fluid collections containing strongly proteolytic pancreatic enzymes. These collections may further become infected, when contaminated with enteric or biliary contents during the surgery or due to a disruption in pancreaticoenteric anastomosis. Finding ways to mitigate POPF and to identify the risk factors for bacterial contamination of the postoperative fluid collections play a crucial role in improving the outcomes after pancreatic surgery.

Groove pancreatitis is a rare form of chronic pancreatitis, which may be difficult to differentiate from a pancreatic cancer. Some authors favour pancreatic surgery as the first-line treatment for groove pancreatitis. However, the results of a more conservative approach to this disease are less reported even though widely used.

Objectives: The aim of this thesis was to study and assess the perioperative pharmacotherapy in mitigating the POPF and other postoperative complications after pancreatic surgery, and the association of bacterobilia during the transection of the biliary tract in pancreatoduodenectomy with surgical site infections. In addition, the natural course of groove pancreatitis and the outcomes of different treatment strategies of this disease were studied.

Materials and Methods: This thesis consists of four studies, which all were carried out at the Helsinki University Hospital, Helsinki, Finland. The patient cohort in **Studies I** and **II** consisted of high-risk patients for POPF who participated in a randomised controlled trial (HYPAR trial) comparing the effects of perioperatively administered pasireotide and hydrocortisone in the prevention of postoperative complications after partial pancreatectomy in a non-inferiority setting. The primary outcome was the mean difference of the comprehensive complication index (CCI), and the non-inferiority margin was set to nine points in CCI. The patients were enrolled between May of 2016 and December of 2018. **Study I** reported the short-term outcomes and **Study II** the long-term outcomes of the HYPAR trial.

Study III was a retrospective cohort study looking into bacterial colonisation of bile and its association to surgical site infections after pancreatoduodenectomy. Special focus was in assessing the risk of second-generation cephalosporin resistance in the intraoperative biliary cultures since the second-generation cephalosporins are recommended and routinely used preoperative prophylactic antibiotics in pancreatic surgery. The patients in this study were operated between May of 2016 and October 2020.

Study IV was a retrospective study looking into the treatment strategies of groove pancreatitis – a rare form of chronic pancreatitis. The cohort of this study was formed retrospectively from the records found in the electronic medical database between January 2005 and December 2015.

Results: In **Studies I** and **II,** a total of 126 patients who underwent a partial pancreatectomy in were randomised to receive either pasireotide or hydrocortisone. Both groups consisted of 63 high-risk patients for POPF. **Study I** reported the short-term outcomes of the HYPAR trial. The mean CCI (SD) was 23.94 (17.06) in the pasireotide group and 30.11 (20.47) in the hydrocortisone group. The mean difference of the CCI score was -6.16 (2-sided 90% CI, –11.73 to –0.60) between the groups. The prespecified -9 CCI points threshold was crossed by the lower limit of the two-sided 90% confidence interval, meaning that hydrocortisone was not non-inferior. In the subgroup of patients undergoing distal pancreatectomy, the mean CCI (SD) was 16.03 (11.94) in the pasireotide and 26.28 (21.76) in the hydrocortisone group and the mean difference was –10.25 (95% CI (-19.34 to -2.12), p=0.03). Also, the POPF rate was lower (37% vs 67%; p = .02) in the pasireotide group compared to the hydrocortisone group in the subgroup of distal pancreatectomies. The long-term results of the HYPAR trial were reported in **Study II** and there was no difference between the study groups in the survival of the patients or in the recurrence of the malignant diseases. The overall survival, disease-free survival and disease-specific survival were all convergent between the study drugs also in the subgroup of distal pancreatectomies, in which the difference in short-term outcomes was shown.

The retrospective patient cohort of **Study III** consisted of 361 patients who had undergone a pancreatoduodenectomy and had an intraoperative biliary culture obtained for the bacterial analysis. Preoperative biliary drainage had been performed for 254 (70%) of the patients. The risk of second-generation cephalosporin-resistant bacteria in the bile during the pancreatoduodenectomy was more than 20-fold, if the patient had undergone a preoperative biliary drainage [n=170/254 (67%) (OR 22.58 (95% CI, 9.61–53.01), p<0.001)] when compared to patients who had not undergone a preoperative biliary drainage [13/107 (12%)]. If the time between preoperative biliary drainage and surgery extended to two months or more, the second-generation cephalosporin resistance in the intraoperative biliary culture significantly increased the risk of surgical site infections (OR 4.14 (95% CI, 1.18–14.51), p=0.027).

In **Study IV,** the search from the electronic medical records brought up 67 patients who had had a suspicion of groove pancreatitis during the course of their disease. After blindly reviewing the imaging studies of these patients, 39 patients were considered to have a high radiological certainty for groove pancreatitis, five of whom eventually had a histologically verified pancreatic cancer instead. Finally, after further reviewing the patients' medical records, a cohort of 33 groove pancreatitis patients was formed. Mostly the patients were middle-aged males with at least moderate levels of alcohol consumption. Nearly half (14 out of 33) of these groove pancreatitis patients did not undergo any kind of invasive intervention. At five years, the patients who were treated conservatively were all asymptomatic. In comparison, only 10 of 16 patients who had undergone at least one invasive procedure due to groove pancreatitis' obstructive symptoms were asymptomatic at five years. Four patients of 33 had undergone a pancreatoduodenectomy and all of them underwent the resection due to a suspicion of pancreatic cancer, but the final histopathological report confirmed the diagnosis of groove pancreatitis.

Conclusions: In the short term, hydrocortisone was not non-inferior to pasireotide in mitigating the postoperative complications in all high-risk patients. In the subgroup of distal pancreatectomies, pasireotide might be beneficial in the prevention of postoperative complications. In the long term, the patients who took either pasireotide or hydrocortisone seemed to have similar outcomes.

Second-generation cephalosporin resistance is common after preoperative biliary drainage. The second-generation cephalosporin resistance increases the risk of surgical site infections, if the time delay between preoperative biliary drainage and surgery is two months or more. These patients could benefit from broader-spectrum antibiotics in the prophylactic setting, and the recommendation of cephalosporins in the prophylaxis of pancreatoduodenectomy seem to be outdated.

Radiologically, groove pancreatitis may resemble pancreatic cancer, and the diagnosis of groove pancreatitis is difficult. Most patients may be treated conservatively, and a step-up approach seems justified in the case of obstructive symptoms.

TIIVISTELMÄ

Taustaa: Haimaan kohdistuvaan kirurgiaan liittyy runsaasti leikkauksen jälkeisiä komplikaatioita. Suurin yksittäinen syy näille komplikaatioille on leikkauksen jälkeinen haimasauman vuoto eli haimafisteli, jonka takia leikkausalueelle syntyy haiman tuottamien ruunasulatusentsyymien sisältäviä kertymiä. Nämä kertymät voivat lisäksi infektoitua leikkauksen aikana tai sen jälkeen maha-suolikanavan bakteereilla. Haimafistelien ehkäisy on tärkeässä asemassa haimakirurgian komplikaatioiden ehkäisyssä.

Groovepankreatiitti on harvinainen pitkittyneen haimatulehduksen muoto, jonka erottaminen haimasyövästä voi olla lähes mahdotonta. Osa tutkijoista ehdottaa kirurgiaa ensisijaiseksi hoitomuodoksi, vaikka käytännössä valtaosa groovepankreatiittipotilaista hoidetaan ilman kajoavia toimenpiteitä. Kirjallisuudesta löytyy vain rajallisesti tuloksia konservatiivisemman hoidon tehosta tässä harvinaisessa taudissa.

Tavoitteet: Tämän väitöskirjan tavoite on tutkia kahden eri lääkehoidon tehoa haimaleikkauksen jälkeisten komplikaatioiden ehkäisyssä sekä näiden lääkkeiden pitkäaikaisvaikutuksia. Toisena tavoitteena on tarkastella haimanpään- ja pohjukaissuolen poistoon tulevien potilaiden sappinesteen bakteerikantoja ja näiden yhteyttä leikkauksen jälkeisiin infektiokomplikaatioihin. Viimeisen osatyön tavoitteena on tutkia ja tarkastella groovepankreatiitin diagnostiikan haasteita, taudinkulkua sekä eri hoitovaihtoehtojen tehoa tähän harvinaiseen tautiin.

Aineisto ja tutkimusmenetelmät: Väitöskirja koostuu neljästä tutkimuksesta, jotka kaikki toteutettiin Helsingin Yliopistollisessa Keskussairaalassa. Ensimmäiseen ja toiseen osatyöhön valikoitiin haiman osapoistoon tulevia potilaita, joilla oli lisääntynyt riski leikkauksen jälkeiseen haimafisteliin. Potilaat satunnaistettiin saamaan perioperatiivisesti joko pasireotidia tai hydrokortisonia. Tutkimusasetelmana oli vertailukelpoisuusasetelma (non-inferiority). Ensimmäisen osatyön päävastemuuttujana oli keskimääräisen kokonaiskomplikaatiotaakan ero tutkimusryhmien välillä 30 vuorokauden kuluessa leikkauksesta, mikä määritettiin käyttämällä kokonaisvaltaista komplikaatiopisteytystä (Comprehensive Complication Index, CCI). Huonommuuden rajaksi asetettiin yhdeksän pistettä, sillä kymmenen pistettä vastaa arviolta yhtä merkittävää komplikaatiota. Väitöskirjan ensimmäinen osatyö raportoi tämän satunnaistetun vertailevan tutkimuksen lyhytaikaiset tulokset ja toinen osatyö pitkäaikaistulokset. Potilaat satunnaistettiin vuoden 2016 toukokuun ja vuoden 2018 joulukuun välisenä aikana.

Kolmannessa osatyössä tutkittiin haimanpään- ja pohjukaissuolen poistoon tulevien potilaiden sappinesteen bakteerikasvustoa ja näiden

yhteyttä leikkauksen jälkeisiin infektiokomplikaatioihin. Erityinen huomio kiinnitettiin siihen, mitkä ovat riskitekijöitä toisen polven kefalosporiiniresistenssille näissä bakteereissa, sillä tämä antibiootti on suositusten mukaan ensisijainen suoja-antibiootti ehkäisemään leikkauksen jälkeisiä infektiokomplikaatioita. Tutkimukseen arvioitiin takautuvasti kaikki haimanpään- ja pohjukaissuolen poistoleikkaukseen tulevat potilaat toukokuun 2016 ja lokakuun 2020 väliseltä ajalta.

Neljännessä osatyössä tutkittiin groovepankreatiitin diagnostiikan haasteita sekä taudinkulkua ja hoitovaihtoehtoja. Tutkimukseen kerättiin takautuvasti potilaat Helsingin ja Uudenmaan sairaanhoitopiirin alueelta vuosien 2005 ja 2015 väliltä. Tutkimusaineisto kerättiin tekemällä konehaku sairaanhoitopiirin yhteisestä potilastietojärjestelmästä avainsanojen ”groove*” ja ”paraduod*” avulla. Hakusana ”paraduod*” viittaa groovepankreatiitin yleisimpään synonyymiin paraduodenaalipankreatiittiin.

Tulokset: Ensimmäiseen ja toiseen osatyöhön satunnaistettiin 126 korkean haimafisteliriskin potilasta, joille tehtiin haiman osapoisto. He saivat 1:1 pasireotidia tai hydrokortisonia. Ensimmäisessä osatyössä 30 vrk:n keskimääräinen CCI (normaalihajonta) oli 23,94 (17,06) pasireotidiryhmässä ja 30,11 (20,47) hydrokortisoniryhmässä. Keskimääräisen CCI:n ero ryhmien välillä oli -6,16 (2-puoleinen 90% luottamusväli: -11,73 - -0,60). Luottamusvälin alaraja ylitti ennalta määritetyn yhdeksän CCI pisteen eron, joten vertailuasetelmassa hydrokortisonin ”ei-huonommuutta” ei voitu osoittaa suhteessa pasireotidiin. Alaryhmäanalyyseissä pasireotidi oli hydrokortinsonia tehokkaampi ehkäisemään leikkauksen jälkeisiä komplikaatioita potilailla, jotka tulivat haimanhännän poistoon [CCI (keskihajonta): pasireotidiryhmässä 16,03 (11,94) ja hydrokortisoniryhmässä 26,28 (21,76)]. Keskimääräinen CCI:n ero oli ryhmien välillä tilastollisesti merkittävä ollen -10,25 (95% luottamisväli: -19,34 - -2,12, p=0.03). Lisäksi haimanhännän poistoon tulleilla potilailla haimafistelien esiintyminen oli vähäisempää pasireotidiryhmässä (37% vs. 67%, p=0.02). Toisessa osatyössä raportoiduissa pitkäaikaistuloksissa ei havaittu eroja tutkimusryhmien välillä. Kokonais-, tautivapaa ja tautikohtainen selviytyminen olivat kaikki yhteneviä koko aineistossa sekä haimanhännän poistoleikkaus potilaiden alaryhmässä eli siinä alaryhmässä, jossa pasireotidista oli hyötyä lyhyen aikavälin tuloksissa.

Kolmannessa osatyössä tutkittiin 361 haimanpään- ja pohjukaissuolen poistoon tulevan potilaan sappinesteen bakteerikasvustoa. Leikkausta edeltävä sappiteiden endoproteesin laitto oli tehty 254 (70%) potilaalle. Riski sille, että leikkauksen aikana otetussa sappinesteen bakteeriviljelyssä kasvoi toisen polven kefalosporiineille resistentti bakteerikanta oli yli 20-kertainen, jos potilaan sappiteihin oli laitettu endoproteesileikkausta edeltävästi [170/254 (67%) (kerroinsuhde 22,58 ja 95% luottamisväli: 9.61 – 53.01), p<0.001)] verrattuna potilaisiin, joilla sappiteitä ei ollut stentattu [13/107 (12%)]. Jos potilaalla oli yli kahden kuukauden aikaväli sappiteiden stenttauksen ja haimanpään- ja pohjukaissuolen poisto välissä ja häneltä löytyi sappinesteen bakteeriviljelyssä toisen polven kefalosporiineille resistentti bakteerikanta, oli hänellä yli nelinkertainen riski saada leikkauksen jälkeinen infektiokomplikaatio (kerroinsuhde 4,14 (95% luottamisväli: 1.18-14.51, p=0.027).

Neljännessä osatyössä löydettiin takautuvasti 67 mahdollista groove-pankreatiittipotilasta. Kaksi kokenutta radiologia tulkitsivat potilaiden kuvantamistutkimukset uudelleen tietämättä lopullista diagnoosia. Groovepankreatiitin radiologisten kriteerien perusteella he arvioivat 39 näistä potilaista todennäköisiksi groovepankreatiitin suhteen. Sairauskertomus-merkintöjen uudelleen arvioinnin jälkeen todettiin, että viidellä 39 potilaasta, joilla groovepankreatiitti oli radiologisesti todennäköinen, olikin lopulta ollut histologisesti varmennettu haimasyöpä. Seuraavaksi kaikkien 67 potilaan sairauskertomusmerkintöjen uudelleen arvioinnin myötä muodostettiin 33 groovepankreatiittipotilaan ryhmä taudin luonteen ja eri hoitomuotojen tehon arviointia varten. Suurin osa groovepankreatiitti-potilaista oli keski-ikäisiä miehiä, joilla oli vähintäänkin kohtalainen säännöllinen alkoholinkulutus. Noin puolet (14 / 33) potilaista parantui oireettomaksi ilman toimenpidettä ja viiden vuoden kohdalla kaikki nämä potilaat olivat oireettomia. Kymmenen potilasta 16:sta, joille oli tehty ainakin yksi joko endoskooppinen tai kirurginen toimenpide groovepankreatiitin tukosoireiden takia, olivat oireettomia. Vain neljälle potilaalle tehtiin haimanpään- ja pohjukaissuolen poisto, eikä kenellekään heistä groovepankreatiitin takia, vaan haimasyöpäepäilyn takia. Kaikkein näiden neljän leikatun potilaan lopullinen histopatologinen diagnoosi paljastui olemaan groovepankreatiitti.

Johtopäätökset: Lyhyellä aikavälillä hydrokortisoni ei ollut ”ei-huonompi” pasireotidiin verrattuna leikkausten jälkeisten komplikaatioiden ehkäisyssä kaikilla korkean haimafisteliriskin potilailla, joille oli tehty haiman osapoisto. Haimanhännän poistoleikkaukseen jälkeen pasireotidi vaikutti vähentävän kokonaiskomplikaatiotaakkaa merkittävästi verrattuna hydrokortisoniin. Pitkällä aikavälillä ei tutkimuslääkkeitä saaneiden potilaiden tuloksissa ollut merkittäviä eroja.

Sappisnesteen bakteerikantojen resistenssi toisen polven kefalosporiineille on yleistä haimanpään- ja pohjukaissuolen poistoleikkauksen aikaan. Etenkin potilaat, joilla on yli kaksi kuukautta väliä sappiteiden endoproteesin laiton ja leikkauksen välissä, voisivat hyötyä toisen polven kefalosporiineja laajakirjoisemmasta antibiootista leikkausta edeltävänä suoja-antibioottina.

Groovepankreatiitin radiologinen diagnostiikka on haastavaa. Sen erottaminen haimasyövästä pelkällä kuvantamisella voi olla lähes mahdotonta. Valtaosa groovepankreatiittipotilaista paranee ilman kajoavia toimenpiteitä ja asteittainen siirtyminen konservatiivisesta hoidosta invasiivisempaan näyttäisi olevan perusteltua, mikäli potilaalla on tukosoireita

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, and these are referred to in the text by respective Roman numerals:

I Tarvainen, T, Sirén, J, Kokkola, A, Sallinen, V. Effect of hydrocortisone vs pasireotide on pancreatic surgery complications in patients with high risk of pancreatic fistula: a randomized clinical trial. *JAMA surgery*. 2020 Apr; 155(4): 291–298.

II Tarvainen, T, Sirén, J, Kokkola, A, Sallinen, V. Long-term Survival Outcomes Following Perioperative Hydrocortisone versus Pasireotide in Patients with High-Risk of Pancreatic Fistula: Prespecified 5-Year Analysis of the HYPAR Randomized Clinical Trial. *Manuscript submitted.*

III Tarvainen T, Bonsdorff A, Kolho E, Sirén J, Kokkola A, Sallinen V. Association of cephalosporin resistance in intraoperative biliary cultures with surgical site infections in patients undergoing pancreaticoduodenectomy. A retrospective cohort study. HPB 2024 Feb; 26(2): 259-269.

IV Tarvainen, T, Nykänen, T, Parviainen, H, Kuronen, J, Kylänpää, L, Sirén, J, Kokkola, A, Sallinen, V. Diagnosis, natural course and treatment outcomes of groove pancreatitis. *HPB*. 2021 Aug; 23(8): 1244–1252.

ABBREVIATIONS

AUROC	area under the receiver operating characteristics curve
CA19-9	carbohydrate antigen 19-9
CCI	Charlson comorbidity index
CCI	comprehensive complication index
CD	Clavien-Dindo
CI	confidence interval
CP	chronic pancreatitis
CRP	C-reactive protein
CT	computed tomography
DGE	delayed gastric emptying
DFS	disease-free survival
DP	distal pancreatectomy
DSS	disease-specific survival
ERAS	enhanced recovery after surgery
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
GI	gastrointestinal
GP	groove pancreatitis
HPB	hepatic, pancreatic and biliary
IBC	intraoperative biliary culture
IQR	interquartile range
ISGPS	International Study Group on Pancreatic Surgery
IPMN	intraductal papillary mucinous neoplasm
LMWH	low molecular weight heparin
MCN	mucinous cystic neoplasm
MRI	magnetic resonance imaging
OS	overall survival
PD	pancreatoduodenectomy
PDAC	pancreatic ductal adenocarcinoma
PG	pancreaticogastrostomy
PJ	pancreaticojejunostomy
pNEN	pancreatic neuroendocrine neoplasm
POPF	postoperative pancreatic fistula
PPAP	postpancreatectomy acute pancreatitis
PPH	postpancreatectomy haemorrhage
PPPD	pylorus preserving pancreatoduodenectomy
PBD	preoperative biliary drainage
PTBD	percutaneous transhepatic biliary drainage
RCT	randomized controlled trial
SCN	serous cystic neoplasm
SD	standard deviation

SPN	solid pseudopapillary neoplasm
SSI	surgical site infection
TP	total pancreatectomy
ua-FRS	updated alternative Fistula Risk Score
WHO	World Health Organization

1 INTRODUCTION

In the field of abdominal surgery, pancreatic surgery carries one of the highest burdens for postoperative complications. The main reason for most of the postoperative complications is POPF in which the pancreatic fluids leak outside the gastrointestinal (GI) tract via a discontinuation in the pancreaticoenteric anastomosis or from the transection line of the pancreas (Schoellhammer et al., 2014). In the case of POPF, the strong proteolytic digestive enzymes, which the pancreas secretes, start to dissolve the surrounding tissues leading to a cascade of abscesses, haemorrhage, sepsis and possibly even death (Schoellhammer et al., 2014; Bassi et al., 2017; Pedrazzoli, 2017). Research into finding the ways to reduce POPF and other postoperative complications in pancreatic surgery has been abundant, and the studied mitigation strategies range from pharmacotherapy to different surgical techniques (Miyasaka et al., 2017; Harrison et al., 2024).

Some of the most studied pharmaceutical agents to mitigate POPF and other postoperative complications after pancreatic surgery are somatostatin analogues. The mechanism by which the somatostatin analogues have been thought to mitigate the POPF is by reducing the secretion of the proteolytic digestive enzymes the pancreas produces (Adiamah et al., 2019). Octreotide has been traditionally the most used somatostatin analogue but during the recent decade, pasireotide – a somatostatin analogue with a higher affinity to somatostatin receptors – has emerged as an alternative, especially after a randomised trial comparing pasireotide to placebo showed pasireotide's superiority in the prevention of POPF (Allen et al., 2014). Corticosteroids have also been studied in the prevention of POPF. After a partial pancreatectomy, the remnant pancreas may be hit with an inflammatory response, which then leads to a postpancreatectomy acute pancreatitis (PPAP) known to increase the risk of POPF (Connor, 2016; Laaninen et al., 2016; Bonsdorff et al., 2022). Corticosteroids are anti-inflammatory agents and are thought to reduce POPF by mitigating the inflammatory response at the site of the resection. Hydrocortisone is a corticosteroid shown to be beneficial in preventing POPF and other postoperative complications when compared to placebo after partial pancreatectomy (Laaninen et al., 2016; Antila et al., 2019). The downside of pasireotide is its relatively high price tag, while the costs of hydrocortisone are practically non-existent. If hydrocortisone were at least equally beneficial as pasireotide, the cost reduction could be significant, which is something not to be overlooked at present when the healthcare is facing austerity. On the other hand, if pasireotide is superior to hydrocortisone, the higher expenses are justified. No studies have previously compared pasireotide and hydrocortisone to each other in the prevention of postoperative complications.

Surgical site infections (SSI) are common postoperative complications after pancreatoduodenectomy (PD) and a preoperative biliary drainage (PBD) is shown to increase the risk of SSIs (Limongelli et al., 2007; Sano et al., 2019; Demir et al., 2020). The preoperative antibiotic prophylaxis in abdominal surgery is well documented in the prevention of SSIs and, for example, the joint guideline by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society and the Society for Healthcare Epidemiology of America recommends the use of cephalosporins in the prophylaxis of pancreatic surgery (Bratzler et al., 2013). More recent data support the use of broader-spectrum antibiotics in the prophylaxis of pancreatic surgery, especially in patients who have undergone a PBD. Some retrospective series suggest the benefit of broader-spectrum antibiotics such as piperacillin/tazobactam in the prophylaxis before PD, and a quite recent randomized controlled trial also suggested the benefit of piperacillin/tazobactam over cephalosporins, especially in patients undergoing PD after PBD (Sano et al., 2019; De Pastena et al., 2021; D'Angelica et al., 2023; Yang et al., 2024). Also, a recent meta-analysis by Kumar et al. suggested the superiority of piperacillin/tazobactam over traditional antibiotics, which were mostly cephalosporins, in patients undergoing a PD (Kumar et al., 2024). At the moment, some of the most commonly used prophylactic antibiotics in pancreatic surgery are cephalosporins, but these recent studies may challenge one to think about the use of broader-spectrum antibiotics. However, the lavish use of broader-spectrum antibiotics will inevitably lead to increasing resistance problems, and the use of broader-spectrum antibiotics needs to be well justified (Marston et al., 2016; Jernigan et al., 2020). It would be important to identify the possible groups of patients who would most likely benefit from the use of broader-spectrum antibiotics, and not to overtreat everyone with the expense of likely harvesting multi-resistant bacteria. The groups of patients undergoing pancreatic surgery that would actually benefit from broader-spectrum prophylactic antibiotics is still somewhat unclear.

Groove pancreatitis (GP) is a rare form of chronic pancreatitis, which affects the groove area between the 2nd and 3rd parts of duodenum and the head of pancreas, and may sometimes mimic pancreatic cancer in the imaging studies (Stolte et al., 1982; Becker & Mischke, 1991; Mittal et al., 2017). Some authors favour major pancreatic surgery such as PD as the first-line treatment for GP (Casetti et al., 2009; Egorov et al., 2014). However, at our centre the use of major pancreatic surgery, such as PD, is practically non-existent in the treatment of GP. The choice of treatment modality for GP has been based on the symptoms of the patient, and not the diagnosis itself. Studies published in recent years have been suggesting a more conservative treatment for GP with convergent results compared to PD (Lekkerkerker et al., 2016; Balduzzi et al., 2020). Even though conservative treatment has been shown to have equal results to surgery, some fairly recent studies still incite pancreatic resection as the first line treatment for GP (Egorov et al., 2021; Teo et al., 2022).

This thesis studies the role of perioperative pharmacotherapy with pasireotide and hydrocortisone in the mitigation strategies of postoperative complications after partial pancreatectomy, the association of resistant bacteria in bile during a PD to SSIs, and the natural course and treatment options of GP - a rare form of chronic pancreatitis.

2 REVIEW OF THE LITERATURE

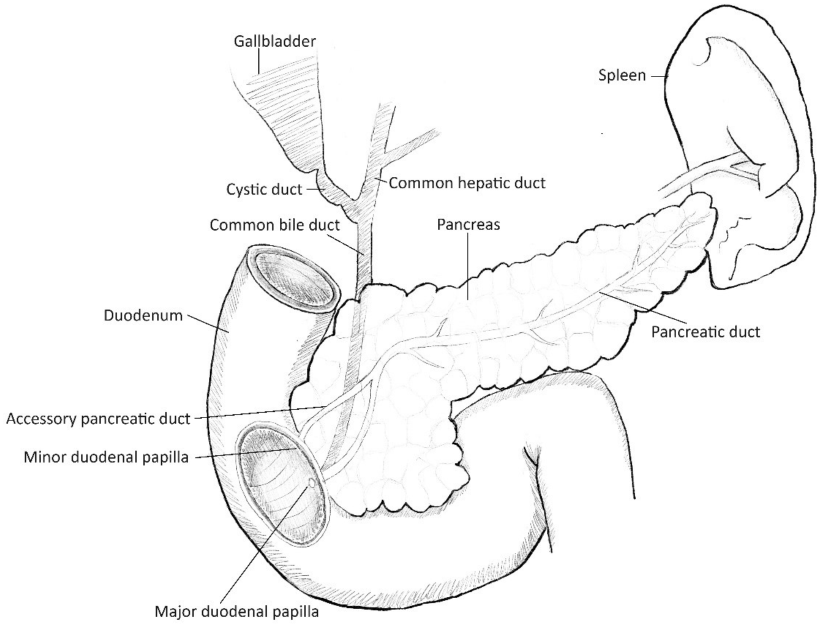
2.1 THE BRIEF HISTORY OF THE PANCREAS

The earliest the word ‘pancreas’ - a Greek word literally meaning “all flesh” - has been found in writings dating back to ancient Greece. In an anatomical context, the word ‘pancreas’ has been found in the writings of well-known philosopher Aristotle (ca. 350 BC) as well as in those of Herophilos of Chalcedon (ca. 300 BC) who is widely considered as the father of anatomy (Busnardo et al., 1983; McClusky et al., 2002; Ceranowicz et al., 2015). However, the first time the word ‘pancreas’ was used to refer to the organ we now know was several hundred years later (ca. 100 AD) in the writings of another Greek anatomist, Rufus of Ephesus (McClusky et al., 2002). Even though there was knowledge of such an organ, the true function of it remained a mystery for a long time. Galen (129-219 AD), the court physician of the Roman emperor, considered the pancreas to be a part of the omentum and serve merely as a cushion for the great vessels lying posterior to it. The dogmas of Galen were fundamental in medicine for over 1,000 years throughout the dark ages, during which there was practically no progress in the knowledge of the pancreas. It was not until the 16th century when the pancreas was next mentioned, in the scientific writings of Dutch-born anatomist Andreas Vesalius. After that, the mystery of the pancreas started to unravel bit by bit, and its history is filled with familiar names such as Wirsüng, Langerhans, Brunner, Halsted, Whipple and even Pavlov (Busnardo et al., 1983).

2.1.1 SURGICAL ANATOMY OF THE PANCREAS

The pancreas is a transversely situated retroperitoneal organ surrounded by multiple critical anatomical structures (Nießen & Hackert, 2022). The pancreas can be divided into four main parts: the head, neck, body and tail. The main pancreatic duct, also known as the duct of Wirsung, runs through the entire pancreas from tail to head, and transfers the pancreatic fluids to the duodenum via an opening called the major duodenal papilla, also known as the papilla of Vater. The common bile duct, which transfers bile from the liver to the duodenum via the papilla of Vater, also runs through the head of the pancreas, and just before the papilla it joins the pancreatic duct. This conjoined area of these two ducts is called the ampulla of Vater. Also, all along the pancreatic parenchyma are smaller side branches, which all eventually drain to the main pancreatic duct. Occasionally, an accessory pancreatic duct can also be found running to the duodenum via its own opening (Figure 1) (Talathi et al., 2022).

Figure 1. Anatomy of the pancreas. Illustration by Heidi Naumanen.



Anteriorly to the pancreas is the lesser sac, which is delimited by the stomach and transverse colon, and this is a loose space to operate in. Posteriorly in close proximity to the pancreas lie many vital vessels such as superior mesenteric vessels, the aorta and the inferior vena cava, which all need to be preserved or reconstructed. In addition, the common bile duct, which may need to be transected during a pancreatic resection, is situated alongside with the portal vein and the proper hepatic artery, which are both vital to the liver (Longnecker, 2014).

2.1.2 PHYSIOLOGY OF THE PANCREAS

The pancreas is a dual-functioning organ, which functions as part of both the endocrine and exocrine systems (Leung, 2010). The physiology of the pancreas, and especially the exocrine part of it, has an extensive role in the risks relating to surgery of the pancreas. The pancreas produces many important endocrine hormones in the islet cells, also known as the islet of Langerhans, such as insulin, glucagon, ghrelin and somatostatin (El Sayed & Mukherjee, 2022). Even though these hormones are critical to the human homeostasis, the production of these endocrine hormones contributes only to 1-2% of the pancreatic functions (Pour et al., 2002). Most pancreatic functions belongs to the exocrine side of the organ. The pancreatic fluid secreted to the duodenum via the main pancreatic duct contains amylases, lipases and proteolyzes produced by the acinar cells of pancreas. These exocrine enzymes are highly dissolvent and are needed to separate nutrients and fats from ingested food. If these enzymes leak out of the GI tract, they start to dissolve into surrounding structures in an undesired fashion (Schoellhammer et al., 2014). This highly proteolytic feature of the pancreatic fluid is one of the main reasons why pancreatic surgery is notorious in the prevalence of postoperative complications (Gouillat & Gigot, 2001).

2.2 SURGERY OF THE PANCREAS

2.2.1 THE HISTORY OF THE PANCREATIC SURGERY

The first pancreatectomies (surgical removal of a part of the pancreas) were performed in the late 19th century with high mortality rates. Friedrich Trendelenburg, a German surgeon whose surname is recognisable to anyone working in the surgical field, performed the first reported distal pancreatectomy (DP) in 1882 for a large spindle cell carcinoma. Postoperative course was complicated by a wound infection and malnutrition, and the patient died due to respiratory failure shortly after being discharged (Witzel, 1886). The first reported operation affecting the head of the pancreas was performed by Italian surgeon, Giuseppe Ruggi, who enucleated a large mass of 650 grams from the head of the pancreas. The histological report showed adenocarcinoma and, even though the postoperative course was uneventful, the patient died due to recurrence after few months (Ruggi, 1890; Schnelldorfer et al., 2008).

On February 9th, 1898 an Italian surgeon Alessandro Codivilla performed the first ever described PD for a cancer involving the stomach and head of the pancreas (Dal Monte, 1899). The resection included the head of the pancreas, distal part of the stomach, duodenum and distal bile duct. The common bile duct and the duodenal stump were closed with sutures, and the continuity of the biliary and GI-tracts was restored with a cholecystojenunostomy and a Roux-en-Y gastrojejunostomy. The remaining pancreas was not anastomosed or closed by any means. The postoperative course was complicated by continuous serous drainage with milky clots from the wound and steatorrhea. The patient eventually died on 18th postoperative day (Dal Monte, 1899; Gamberini & Dig, 1949). Less than a week after the Codivillas operation on February 14th, 1898, an American surgeon William Stewart Halsted performed a transduodenal papillectomy for a papillary tumour with the respective pancreatic and bile duct anastomosis. This was the first time a pancreatico-enteric anastomosis had been described. The patient largely recovered well, but after few months developed a stenosis in the bile duct anastomosis needing a cholecystoduodenostomy and, shortly after that, the cancer recurred leading to the death of the patient (Halsted, 1899).

The first PD with a pancreatic anastomosis was performed by German surgeon, Walther Kausch, in 1909. He performed a two-stage PD where at the first stage a cholecystojejunostomy was performed to relieve jaundice and, after two months at the second stage, the resection of the head of the pancreas and major part of the duodenum was done. The body of the pancreas was then placed inside the duodenum and sutured in two layers (Kausch, 1912). Postoperatively, the patient suffered a leakage of pancreatic fluids through the wound and the inability to tolerate oral intake, which eventually resolved, and the patient was discharged after two months. Nine months after the second operation, the patient developed septic cholangitis and died shortly after readmission (Schnelldorfer et al., 2008).

After these aforementioned operative descriptions, one can find a limited number of descriptions of PDs either with or without some kind of a pancreatico-enteric anastomosis until the 1935 landmark publication by American surgeon, Allen O. Whipple. In this publication, Whipple described three PDs performed due to ampullary cancers without restoring the continuity of the pancreatic duct (Whipple et al., 1935; Schnelldorfer et al., 2008). By this time, the PD was performed in a two-stage fashion as previously described, which then ultimately changed to a one-stage operation due to a false preoperative diagnosis of one of Whipple's patients. In 1940, he operated on a patient whom he thought had distal gastric cancer. However, after the transection of the stomach, Whipple found that, instead of the stomach, the cancer originated from the head of the pancreas infiltrating the antrum of the stomach. Whipple proceeded to perform a PD and respective reconstructions without pancreatico-enteric anastomosis in this same operation, and this operation eventually became the basis for modern one-stage PD, also known as Whipple's procedure (Whipple, 1945). By this time the dreaded complication of the pancreatic fistula was already well acknowledged, but the need for reconstruction of the pancreatic tract was not recognised until Charles G. Child III described a series of four PDs with pancreatico-jejunostomies (PJ) without any significant pancreatic fistula. After that, the PJ became the gold standard for reconstruction after PD (Child III, 1944).

The high rate of postoperative mortality overshadowed pancreatic surgery and especially PD for many decades. The mortality rate prior 1940 for the 41 PDs reported in literature was overwhelming at 34% (Schnelldorfer et al., 2008), which then decreased to a level of 10-20% by the 1960s (Mongé et al., 1964) and there has been a gradual improvement in outcomes decade by decade. In modern times, the mortality rates after PD are no more than 1-3% (Kokkinakis et al., 2022).

2.2.2 INDICATIONS FOR ELECTIVE SURGERY

The indications for a non-emergency pancreatectomy can be roughly divided into three categories: 1) malignancies, 2) potentially malignant lesions, and 3) benign, but symptomatic lesions including chronic pancreatitis (Bouwense et al., 2019; van Roessel et al., 2019). The two most common pancreatectomies are PD and DP and between these two, the scale of indications varies slightly. Regardless of this, cancer is the leading cause for both operations. The prevalence of malignancies in patients undergoing PD is 60-90% (Newhook et al., 2015; van Roessel et al., 2019; Mungroop et al., 2021; Bonsdorff et al., 2022), while in DPs the benign indications are slightly more present, but the prevalence of cancers in resected specimen is still as high as 50-70% (Klompmaker et al., 2021; Bonsdorff et al., 2022; van der Heijde et al., 2022). Other less common types of pancreatectomies are total and median pancreatectomy, which can be used in either malign or benign indications, and pancreatic parenchyma preserving enucleation, which is mostly used in benign conditions or lesions of low malignant potential (Chua et al., 2016; Del Chiaro et al., 2016).

2.2.2.1 Malignancies

The most common indication for pancreatectomy is cancer, which most often originates from the pancreas itself, but malignancies at the distal bile duct, ampullar or duodenum may also necessitate a partial pancreatectomy (Giuliano et al., 2017). There are several types of cancers originating from the pancreatic tissue, of which the pancreatic ductal adenocarcinoma (PDAC) is by far the most common, covering 90% of all pancreatic cancers (Fitzgerald et al., 2008). The remaining pancreatic cancers form a heterogenous group of rare or relatively rare tumours such as mucinous cystadenocarcinomas (5%) and pancreatic neuroendocrine neoplasms (pNEN) (2-3%). Rare malignancies like acinar cell carcinoma and adenosquamous carcinoma make up only a tiny fraction of cases (Fitzgerald et al., 2008).

Surgery is a vital part in the treatment of pancreatic malignancies. Pancreatic resection and adequate lymphadenectomy preferably combined with neoadjuvant and/or adjuvant oncological treatment is the only way to cure a patient with a PDAC. However, at the time of diagnosis, only 15-20% of PDACs are non-metastatic and can be considered to be resectable (Ducreux et al., 2015; Michl et al., 2021). Furthermore, approximately 80% of patients undergoing surgery for PDAC have had preoperatively non-visible micrometastatic disease leading to a recurrence in near future (Michl et al., 2021). Due to these factors, the survival rate at five years after the diagnosis of a PDAC is less than 5% for all patients and 15-20% for the selected patients who have undergone pancreatic resection with a curative intent (Coupland et al., 2012; Ducreux et al., 2015; Strobel et al., 2022).

For the patients who have undergone surgery for a pNEN, five-year survival is nearly 90% (Jilesen et al., 2016). In non-metastatic pNENs including both resectable and non-resectable tumours, disease-specific survival after 20 years is greater than 50%, and the median overall survival is five years, even with a metastatic pNEN (Dasari et al., 2017; Chi et al., 2018). Cancers arising from the ampulla of Vater, or its near proximity - the periampullary cancers - may originate from the ampulla itself, the distal parts of pancreatic or biliary tract or the duodenum (Sarmiento et al., 2001). These periampullary cancers may produce symptoms such as jaundice or gastrointestinal bleeding at lower stages of the cancer, leading to earlier diagnosis and most likely also favouring the prognosis (Burasakarn et al., 2021). An English registry study on hepatic, pancreatic and biliary (HPB) cancers showed five-year survival rates of 20.8% for ampullary, 16.1% for duodenal and 2.6% for PDAC (Coupland et al., 2012). The five-year survival rates for the patients undergoing surgery for ampullary or duodenal cancer has been reported to be at 35-45% (Klein et al., 2014; Zhou et al., 2020) and 40-60% (Jiang et al., 2016; Lee et al., 2018), which are markedly higher than for patients with a PDAC.

2.2.2.2 Pancreatic cystic lesions

Pancreatic resection might also be needed for benign cystic neoplastic lesions known to have malignant potential. These pancreatic cystic lesions can be divided into four main types: intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), solid pseudopapillary neoplasm (SPN) and serous cystic neoplasm (SCN) (Brugge, 2015). Apart from SCN, these cystic neoplasms have a potential to turn malignant and need to be either resected or followed for a certain period, if the patient is thought to be fit for surgery in the future (Karoumpalis & Christodoulou, 2016; Perri et al., 2020). The decision between surveillance and resection depends on several risk factors based on the radiological and biological features of the cystic neoplasm as well as the patient's comorbidities and overall performance status (Pancreas, 2018; Perri et al., 2020).

European guidelines on pancreatic cystic neoplasm recommends pancreatic resection for IPMN in the presence of risk factors seen in Table 1, if the patient is fit for pancreatic surgery (Pancreas, 2018). If these risk factors are present, the risk of cancer or high-grade dysplasia can be as high as 40-100% in the main duct IPMNs and also up to 40% in branch duct IPMN based on surgical series (Pancreas, 2018; Marchegiani et al., 2023). If the diameter of the MCN exceeds 4 cm, the risk of malignancy can be up to 30%, and these MCNs are recommended to be surgically removed. As in IPMNs, in MCNs the risk of malignancies is also based on surgical series, which overemphasises the risks compared to all patients with these conditions. However, the risk of cancer in an MCN less than 4 cm in diameter is extremely low - less than 0.5% - and these can be safely followed (Nilsson et al., 2016; Pancreas, 2018). SPNs are always recommended to be resected regardless of their size due to the high malignant potential and typical emergence in younger patients (Kim et al., 2014; Pancreas, 2018). Contrary to the risk of malignancy in other cystic neoplasms, the risk in SCN has been a subject of debate. European guidelines on pancreatic cystic neoplasms state that SCN has a benign nature and surgery should be considered only if there are symptoms related to the size or location of the SCN (Pancreas, 2018).

Table 1. European guidelines of the indications for surgery in IPMN(Pancreas, 2018).

Absolute indications	Relative indications
Positive cytology for malignant/high grade dysplasia	Grow-rate ≥ 5 mm/year
Solid mass	Increased levels of CA19-9 (≥37U/ml)
Jaundice (tumor related)	MPD dilatation 5-9.9 mm
Enhancing mural nodule(s) (≥ 5mm)	Cyst diameter ≥ 40 mm
MPD dilatation ≥ 10mm	New onset diabetes mellitus
	Acute pancreatitis (caused by IPMN)
	Enhancing mural nodule (< 5mm)

CA19-9, cancer antigen 19-9; MPD, main pancreatic duct

2.2.2.3 Chronic pancreatitis

Pancreatic resection or another type of surgery involving the pancreas might also be needed in chronic pancreatitis (CP). The excruciating abdominal pain that it may cause is the main reason for any intervention in CP (Bouwense et al., 2019). Around 80-90% of patients with CP experience chronic abdominal pain and almost half of them use pain medication on a daily basis (Gardner et al., 2010; Mullady et al., 2011). Traditionally surgery has been the last resort for refractory pain in CP even though observational series suggest better long-term outcomes for pain relief with surgery at an earlier stage (Yang et al., 2014; Ke et al., 2018). Fairly recently, a randomised controlled trial (RCT) addressing the timing of surgery in CP shed more light on this subject. In this ESCAPE trial, the authors found that the pain reduction rate was significantly higher in the group that underwent earlier surgery. During the follow-up at 18 months, the Izbicki pain score, which consists of four areas 1) pain severity, 2) pain frequency, 3) needed pain medication and 4) disease-related inability to work (Bloechle et al., 1995), was significantly lower in the earlier-surgery group compared to the patients who first underwent endoscopic treatments (37 vs. 49, -12 points difference [95% CI, -22 to -2]; p=0.02). Also, the complete or partial pain relief was lower at 18 months in patients who had undergone earlier surgery, but this difference did not reach statistical significance (58% vs. 39%, p=0.10) (Issa et al., 2020). Further benefits of the earlier surgery were shown in a cost-effectiveness analysis of the ESCAPE trial. The authors stated that, in 75% of the patients with a painful CP, earlier surgery would be cost-effective compared to the endoscopy-first strategy (Kempeneers et al., 2023). Due to these findings "International consensus guidelines for surgery and the timing of intervention in CP" recommends surgery at an earlier stage of CP (Kempeneers et al., 2020).

2.2.3 TYPES OF PANCREATIC SURGERY

2.2.3.1 Pancreatoduodenectomy

PD is the gold standard of surgery involving the head of the pancreas and is traditionally called Whipple's or less commonly the Kausch-Whipple operation based on the names of the surgeons who were the earliest to describe the operation in detail (Kausch, 1912; Whipple et al., 1935). Modern PD includes en-bloc resection of the head of the pancreas, distal stomach, duodenum, proximal jejunum, common bile duct and gallbladder with the respective reconstructions (Figure 2). In a modification of pylorus preserving PD (PPPD), the proximal line of GI tract division is done approximately 2 cm past the pylorus (Figure 3). Sometimes in order to achieve radical operation, additional resection of adjacent structures such as portal/superior mesenteric veins might be included (Bachellier et al., 2001; Warshaw & Thayer, 2004). Also, even more extensive surgery with synchronous resection of liver metastasis has produced conflicting results, and the current literature does not provide a clear conclusion on whether it improves survival rates compared to palliative surgery and oncological treatment alone (Gleisner et al., 2007; Yamada et al., 2009; Hackert et al., 2017; Shao et al., 2021).

Figure 2. Standard pancreatoduodenectomy. Illustration by Heidi Naumanen.

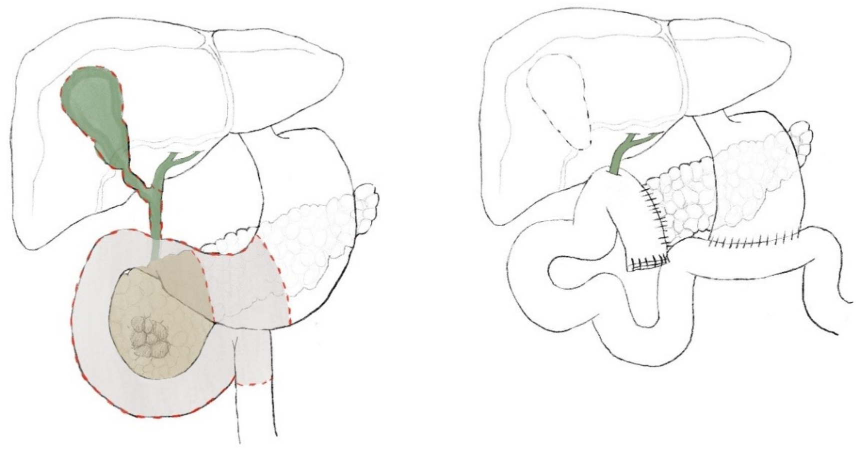
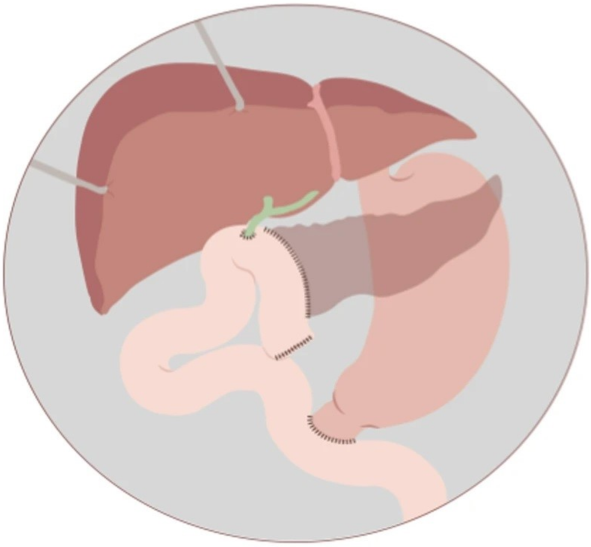


Figure 3. Pylorus preserving pancreatoduodenectomy.



Modified figure from Florentin et al. original article, which is licensed under a Creative Commons Attribution 4.0 International License allowing reuse in theses http://creativecommons.org/licenses/by/4.0/ (Florentin et al., 2022)

After resection, the continuity of the GI-, biliary and pancreatic tracts need to be restored. The GI-tract is reconstructed anastomosing the jejunum to the stomach, and the biliary tract is commonly reconstructed with an end-to-side hepaticojejunostomy. The most important part of the reconstruction is the pancreaticoenteric anastomosis, which has been widely studied and numerous of different techniques have been described. The most commonly used reconstructive methods are PJ and pancreaticogastrostomy (PG) (Barreto & Shukla, 2017) and no significant differences in outcomes have been shown between different types of pancreatic anastomoses (Shrikhande et al., 2017). Pancreatic anastomosis may be performed in a duct-to-mucosa fashion, or by invaginating the pancreatic remnant inside the GI-tract (Kennedy & Yeo, 2011). Studies do not show significant differences in the major outcomes such as POPF between the duct-to-mucosa and invagination techniques (Hai et al., 2022).

2.2.3.2 Distal pancreatectomy

DP is the resection of the body and/or tail of the pancreas for left-sided pancreatic lesions, which can be performed either with or without en-bloc resection of the spleen, depending on the indication for the surgery. The spleen can be preserved in benign lesions or in lesions with a low malignant potential but should be resected if dealing with a cancer (Butturini et al., 2012; Moekotte et al., 2020). The splenic vessels run transversely in the posterocranial aspect of the pancreas and, traditionally when performing the spleen preserving DP, the surgeon would dissect the splenic vessels apart from the pancreatic parenchyma in order to be able to transect the pancreas. However, in the Warshaw technique, the surgeon resects the splenic vessels alongside the pancreatic body after which the blood supply for the spleen is dependent on the short gastric vessels. This technique is reported to be associated with less blood loss and shorter operating time, but will result in perigastric varices formation due to the increased blood flow in the short gastric vessels after the operation (Rodríguez et al., 2007; Ferrone et al., 2011; Maehira et al., 2024).

More extensive resection might be needed if a left-sided PDAC infiltrates adjacent structures. If the cancer is posteriorly in contact with the renal fascia or perirenal fat, a radical antegrade modular pancreatosplenectomy (RAMPS) might be needed in order to achieve radicality by removing the anterior renal fascia, perirenal fat en-bloc with the spleen and the body/tail of the pancreas (Strasberg et al., 2003; Abe et al., 2016). In posterior RAMPS, the resection is extended to include the left adrenal gland, while in the anterior RAMPS it is preserved. If there is no infiltration to periadrenal space, the anterior RAMPS has equal outcomes to posterior RAMPS (Kwon et al., 2021).

Modified Appelby operation is another more extensive version of DP, which may be performed if PDAC infiltrates arteries rising from the celiac axis (Nakamura et al., 2016). In this operation, the celiac axis is resected en-bloc with the body and tail of the pancreas and the common hepatic artery is divided. After this resection, the arterial blood supply of the liver is dependent on the collaterals running from the superior mesenteric artery (Cannella et al., 2019).

2.2.3.3 Other pancreatic resections

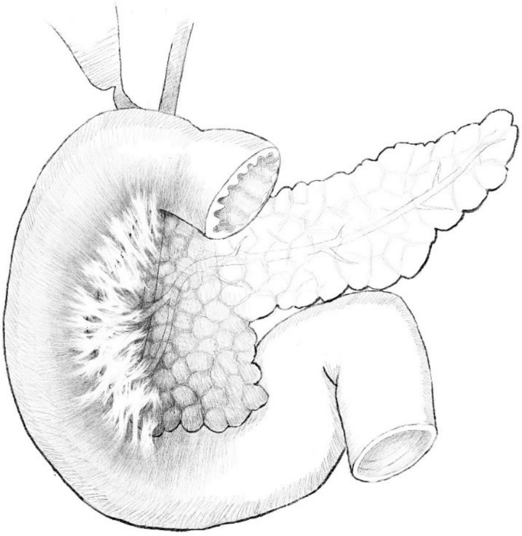
Total pancreatectomy (TP) is an extended version of PD in which the body and tail of pancreas are also removed with or without the spleen. The reconstruction of the GI and biliary tracts follows the same principles as in PD, but there is no pancreaticoenteric anastomosis since there is no pancreas preserved. TP may be needed when treating multifocal or widely throughout the pancreatic parenchyma-spread cancers, refractory pain due to chronic pancreatitis or if the risk and consequences of POPF are considered to be too high (Garcea et al., 2009; Marchegiani et al., 2021). After TP, patients will inevitably exhibit severe insulin-dependent diabetes and exocrine insufficiency needing pancreatic enzyme supplementation, which heavily affects the patients quality of life (Marchegiani et al., 2021).

Median pancreatectomy and enucleation are less frequently used parenchyma-preserving resections. These are mostly used in small benign or pre-malignant lesions where the lymphadenectomy is not needed and there is a desire to reduce the volume of pancreatic parenchyma as little as possible to avoid endo- and exocrine insufficiency (Marchese et al., 2021). In median pancreatectomy, by definition the surgeon removes the middle part of pancreas, leaving the head and tail in place. Due to the nature of this resection, one does not need to do biliary anastomosis, but the main pancreatic duct in the tail of the pancreas needs to be anastomosed to the GI-tract with a PJ or PG. The rate for POPF is relatively high after median pancreatectomy, possibly since there are two possible sites for leakage, which are the transection line left of the head of the pancreas and the PJ or PG in its tail (Marchese et al., 2021). In enucleation, only the pancreatic lesion is removed along the borders of this lesion, sparing as much parenchyma as possible. The risk of POPF is also significantly elevated after enucleation, but the incidence of other major complications is low, favouring enucleation in selected situations (Strobel et al., 2015).

2.3 GROOVE PANCREATITIS

GP is a rare form of CP affecting the groove area between the head of the pancreas, C-loop of the duodenum and the common bile duct (Figure 4) (Stolte et al., 1982; Becker & Mischke, 1991). GP is divided into two forms, which have distinguished radiological and histological features. These are the pure and the segmental form, the latter of which extends inside the head of the pancreas and can radiologically mimic a pancreatic neoplasm (Tezuka et al., 2010; Mittal et al., 2017; Addeo et al., 2019). The inflammation process in the groove area can lead to the obstruction of the duodenum, common bile duct or main pancreatic duct, which all may need an intervention (Arvanitakis et al., 2014; Ukegjini et al., 2023). The close radiological resemblance to a malignant lesion and the possible obstructive nature of the inflammation can create a challenge for physicians since it may be difficult to preoperatively differentiate a GP from a pancreatic cancer. Due to these features, sometimes these patients are treated as if they had a cancer, and the final GP diagnosis is revealed only after the histopathological report of the surgical specimen (Oza et al., 2015).

Figure 4. Illustration of the groove area. Illustration by Heidi Naumanen.



2.3.1 ETIOLOGY, INCIDENCE AND SYMPTOMS

GP as any other type of CP mostly affects middle-aged men with a history of alcohol consumption and smoking (Rebours et al., 2007; Casetti et al., 2009; Ukegjini et al., 2023). Conversely, other common causes for pancreatitis such as gall stones or certain medications are not shown to be risk factors for GP (Becker & Mischke, 1991; Adsay & Zamboni, 2004). There are no estimates of the incidence or prevalence of GP in the general population due to its rarity, lack of epidemiological data and possible under-recognition of the disease (DeSouza & Nodit, 2015). In a selected patient cohort of 893 patients with a CP from Italy, the prevalence of GP was 6% (55 out of 893) (Frulloni et al., 2009). In comparison, the incidence of CP in Finland is 100-130/1,000,000 per year (Jaakkola & Nordback, 1993) and, by extrapolating these numbers, the incidence of GP would be roughly 6-8/1, 000,000 per year.

The scale of symptoms in GP is related to other forms of CP ranging from mild abdominal pains to chronic crippling disease with a need for repeated interventions (Arvanitakis et al., 2014; Ukegjini et al., 2023). The only somewhat congruent symptom with GP patients is abdominal pain, and the other symptoms are more or less dispersed. If the inflammation process in GP causes obstruction of the duodenum, common bile duct or main pancreatic duct, the patients might develop obstructive symptoms such as vomiting, weight loss, jaundice or the onset of acute pancreatitis (Rebours et al., 2007).

2.3.2 DIAGNOSTICS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of GP is based on the clinical status and radiological imaging with some help from laboratory tests. There are no distinctive laboratory parameters that lead to a diagnosis to GP. Consistently, only an elevation in carbohydrate antigen 19-9 (CA19-9) has been shown to help at the differential diagnosis of GP and pancreatic and peripancreatic cancer, but other than that the value of laboratory parameters in the diagnostics of GP is close to zero (Tezuka et al., 2010; Lekkerkerker et al., 2016; Jun et al., 2018). A computed tomography (CT) scan or a magnetic resonance imaging (MRI) is essential in confirming the suspicion of GP (Addeo et al., 2019). In recent years, the role of endoscopic ultrasound (EUS) has grown markedly in the diagnostics of GP. Compared to CT, it has been suggested that the EUS detects more accurately the changes in the duodenal wall and also allows obtaining histological samples (She & Ge, 2023). However, even after radiological imaging studies, there is still a risk of misdiagnosis of GP as a neoplastic lesion and vice versa (Mittal et al., 2017). The diagnosis of GP is fully certain only from the histopathological report of a pancreatic specimen. Pancreatic head resection, however, is not needed in every GP patient, so in some cases there is some uncertainty with the GP diagnosis (Egorov et al., 2014; Lekkerkerker et al., 2016; Mittal et al., 2017).

The radiological criteria for GP are well established. There are two forms of GP: the pure and the segmental form, both of which can be either cystic or non-cystic. In the pure form of GP, the inflammation process is limited to the groove area, while in the segmental form the inflammation continues to the pancreatic head (Mittal et al., 2017). Due to its solid and invasive appearance, the non-cystic segmental form is especially difficult for radiologists to differentiate from pancreatic or peripancreatic neoplasms. It might be impossible even for experienced radiologists to differentiate this type of GP from a pancreatic cancer and vice versa (Lekkerkerker et al., 2016).

2.3.3 TREATMENT OPTIONS AND OUTCOMES

Due to the rarity of GP, there are no guidelines on how to treat this disease. The published data consists mostly of case studies and small retrospective series of five to 120 patients (Ukegjini et al., 2023). Cohort studies reporting different treatment strategies are summarised in the Table 2. By consulting the literature, it seems that, in the past, the gold standard for treatment of GP has been pancreatic head resection, most commonly a PD. Some series even report as high as 60-100% resection rates for GP (Table 2). However, in the past few years there has been a paradigm shift towards more conservative treatment of GP favouring invasive interventions only if there are obstructive symptoms or conservative treatment has failed. Even though there is growing evidence of a more conservative approach, there are still some authors favouring major invasive surgery as the first-line treatment for GP (Lekkerkerker et al., 2016; Balduzzi et al., 2020; Egorov et al., 2021).

In a retrospective study of 28 GP patients, 14 were treated conservatively, seven underwent a PD, one a hepaticojejunostomy and the rest had an ERCP due the obstructive symptoms. While seven of the 28 GP patients underwent PD, only 2 of these surgeries were performed specifically for a symptomatic GP and the rest were due to a suspicion of PDAC. Despite the limited number of patients requiring PD for GP, the overall treatment success was high, with 26 of 28 patients reporting symptom relief (Lekkerkerker et al., 2016). Also, another retrospective study reports rather low numbers of PD for GP. In this study of 51 GP patients by Arvanitakis et al., most of the patients were treated with ERCP, six patients of 51 underwent a PD, and the PD was an initial treatment only for two patients. In addition, six patients underwent a surgical bypass of either the duodenum or biliary tract due to the failed treatment of this obstruction with ERCP. The complete resolution of symptoms after ERCP was over 70% and the role of PD in the treatment algorithm of GP was rather minimal (Arvanitakis et al., 2014). In long term, PD has also been associated with a higher incidence of diabetes than conservative treatment for GP so, even if the short-term complications were bearable, there can be significant adverse long-term consequences (Balduzzi et al., 2020).

Based on the current literature, it seems that PD should not be a first-line option for treatment of GP. Even though the risk profile for postoperative complications after pancreatic head resection is lower if the patient has CP, PD always carries a high risk of adverse events and even mortality (Mungroop et al., 2021). The treatment algorithm for GP should be based on the symptoms and not the diagnosis itself and only a fraction of GP patients' need a PD. Most of the patients' symptoms are resolved without a high-risk surgery such as pancreatic resection, and obstructive symptoms can be relieved endoscopically or with surgical bypasses in most cases (Arvanitakis et al., 2014; Lekkerkerker et al., 2016).

Table 2. The proportions of patients with conservative versus invasive treatment for groove pancreatitis in different cohort studies.

Author	Country	No. of GP patients	Conservative treatment, n (%)[a]	Endoscopic treatment, n (%)[a]	Surgery,n (%) [a]
Jouannaud *et al.* *(Jouannaud et al., 2006)*	France	23	9 (39)	0	14 (61)
Rebours *et al.* *(Rebours et al., 2007)*	France	105	70 (67)	6 (6)	29 (28)
Rahman *et al.* *(Rahman et al., 2007)*	UK	11	0	0	11 (100)
Casetti *et al.* (Casetti et al., 2009)	Italy	58	0	0	58 (100)
Arvanitakis *et al.* *(Arvanitakis et al., 2014)*	Belgium	51	na[b]	30 (52)	12 (21)
Egorov *et al.* *(Egorov et al., 2014)*	Russia	62	10 (16)	0	52 (84)
Oza *et al.* *(Oza et al., 2015)*	USA	13	4 (31)	0	9 (69)
Lekkerkerker *et al.* *(Lekkerkerker et al., 2016)*	Netherlands	28	14 (50)	6 (21)	8 (29)
de Pretis *et al.* *(de Pretis et al., 2017)*	Italy	120	39 (33)	0	81 (67)
Balduzzi *et al.* *(Balduzzi et al., 2020)*	Italy	75	28 (38)	0	47 (62)
Egorov *et al.* *(Egorov et al., 2021)*	Russia	84	12 (14)	0	72 (86)
Vujasinovic *et al.* *(Vujasinovic et al., 2022)*	Sweden	35	19 (54)	9 (26)	7 (20)
Okasha *et al.* *(Okasha et al., 2023)*	Egypt, Saudi Arabia, Marocco	21	14 (67)	5 (24)	2 (10)

GP, groove pancreatitis

[a]The patients were categorised by the most invasive treatment they received i.e. a patient who had undergone both endoscopic intervention and surgery was categorised in “Surgery”.

[b]The number of patients treated without endoscopic or surgical intervention is not clearly stated in the study.

2.4 POSTOPERATIVE COMPLICATIONS IN PANCREATIC SURGERY

Pancreatic surgery is notorious for its high rates of postoperative complications. It has all the typical risks of any major abdominal operation and a set of unique pancreatic resection-associated complications such as POPF, post-pancreatectomy haemorrhage (PPH) and delayed gastric emptying (DGE) (Karim et al., 2018; Bonsdorff et al., 2022).

2.4.1 GRADING OF THE COMPLICATIONS

Reporting complications is an important aspect of surgical literature. In the short term, the postoperative complications are the most descriptive way to assess the safety and efficacy of an operation. In order to compare studies conducted by different institutions, the reporting and grading of complications should be somewhat comparable. A grading system of Clavien-Dindo (CD) classification was introduced 20 years ago to help the comparison, and since then it has become a fixture of surgical literature (Table 3) (Dindo et al., 2004).

In CD classification the complications are graded by the therapy needed to treat the complication. The classification consists of five grades where grade I does not greatly affect the patient's postoperative course and grade V leads to the death of the patient (Dindo et al., 2004). Typically, in literature CD grades I and II are stated as minor and III to V as major complications, since grade III is a cut-off line for the need of invasive interventions (Clavien et al., 2009).

Table 3. Clavien-Dindo classification of different complications (Dindo et al., 2004).

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

The problem with CD classification is that it only grades the individual complications but does not estimate the total burden of these complications on a patient. For this assessment a comprehensive complication index (CCI) was introduced ten years ago (Table 4). In CCI, every grade of CD has its own value, and the total burden is calculated with a specific formula where the effect of a single complication becomes smaller if the patient has multiple complications (Figure 5). The patient's overall complication burden gets a number between zero and 100, where zero means an uneventful postoperative course and 100 a postoperative mortality (Slankamenac et al., 2014). CCI has been widely validated and used throughout the surgical field. It has proved to be a reproducible and illustrative way of assessing and also predicting the patient's postoperative course, and should be used in modern literature (Kowalewski et al., 2021; Lai et al., 2021; Tamini et al., 2021). Another benefit of CCI is that, by using it as the primary outcome when planning a clinical trial, the needed sample sizes are reduced drastically. This makes conducting trials more feasible and also decreases the risk of type II errors. In a hallmark study by Slankamenac et al., the authors found that, by using CCI as the primary outcome, the needed sample sizes were up to nine times lower than if a categorical outcome such as incidence of POPF was used (Slankamenac et al., 2014).

Table 4. Comprehensive Complication Index (Slankamenac et al., 2014).

CD grade	wC	CCI Single Value
Grade I	300	8.7
Grade II	1750	20.9
Grade IIIa	2750	26.2
Grade IIIb	4550	33.7
Grade IVa	7200	42.4
Grade IVb	8550	46.2
Grade V	*	100

wC, weight of Complication; CCI, Comprehensive Complication Index
*Grade V is the death of a patient leading to a CCI value of 100.

Figure 5. Mathematical formula of CCI (Slankamenac et al., 2014).

$$CCI = \frac{\sqrt{wC_1 + wC_2 + \cdots wC_x}}{2}$$

2.4.2 PANCREATIC RESECTION-ASSOCIATED COMPLICATIONS

As CD grading and CCI have unified the reporting and analysing of complications in surgical literature, the definitions and grading of pancreatic resection-associated complications by the International Study Group on Pancreatic Surgery (ISGPS) have established an important role in the literature concerning pancreatic surgery (Wente et al., 2007; Wente et al., 2007; Bassi et al., 2017; Besselink et al., 2017; Marchegiani et al., 2022). These definitions have unified the reporting of these complications, most importantly POPF, DGE and PPH, which cause most of the morbidity after a pancreatectomy. By having unified definitions and gradings, it is possible to compare the outcomes of different studies conducted at different institutions (Dusch et al., 2017).

2.4.2.1 Postoperative pancreatic fistula

POPF is the single most important complication after a pancreatic resection and many of the other pancreatic resection-associated complications are due to underlying POPF (Schoellhammer et al., 2014). In a POPF, the pancreatic juices leak outside the pancreatic ductal system via abnormal connection into the peripancreatic space or abdominal cavity. The pancreatic exocrine enzymes are strongly proteolytic digestive enzymes and, when leaking outside the pancreatic ducts either from the leaking pancreaticoenteric anastomosis or the pancreatic resection line, they start to dissolve the normal tissues, which can lead to a cascade of complications such as abscesses, sepsis, pseudoaneurysms or even a fatal haemorrhage (Schoellhammer et al., 2014; Bassi et al., 2017; Pedrazzoli, 2017).

The most widely used definition of POPF is outlined in the updated version of ISGPS's consensus statement and is presented in Table 5 (Bassi et al., 2017). POPF is graded either as a non-relevant fistula called a biochemical leak, or as clinically relevant POPF, which is divided into two grades (grades B and C) based on the needed therapy to treat the patient with a POPF (Table 5). In a biochemical leak, the POPF does not affect the patient's postoperative course in any way. In a grade B fistula, there is either a prolonged output of amylase-rich fluid from the drains for over three weeks, the treatment of fistula needs an intervention such as CT or EUS guided drainage but not reoperation, or there are signs of infection without organ failure. In the most severe POPF, grade C, there is either fistula-related infection with organ failure, the patient needs a reoperation due to the fistula, or the complication cascade origin from the fistula leads to the death of the patient (Bassi et al., 2017).

Table 5. POPF grades based on ISGPS definition (Bassi et al., 2017).

Biochemical leak	Grade B POPF	Grade C POPF
Amylase > 3 times upper limit of normal serum amylase OR Persistent drainage > 3 weeks without additional percutaneous drainage	Amylase > 3 times upper limit of normal serum amylase AND Percutaneous drainage or angiographic procedure	Amylase > 3 times upper limit of normal serum amylase AND Reoperation Organ failure Death

POPF, postoperative pancreatic fistula; ISGPS, International Study Group on Pancreatic Surgery

The incidence of a clinically relevant POPF is reported to be 10-15% after a PD and little bit higher after DP at approximately 20% (Goh et al., 2008;

McMillan et al., 2016; Ecker et al., 2019; Luu et al., 2020; Williamsson et al., 2020).

2.4.2.2 Delayed gastric emptying

The most frequent pancreatic resection-associated complication is DGE, which can occur in up to half of patients after PD (Wente et al., 2007) and also in 10% after DP (Degisors et al., 2022). The lower incidence after DP is mostly due to the fact that there are no gastric or bowel resections and subsequent GI-tract reconstructions (Varghese et al., 2021; Degisors et al., 2022). Although the incidence of DGE is high, the overall complication burden after it is rather low and DGE can be secondary to another complication such as POPF (Marchegiani et al., 2023).

As for POPF, the ISGPS also published a consensus statement of the definition and grading of DGE, and it is widely used in surgical literature (Table 6) (Wente et al., 2007). The symptoms of DGE are nausea, gastric fullness, early satiety, epigastric pain and vomiting (Degisors et al., 2022). Sometimes these symptoms can be caused by a mechanical obstruction, so the patency of gastroenteric and enteroenteric anastomoses need to be verified before a diagnosis of DGE can be made. DGE is graded in three grades, A, B and C, of which A is the mildest. The grading of DGE is based on the need for a nasogastric tube, the number of days it took for the patient to tolerate oral intake, vomiting status and possible need for prokinetics. Grade A DGE does not greatly affect the postoperative course but, as in POPF, grades B and C markedly lengthen the stay and lead to a need for nutritional support and possibly also to invasive interventions. If a reoperation is needed due to DGE, the grade is C despite the other criteria (Wente et al., 2007). As in POPF, it has been recently suggested that DGE grades B and C be called clinically relevant DGE (Marchegiani et al., 2023).

Table 6. Grading of DGE based on ISGPS definition (Wente et al., 2007).

Grade	Nasogastric tube needed	Unable to tolerate solid diet by postoperative day	Treatment or intervention
A	4-7 days or reinsertion after postoperative day 3	7	Possibly prokinetics
B	8-14 days or reinsertion after postoperative day 7	14	·Prokinetics ·Parenteral nutrition < 3 weeks ·No need for invasive interventions
C	> 14 days or reinsertion after postoperative day 14	21	·Prokinetics ·Parenteral nutrition ≥ 3 weeks ·Possibly a radiological/surgical intervention

DGE, delayed gastric emptying; ISGPS, International Study Group on Pancreatic Surgery

2.4.2.3 Postpancreatectomy haemorrhage

One of the most severe and dreaded complications after pancreatic resection is PPH, which may lead to a rapid deterioration and need for an emergency intervention to save the patient (Wente et al., 2007; Wellner et al., 2014). Luckily, the incidence of severe PPH is rather low at less than 3% after a pancreatic resection (Wellner et al., 2014). A diagnosis of PPH is made when there is blood loss through the drains or nasogastric tube, the patient has melena or hematemesis, or there are signs of bleeding in laboratory tests or in radiological imaging. The symptoms depend on the severity of PPH. In mild PPH, the patient's clinical condition is often good but, in severe PPH, the patient has symptoms of hypovolemia such as hypotension, tachycardia or even organ failure (Wente et al., 2007). Up to 12 hours before a massive haemorrhage, there might be a smaller visible amount of blood coming through drains or nasogastric tube, called sentinel bleeding, and the recognition of this is crucial to prevent fatal outcomes (Wente et al., 2007; Ansari et al., 2017).

The ISGPS consensus statement defines PPH by onset, location and severity of bleeding (Table 7) (Wente et al., 2007). PPH is either early or late where the cut-off is the first 24 hours after the operation. Early PPH is most often due to a technical error and late is erosion bleeding after a concomitant POPF (Wellner et al., 2014). PPH can be either intra- or extraluminal and the site for the bleeding can be practically anywhere where the surgery has extended to. PPH is considered mild if there is no need for invasive interventions and the impairment is corrected successfully with a maximum transfusion of three units of packed red blood cells. The PPH is considered severe if there is a larger blood volume loss and the needed transfusion is more than three units of packed red blood cells or there is a need of invasive intervention to stop the bleeding (Wente et al., 2007).

Table 7. Grading of PPH based on ISGPS definition (Wente et al., 2007).

Grade	Time of onset, location, clinical impact of bleeding	Clinical condition	Diagnostic consequence	Therapeutic consequence
A	·Early ·Intra- or -extraluminal ·Mild	Good	Observation, blood count, ultrasound, and CT if necessary	No
B	·Early ·Intra- or extraluminal ·Severe or ·Late ·Intra- or extraluminal ·Mild	Often good/ intermediate, very rarely life-threatening	Observation, blood count, ultrasound, CT, angiography, endoscopy	Transfusion of fluid/blood, ICU, therapeutic endoscopy, embolisation relaparotomy for early PPH
C	·Late ·Intra- or extraluminal ·Severe	Severely impaired, life-threatening	CT, angiography, endoscopy	Localisation of bleeding, angiography and embolisation, relaparotomy, ICU

PPH, postpancreatectomy haemorrhage; ISGPS, International Study Group on Pancreatic Surgery; CT, computed tomography; ICU, intense care unit

2.4.2.4 Postpancreatecomy acute pancreatitis

PPAP is a complication that was defined by the ISGPS fairly recently in 2022. The definition of PPAP is an acute inflammation process of the remnant pancreas after a partial pancreatectomy. The onset of the inflammation should be in the first three postoperative days, otherwise it is not regarded as PPAP (Marchegiani et al., 2022).

The diagnosis of PPAP is based on elevated serum amylase levels and the signs of pancreatitis in radiological imaging studies. The severity of PPAP is graded by the clinical impact of the inflammation to non-relevant PPAP called postoperative hyperamylasaemia and to clinically relevant PPAP, which means that there is a need for an alteration in the patient's postoperative management due to PPAP. Clinically relevant PPAP is divided into two grades, B and C. PPAP grade C is means that the patient has persistent organ failure lasting at least 48 hours, or there is a need for a reoperation, or the PPAP leads to death of the patient (Marchegiani et al., 2022).

There is a correlation between clinically relevant PPAP and overall postoperative complication burden (Bannone et al., 2021; Bonsdorff et al., 2022). It has been speculated that PPAP might be an underlying reason for many of the pancreatic resection-associated complications, and the association between PPAP and POPF in particular has been shown to be significant (Connor, 2016; Nahm et al., 2018; Bannone et al., 2021; Bonsdorff et al., 2022). Just recently, postoperative hyperamylasaemia – persistent elevation in serum amylase during the first two postoperative days – was also reported to be noted significantly more often in patients who eventually developed clinically relevant POPF, and it may be used as a predictor (Perri et al., 2024).

2.4.2.5 Bile leakage

Bile leakage is a possible complication after PD, and is associated with increased pancreatic resection-associated complications (Perri et al., 2022). The site for the leakage can be from hepatico/choledochojejunostomy, PJ or both (Andrianello et al., 2017; Henry et al., 2022). Postoperative bile leakage is defined in the International Study Group of Liver Surgery's consensus statement as three or more times higher bilirubin levels in the drain fluid than in the patient's serum on the third postoperative day or later, or there is a need for an intervention due to biliary collection or bile peritonitis. The severity of bile leakage is graded by the needed treatment in grades A, B and C. As in pancreatic resection-associated complications, a grade A bile leak does not affect to the postoperative course, but grades B and C cause a change in the patient's postoperative management. If a reoperation is needed, the bile leakage is graded C (Koch et al., 2011).

The most important risk factor for bile leakage is the small diameter of the common bile duct at the site of resection, which makes the suturing of the anastomosis more difficult (Andrianello et al., 2017). The incidence of bile leakage after PD varies between 3 and 8%, but the bile leakage is often accompanied with other complications (Duconseil et al., 2014; Andrianello et al., 2017; Henry et al., 2022; Perri et al., 2022).

Recently it has been described that 70 to 94% of the bile leakages could be treated with percutaneous transhepatic biliary drainage (PTBD) and reoperation is mostly needed only in early leakages referring to a technical problems in hepatico/choledochojejunostomy or if there is a concomitant persistent grade C POPF (Henry et al., 2022; Perri et al., 2022). However, patients with concomitant bile leakage and POPF are at greater risk of treatment failure and even mortality (Andrianello et al., 2017; Henry et al., 2022; Perri et al., 2022). In PTBD a biliary stent is introduced to the intrahepatic biliary tract percutaneously through the liver parenchyma and reaching over to jejunum covering the leak site in hepatico/ choledochojejunostomy also allowing external drainage. It has been described as also working if the bile leakage arises from the PJ by diverting the bile away from the leaking anastomosis and the PJ has better chances to heal (Henry et al., 2022).

2.4.2.6 Chyle leakage

Chyle is lymphatic fluid transporting the ingested fats from the intestine to the bloodstream. Lymphatic ducts are prominent in the retroperitoneal region and any surgery extending to this area can be complicated by a chyle leakage (Besselink et al., 2017; Rose et al., 2022). At the level of pancreatic head and anterior to the first lumbar vertebrae lies the cisterna chyli and its major branches, which are important parts of lymphatic system. These structures may be damaged during a pancreatic resection, which then leads to a chyle leakage (Besselink et al., 2017).

By the ISGPS consensus statement, the chyle leak is diagnosed if there is visible milky output from drains or the wound after the third postoperative day and the measured triglyceride levels from this fluid is 1.2 mmol/l or more. As with other pancreatic resection-associated complications defined by the ISGPS, chyle leakage is also graded A, B and C, of which grade A leakage does not greatly affect the postoperative course and is treated at most with a non-fatty diet combined with medium-chain triglycerides. If the patient needs nutritional support with total parenteral nutrition or other drugs, or an intervention other than reoperation to treat the chyle leakage, it is considered a grade B leakage. If there is a need for a reoperation, or signs of an organ failure leading to admission to intensive care unit or mortality, the chyle leakage is graded as C (Besselink et al., 2017).

Chyle leakage is rather common, and the incidence of any grade has been reported to be 5-10% after a pancreatic resection (Strobel et al., 2016; Varghese et al., 2022; Augustinus et al., 2023). However, it has far less clinical impact than other pancreatic resection-associated complications and, in the vast majority of the cases, it responds well to conservative treatment (Besselink et al., 2017). Grade C chyle leakages are extremely rare and the rate of grade C chyle leak is only a few parts per thousand or less (Paiella et al., 2018; Varghese et al., 2022; Augustinus et al., 2023).

2.4.2.7 Endocrine and exocrine insufficiency

After TP, endo- and exocrine insufficiency is naturally inevitable (Marchegiani et al., 2021), but pancreatic insufficiency is rather common also after partial pancreatectomy (Thomas et al., 2022). Endocrine insufficiency appears as a newly onset diabetes needing medication (Thomas et al., 2022) and exocrine insufficiency as fatty diarrhoea leading to malnutrition and weight loss, which can be treated with per oral enzyme supplements (Moore et al., 2021). In a large medical register-based study from the United States of almost 5,000 patients who had undergone either PD or DP, the newly onset endocrine insufficiency was 14% after PD and 25% after DP (Thomas et al., 2022). The respective prevalence of exocrine insufficiency is reported to be 33% and 12% (Moore et al., 2021). In the long term, pancreatic insufficiency markedly lowers quality of life. Even when comparing patients who have undergone a TP to patients at high risk of PJ-related complications after PD, most importantly POPF, quality of life was significantly lower for the patients who had undergone a TP, most notably due to diabetes-related medical and psychosocial issues (Marchegiani et al., 2021).

2.4.3 SURGICAL SITE INFECTIONS

SSI is defined as a bacterial infection of the operation field occurring during the postoperative course (CDC, 2021). SSIs are the most common complications after any surgery and the risk of a SSI increases if the operation field gets contaminated during surgery (Sugiura et al., 2015). SSIs are categorised by the Centres for Disease and Control and Prevention criteria as superficial incisional, deep incisional and organ/space depending on the affected site. In superficial incisional SSI, the infection extends only to the skin and the subcutaneous tissue, in deep incisional SSI it extends to the fascial and muscle layers of the incision, and in organ/space SSI to any deeper part of the body that was in the operation field (CDC, 2021).

There are patient- and operation-related factors, which increase the risk of SSIs. Obesity, poorly treated diabetes, malnutrition, immunosuppression, smoking, the duration of the operation and bacterial contamination during the operation all increase the risk of SSIs (Owens & Stoessel, 2008). Some of these cannot be altered before the operation. However, there are also many easy ways to reduce SSIs. Taking care of aseptic routines (Berríos-Torres et al., 2017), giving a correctly timed preoperative prophylactic dose of antibiotics (De Jonge et al., 2017), using wound protectors (Edwards et al., 2012) and changing instruments and gloves before closing the wound (Ademuyiwa et al., 2022) have all been documented to reduce the rate of SSIs significantly. Also, more innovative techniques have been studied. For example, since organ-space SSIs are relatively common after PD - mostly due to the POPF - an active irrigation-suction method via the intra-abdominal drains placed during PD has been studied in a recent randomised trial. The authors of this study reported a decrease in intra-abdominal infections without a change in the rate of POPF (Lin et al., 2023).

2.4.4 VENOUS THROMBOEMBOLIC COMPLICATIONS

Surgery increases the risk of venous thromboembolic events and the risk is two to three times higher after surgery if the patient is undergoing an operation for cancer compared to other indications (Agnelli et al., 2006). If the cancer stems from the pancreas, the risk is even higher: fourfold after surgery compared to other cancer operations (Horsted et al., 2012). The overall risk of venous thromboembolic events after pancreatic surgery is 3% even with adequate prophylaxis (Tzeng et al., 2014).

Postoperative venous thromboembolic complications range from an asymptomatic deep venous thrombosis to fatal pulmonary embolism. These two represent two ends of the same venous thromboembolic event. Often a pulmonary embolism is the first manifestation and the preceding deep venous thrombosis of an extremity may be priorly unnoticed (Aziz et al., 2015).

Guidelines suggest using low molecular weight heparins in the prevention of venous thromboembolic complications after major abdominal surgery such as pancreatic surgery (Farge et al., 2016; Clancy et al., 2022). The routine protocol is a single dose of low molecular-weight heparin once per day starting pre- or postoperatively and continuing until discharge or up to four weeks in case of a cancer (Farge et al., 2016; Hanna-Sawires et al., 2019; Melloul et al., 2020). The use of direct oral anticoagulants in postoperative prophylaxis after pancreatic surgery has been studied only in a small cohort of studies, and one cannot draw any conclusions as to whether or not these could be safely used in this setting (Rashid et al., 2019).

Even though enhanced recovery after surgery (ERAS) guidelines recommend already starting low molecular-weight heparin (LMWH) 2-12 hours before the operation (Melloul et al., 2020), there are only some retrospective studies in the field of HPB surgery addressing this issue, but no randomised trials. These retrospective studies have had mixed results. Some report a decrease in venous thromboembolic complications when using perioperative prophylaxis without a significant increase in bleeding (Reinke et al., 2012; Ainoa et al., 2021). However, the study of Ainoa et al. included only patients undergoing liver surgery while Reinke et al. focused on pancreatic surgery. Also, opposite findings have been reported. In a large retrospective study by Fong et al. of nearly 1,500 patients who had undergone pancreatic resection, in the group starting with LMWH already preoperatively, there were significantly more venous thromboembolic complications than in the postoperative prophylaxis group. However, in this study the reported results were found after adjusting the retrospective cohort by factors such as anaemia, diabetes and length of stay, but leaving out cancers, smoking or a previous history of venous thromboembolisms (Fong et al., 2020). This methodological decision by Fong et al. can be considered questionable and inevitably affects the interpretation of the results.

There are no published randomised trials addressing this issue in pancreatic surgery, but there are some randomised trials from the field of other abdominal surgeries. PERIOP-01 trial by Auer et al. randomised patients undergoing resection for local colorectal adenocarcinoma to receive either perioperative thromboembolism prophylaxis or postoperative prophylaxis with LMWH. Both groups had equal ratios of venous thromboembolisms (five out of 307 (2%) patients in perioperative and four of 307 (1%) patients in postoperative group, p=0.80) (Auer et al., 2022). In contrast, a large non-inferiority trial with 4,413 randomised patients comparing postoperative LMWH to perioperatively administered LMWH in patients undergoing major abdominal or pelvic surgery, did not demonstrate the non-inferiority of postoperative LMWH to perioperative LMWH. In this trial, approximately 80% of the patients in both groups were operated due to a cancer, but the exact operations were not stated. Also, the study design was changed from a superiority to non-inferiority setting after the sample size calculations, which may affect the interpretation of the results (Kakkar et al., 2014).

The studies show mixed results as to whether or not the perioperative prophylaxis would be better than the postoperative prophylaxis. There are still a couple of ongoing Nordic trials in the field of HPB surgery focusing on the perioperative prophylaxis, and hopefully these shed some more light on this subject (clinicaltrial.gov identifiers: NCT05245877 and NCT04731558).

2.4.5 MORTALITY AFTER PANCREATECTOMY

The mortality rate after pancreatic surgery has decreased drastically since the early days of pancreatic surgery. Prior to the 1940s, the mortality after a PD was as high as 30-40% (Schnelldorfer et al., 2008), but this has decreased to a level of 1-3% at high-volume centres in the modern era (Amini et al., 2015; Kokkinakis et al., 2022). Of all types of pancreatic resections, mortality is highest after a TP, which still has a relatively high rate of 6-8% (Suzuki et al., 2017).

The growing knowledge of pancreatic diseases, perioperative care of the patients, technical evolution and the centralisation of pancreatic surgery, to name but a few factors, have all played an important role in the decrease in mortality (Ho et al., 2005). Nowadays, probably the most notable decrease in mortality can be achieved with centralisation. At high-volume centres, not only the surgeons carry out enough repetitions to be able to perform the surgery safely, but also the early detection and active treatment of complications are better acknowledged, and the failure-to-rescue ratio is lower (Ahola et al., 2020).

2.4.6 EFFECTS OF COMPLICATIONS ON LONG-TERM SURVIVAL

If pancreatic resection is due to a cancer, possible complications may affect not only the immediate postoperative course, but also long-term survival (Kamphues et al., 2012). Adjuvant chemotherapy increases survival in resectable pancreatic cancer and severe complications may have a sufficiently adverse effect on the patient that the timeframe for starting adjuvant chemotherapy passes before the patient is recovered enough to be fit for the treatments (Merkow et al., 2014). However, it might be more than the delay or omission of adjuvant chemotherapy that lowers survival rates in patients with severe postoperative complications. Multiple studies have shown that postoperative complications also act as an independent risk factor for lower survival rates (Nathan et al., 2017; Watanabe et al., 2017; Sandini et al., 2019). The pathophysiology behind this correlation is not yet fully understood and has also been shown to occur after colorectal and liver cancer surgeries. It has been hypothesised that the prolonged inflammatory process resulting from the complications might lead to a state of immunosuppression, which favours the growth or metastasis of tumour cells (Mintziras et al., 2021).

2.5 RISK FACTORS FOR COMPLICATIONS AFTER PANCREATIC SURGERY

2.5.1 TEXTURE OF THE PANCREAS AND THE MAIN PANCREATIC DUCT

The most relevant complication after a pancreatectomy is POPF and the most important risk factors for POPF are the soft texture of the pancreas and the small diameter of the main pancreatic duct. Individually, both these factors have a strong correlation with POPF (Callery et al., 2013; Kantor et al., 2017; Mungroop et al., 2021). Of these two main features, the association with POPF is stronger in the soft texture of the pancreas than it is in the small duct size, but unfortunately these two features tend to coexist since they are both present in a non-atrophic normal pancreas (Sugimoto et al., 2017; Schuh et al., 2022).

A soft pancreas and a small pancreatic duct make it more technically demanding to suture a solid pancreaticoenteric anastomosis (Belyaev et al., 2013). However, there is also more to it than the technical side of things in the formation of POPF. A soft pancreas indicates that the pancreas is normal and has more exocrine activity than a firm pancreas, which in turn indicates atrophic parenchyma where acinar cells are replaced with connective tissue (Korpela et al., 2022). A normal soft pancreas leads to more leaking proteolytic enzymes, which can then more easily lead to a clinically relevant POPF and complications related to it (Schuh et al., 2022). Also, a normal soft pancreas has more ductal side branches, which may be the origin of leakage even if the sutures in the main pancreatic duct after the formation of PJ hold (Koga et al., 2009).

On the technical side, the sutures cut more easily through the soft pancreas, which has less fibrotic connective tissue (Korpela et al., 2022) and this may lead to discontinuity of the anastomosis (Belyaev et al., 2013). Sutures seem hold better if they are brought through the main pancreatic duct, which is understandably more difficult if the diameter of the main duct is small (Belyaev et al., 2013). There are different ways of performing or reinforcing the pancreaticoenteric anastomosis to mitigate the risk of POPF in a high-risk pancreas and these topics will be addressed later in their respective chapters.

A soft pancreas and the small diameter of the pancreatic duct may lead to a complication rate of 80-90% after PD. The rate of clinically relevant complications – meaning a need for alteration in the treatment at the post operative course (CD class 2 or more) – is a bit lower but still as high as 70-80% (Vuorela et al., 2020; Marchegiani et al., 2021). Also, the soft pancreas and small duct seem to increase the risk of PPAP, which further increases the risk of POPF and other postoperative complications (Bonsdorff et al., 2022).

2.5.2 PREOPERATIVE BILIARY DRAINAGE

A process affecting the head of the pancreas may obstruct the biliary tract leading to a need for PBD. If the patient's bilirubin level is over 250 µmol/l and it is not possible to proceed to surgery within a few weeks, for example due to a need for neoadjuvant therapy, or there is an active cholangitis, the guidelines suggest performing a PBD to relieve the jaundice and mitigate the risks that prolonged obstruction presents for liver functions (Ducreux et al., 2015). PBD is an invasive procedure with a possibility of serious complications such as cholangitis, pancreatitis and duodenum perforations, and it should be reserved for those in need of it (van der Gaag et al., 2010).

There are mixed results concerning whether a PBD increases the risk of postoperative complications after PD. PBD allows the bacteria from the duodenum to transfer more freely upstream to contaminate the bile (Limongelli et al., 2007). In some studies, this bacterobilia is reported to increase postoperative complications such as SSIs, and this is thought to be due to the fact that, at the time of biliary tract transection in PD, the operative field gets contaminated with bile and its possible bacteria (Limongelli et al., 2007; Sano et al., 2019). However, there are also opposite findings. A large register-based study of nearly 6,000 patients who underwent a PD showed no difference between postoperative complications after PBD compared to patients without PBD (Hamidi et al., 2021).

Both plastic and metallic stents may be used in PBD. A retrospective study by Cavell et al. showed fewer SSIs in patients who had a plastic stent compared to a metallic one [22 of 71 (31%) vs 19 of 149 (13%) patients, $p<0.001$] (Cavell et al., 2013). Further studies have failed to reproduce these findings. More recent systemic reviews and meta-analysis have not been able to show differences in SSIs between the used stent types. However, there are some differences between stent types. In these reviews, plastic stents seem to be more prone to occlude, and studies show consistently that, by using metallic stents, patients need fewer endoscopic reinterventions, which also reduces direct costs (Liu et al., 2018; Watanabe et al., 2023).

2.5.3 EXTENDED RESECTIONS

A locally advanced pancreatic cancer may infiltrate nearby vessels or organs and need an extended resection to achieve radicality. The development of surgical techniques has increased the number of patients whose pancreatic cancer may be treated with a curative intent, and the resection of portal or mesenteric veins has become a routine procedure (Hartwig et al., 2016; Mihaljevic et al., 2021).

In a borderline resectable pancreatic cancer, the resection and reconstruction of the portomesenteric venous axis including the portal vein, superior mesenteric vein and splenic vein increase the operative time, blood loss and overall postoperative complications (Kleive et al., 2017; Belfiori et al., 2021). There are mixed results as to whether or not patients who need a venous resection have poorer long-term outcomes compared to those who do not need one. A large retrospective study of 1,375 patients, 198 of whom had a venous resection, suggested convergent long-term outcomes if a radical resection was achieved (Vuorela et al., 2022). In contrast, other studies show poorer outcomes regardless of the histological radicality of the operation, if there is a venous involvement and resection of the portomesenteric veins (Belfiori et al., 2021; Groen et al., 2022). However, in the subgroup of patients who received neoadjuvant therapy, overall survival seems to be roughly equal between patients who needed or did not need a venous resection (Groen et al., 2022).

Extending the surgery even more and beyond the portomesenteric veins further increases the number of patients who may be treated with curative intent, but this also further increases the postoperative complications and not all patients are fit for these extended resections (Mihaljevic et al., 2021). Mihaljevic et al. proposed a classification of PDs in four types based on the extent of the resection. Type 1 is the standard PD, type 2 is PD with portomesenteric venous resection, type 3 is PD with resection of adjacent organs and type 4 is PD with arterial resection. In types 1 and 2, no significant difference was found between morbidity or mortality, but in types 3 and 4, the risk of major complications was significantly higher (Kleive et al., 2017; Belfiori et al., 2021; Mihaljevic et al., 2021). Based on the current literature, portomesenteric venous resection and reconstruction have become quite standard care and the results are comparable with standard PD. The more extensive resections need careful patient selection since complication rates increases significantly when the resection is extended beyond the portomesenteric veins (Schneider et al., 2021).

2.5.4 NEOADJUVANT THERAPY

In pancreatic cancer surgery, achieving radical resection - 1 mm or more (R0) of a cancer-free margin - is one of most important prognostic factors in cancer recurrence (Leonhardt et al., 2022). Borderline resectable or locally advanced tumours may need neoadjuvant treatment to increase the rate of R0 resections (Uson Junior et al., 2023). Also, patients with biologically borderline resectable PDAC may benefit from neoadjuvant therapy in the long term. Biologically borderline resectable PDAC means a tumour that is anatomically resectable but has biological features, such as elevated CA19-9 levels of over 500 units/ml indicating a higher probability of a micrometastatic disease (Petrelli et al., 2017; Lambert et al., 2021).

Even though chemotherapy agents are known for their abundance in side effects, studies have consistently shown that neoadjuvant treatment does not adversely affect the patients' postoperative course, and postoperative morbidity is comparable with patients undergoing upfront surgery (Verma et al., 2016; Araujo et al., 2020). There is even some evidence that neoadjuvant chemoradiotherapy reduces the risk of POPF after PD. A large retrospective cohort study including more than 2,000 patients who had undergone PD found that neoadjuvant chemoradiotherapy reduced the risk of POPF significantly when compared to upfront surgery (OR, 0.21; 95%CI (0.03-0.69), p=0.033). The same risk reduction was not found in patients who received neoadjuvant chemotherapy without radiotherapy. This reduction in POPF was thought to be due to the higher prevalence of pancreatic fibrosis in the resected specimens of patients who had had neoadjuvant chemoradiotherapy compared to upfront surgery (77% vs 53%, p<0.001) (Wismans et al., 2024).

The role of neoadjuvant treatment has also been studied in patients with primarily resectable pancreatic cancers (Oba et al., 2020). A randomised trial (PREOPANC) comparing neoadjuvant chemoradiotherapy to upfront surgery in both resectable and borderline resectable tumours, found a significant improvement in R0 resections for borderline resectable tumours. Also, the patients treated with neoadjuvant chemotherapy had significantly increased five-year overall survival compared to patients who underwent upfront surgery [20.5% (95%CI, 14.2-29.8) vs. 6.5% (95%CI, 3.1-13.7), p=0.025] (Versteijne et al., 2022). Recently a Nordic multicentre trial comparing the efficacy of neoadjuvant treatment (FOLFIRINOX) in patients with resectable PDAC failed to show any benefit of neoadjuvant treatment compared to upfront surgery. However, only the median overall survival rate was published and, to evaluate reliable long-term benefits, a five-year follow-up is needed. Also, the preoperative histopathological verification of PDAC was not needed before randomisation and eventually 11 of 140 (8%) randomised patients had a disease with a more favourable prognosis then PDAC (Labori et al., 2024). More studies seem to be needed and the role of neoadjuvant treatment in resectable pancreatic cancer is being extensively researched. At the moment, there are still few ongoing trials comparing neoadjuvant therapy to upfront surgery in resectable pancreatic cancers (clinicaltrials.gov identify numbers NCT05529940, NCT05679583 and NCT04340141).

2.5.5 EFFECT OF HOSPITAL VOLUME

Centralisation of pancreatic surgery to larger units with higher yearly volumes has been shown internationally by many studies particularly to reduce postoperative mortality and the failure-to-rescue ratio (Polonski et al., 2019; Ahola et al., 2020). It is not just that there are surgeons performing an adequate number of pancreatic resections per year to improve the technical aspects of the operation, but also the interdisciplinary cooperation with anaesthesiologists, intensivists, on-call surgeons, interventional radiologists and nurses who have gained enough experience working with these types of patients, which all work in favour of better outcomes. At a high-volume centre, recognition and early intervention in a case of postoperative complication are at high level, which leads to better quality and outcomes (Polonski et al., 2019; Ahola et al., 2020; Ratnayake et al., 2022).

In the literature, the cut-off value for a high-volume centre in pancreatic surgery varies between the studies and is mostly studied for PD. In a review article looking into studies reporting the results of high- and low-volume centres, the annual cut-off value for a high-volume centre for PD varied from 20 to 40 PDs between the studies (Ahola et al., 2020). Also, a large-registry study from the United States, which included 42,402 PDs and 1,238 hospitals concluded that the cut-off for a high-volume centre is 35 PDs per year (Panni et al., 2021). Independent of the hospital volume, the surgeon's personal experience in PD plays a significant role. If the surgeon has passed the learning curve and mastered PD, the effect of annual hospital volume seems to become less significant in terms of postoperative outcomes (Schmidt et al., 2010).

2.5.6 COMORBIDITIES AND AGE

To be able to recover from major abdominal surgery such as a pancreatic resection, the patient needs to be fairly fit to begin with (Dias-Santos et al., 2015). The patient needs to be able to handle the possible complications, which are rather common after pancreatectomy. For example, in the setting of a soft pancreas, 70-80% of patients get a clinically relevant complication after PD (CD class 2 or more) (Vuorela et al., 2020; Marchegiani et al., 2021). Many tools and scoring systems have been developed to preoperatively assess the postoperative risks and these may be useful when the patient is elderly or has significant comorbidities.

The Charlson Comorbidity Index (CCI) (Table 8) has been shown to be useful in preoperative planning when there is doubt based on the patients comorbidities as to whether or not the patient might tolerate major surgery such as pancreatic resection (Charlson et al., 1994; Dias-Santos et al., 2015). The age factor may be added to CCI. Dias-Santos et al. showed that, if CCI accompanied by the patient's age was more than 4, the patient was at higher risk of postoperative complications and mortality during the first year after pancreatectomy. If the score was 6 or more, the risk of mortality during the first year was even higher increasing three-fold (Dias-Santos et al., 2015). In the long term, patients with higher comorbidity index scores tend to also receive less adjuvant therapy, which is most likely also one of the reasons for poorer rates of survival (Dias-Santos et al., 2015; Asano et al., 2017).

The downside of CCI is that it does not consider what the specific operation is going to be, and the possible risk estimations should be extrapolated from studies looking into these specific operations. Also, CCI is a little outdated since it was developed more than three decades ago. Due to this, an updated version of CCI has been proposed, with re-evaluated and re-validated scoring for comorbidities to better match today's demands (Table 8) (Quan et al., 2011). However, many studies using CCI use the original and not the updated version of this score.

Table 8. The classic Charlson Comorbidity Index, the Charlson Age Comorbidity Index, and the updated Charlson Comorbidity Index.

Comorbidity	cCCI	uCCI		Comorbidity	cCCI	uCCI
Coronary disease/myocardial infarction	1	0		Cancer, local	2	2
Congestive heart failure	1	2		Leukaemia	2	*na*
Peripheral vascular disease	1	0		Lymphoma	2	*na*
Diabetes without complications	1	0		Liver disease, moderate/severe	3	4
Dementia	1	2		Cancer, metastatic	6	6
Chronic pulmonary disease	1	1		AIDS	6	4
Connective tissue disease	1	1		**Age**	**Score**	
Peptic ulcer	1	0		<50	0	
Liver disease, mild	1	2		50-59	1	
Hemiplegia	2	2		60-69	2	
Diabetes with complications	2	1		70-79	3	
Kidney disease, moderate/severe	2	1		≥80	4	

cCCI, classic Comorbidity Index; uCCI, updated Comorbidity Index; na, not applicable

Other ways to preoperatively assess postoperative risks based on age and comorbidities are the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) surgical risk calculator and the Portsmouth edition of Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (P POSSUM) score. Both calculators can be found online for free-of-charge use. The ACS NSQIP surgical risk calculator works fairly well in assessing the general risks a major abdominal operation such as pancreatectomy carries, but it lacks the effect of pancreatic resection-associated complications (Cusworth et al., 2017). Also, the P

POSSUM score has been shown to give a fairly good estimate of the risks of elderly patients after HPB surgery, but it does not take into account pancreatic resection-associated complications and most likely will not work optimally in this setting (Hu et al., 2020; Dutton et al., 2021). Patients who are in better physical condition can tolerate better and also tend to have fewer postoperative complications. In a study by Reddy et al., patients who were scheduled for an elective abdominal operation [58% (17) of whom were scheduled for pancreatic surgery] were asked to walk up and down one set of stairs (seven steps one way), while being timed. The surgical complication rate was significantly lower in patients who were able to accomplish the test in under 15 seconds. The stair-walking time remained the only significant factor for postoperative complications after multivariate analysis [OR 1.11 (95% CI, 1.06-1.16), p<0.0001] (Reddy et al., 2016).

These risk calculators can be useful tools when assessing if a patient can tolerate the risks of the operation. However, all of them seem to underestimate the procedure-based risks of pancreatic resections since these scores are universal and not pancreatic resection associated. Also, another problem with the aforementioned risk calculators is that they have not been externally validated, which inevitably affects their use and decreases their significance outside the area for which they have been developed. In addition to these scores, it would be advisable also to use POPF risk calculators to get a better assessment of overall risk after pancreatic resection (McMillan et al., 2017; Dave et al., 2019; Dutton et al., 2021).

2.5.7 POSTOPERATIVE PANCREATIC FISTULA RISK CALCULATORS

POPF is the driving force for complications after pancreatic resection, and numerous fistula risk scores have been developed to assess the risk of POPF. These risk score calculators are important not only in clinical practice but also when studying ways to mitigate the risks of POPF. These risk calculators help researchers identify different risk groups since not all pancreases are equal and there are significant differences between the risk profiles of POPF based on the features of the pancreas (Callery et al., 2013; Kantor et al., 2017; Mungroop et al., 2021; Bonsdorff et al., 2022; Schuh et al., 2022).

Most of the POPF risk score calculators have been developed and validated for PD. A systematic review of POPF risk calculators in PD by Pande et al. in 2021 found 34 different prediction models but only six of them had been externally validated. All these six models included the width of the pancreatic duct, but other variables were rather fragmented. A year after Pande et al.'s review, the ISGPS published another systemic review and meta-analysis of the same topic, after which they proposed a simple four-category prediction model for POPF after PD. In this model, the only variables were the width of the pancreatic duct and the texture of the pancreas (Table 9), which facilitates adaptation to daily practice (Callery et al., 2013; Kantor et al., 2017; Mungroop et al., 2021; Pande et al., 2022; Schuh et al., 2022). However, by oversimplifying the scoring, some of the predictive power of the model is inevitably lost.

Table 9. Simple classification for POPF in patients undergoing PD by ISGPS

Risk class for POPF	Texture of the pancreas	Width of the MPD	Rate of POPF* (%)
A	firm/hard	>3 mm	3.5
B	firm/hard	≤ 3mm	6.2
C	soft	>3 mm	16.6
D	soft	≤ 3mm	23.2

POPF, postoperative pancreatic fistula; MPD, main pancreatic duct; ISGPS, International Study Group on Pancreatic Surgery
*Based on a validation group of 5,533 pancreatoduodenectomies (Schuh et al., 2022).

The development of fistula risk scores for DP has not been as intense as for PD. To date, only two different fistula risk scores for DP have been published and both of them just fairly recently. A Finnish-Swedish DISPAIR score was published in 2022, and the multinational D-FRS later in 2023 (Bonsdorff et al., 2022; De Pastena et al., 2023). Both models can be used preoperatively to assess the risk of POPF using parameters that are obtainable from patients' radiological imaging studies and medical history. D-FRS has an additional intraoperative model where pancreatic texture and operative time are additional variables. All in all, these two are rather similar with the only striking difference being that D-FRS uses pancreatic thickness at the level of the pancreatic neck regardless of where the transection line is, whereas DISPAIR uses pancreatic thickness at the level of the transection site. Both DISPAIR and D-FRS have been externally validated and the area under the receiver operating characteristics curves (AUROC) for both indicate acceptably working prediction models. The AUROC for DISPAIR was 0.80 (0.75 to 0.85) while for D-FRS it was slightly lower at 0.73 (0.70-0.76) (Bonsdorff et al., 2022; De Pastena et al., 2023). There are also some studies, which have externally validated and compared these two prediction models. Based on their results, it seems that both the risk score calculators work rather equally (Xu et al., 2023; Tang et al., 2024).

2.6 MEANS TO REDUCE COMPLICATIONS IN PANCREATIC SURGERY

Due to the nature of pancreatic surgery and its abundance of postoperative complications, different mitigation strategies of these complications have been extensively studied. These mitigation strategies vary from surgical techniques to pharmacotherapy and pre- and rehabilitation.

2.6.1 OPERATIVE TECHNIQUES

2.6.1.1 Pancreaticoenteric anastomosis

The two main types of pancreaticoenteric anastomosis in PD are PJ and PG. Both of those have modifications where, for example, the remnant of the pancreas is dunked inside the respective part of GI-tract, or some tissue or synthetic material is brought to reinforce the anastomosis (Barreto & Shukla, 2017).

The differences between PJ and PG have been widely studied. A Cochrane review of 10 randomised trials comparing PJ and PG in 1,629 patients prior to 2017 did not find any significant difference between postoperative complications after either of these reconstruction methods (Cheng et al., 2017). After this review, Hartman et al. presented somewhat concerning results in 2022 regarding PPH after PG. In their prospective database of 274 patients who underwent PD, PG was done for approximately 30% and PJ for 70% of the patients. Late severe grade C PPH occurred in 24% of the patients with PG versus 5% of the patients with PJ. However, these data have only been presented in an abstract at a scientific meeting and a peer-reviewed article is had not yet published at the time of writing this thesis, so the results cannot be thoroughly evaluated (Hartman et al., 2022). Similar to the findings of Hartman et al., Kazantsev et al. also found that there were more PPH in patients with PG compared to patients with PJ. They also found that, in high-risk patients (soft pancreas and small pancreatic duct), PG decreased the risk of clinically relevant POPF, but this reduction was overshadowed by the significant increase in the potentially fatal complication of PPH (Kazantsev et al., 2023). Likewise, in 2020 a Swedish registry study of 2,503 patients who had undergone PD, suggested that the risk of clinically relevant POPF was higher in patients with PJ than with PG (Williamsson et al., 2020).

Regarding other pancreatic resection-associated complications, recently a Swedish registry-based study using the same registry as Williamson et al. suggested that PG would also decrease the risk of DGE compared to PJ (Zdanowski et al., 2023). Similar results were already published at the beginning of this millennium when Bassi et al. found that PG was associated with less DGE but similar rates of other pancreatic resection-associated complications when compared to PJ (Bassi et al., 2005). However, there also studies reporting opposite findings where PG increased the incidence of DGE (Hayama et al., 2020) and the results of a randomised trial comparing PG and PJ with externalised stents and somatostatin analogues in high-risk patients suggested that PJ was favourable for high-risk patients in reducing the overall complication burden (Andrianello et al., 2020). All in all, the current literature reports mixed results as to whether PJ is superior to PG or vice versa, and it may be safe to say that, until stronger evidence is shown, the surgeon should perform the type of pancreaticoenteric anastomosis that he or she is most familiar with.

The two most common ways to perform a PJ are the duct-to-mucosa and invagination methods. In the duct-to-mucosa method, the pancreatic duct is carefully sutured into a small hole in the jejunum and the jejunum is further sutured to the pancreatic remnant as a second layer. In the invagination method, the whole pancreatic stump is invaginated into the jejunum and the jejunum is sutured around the remnant in two layers (Kennedy & Yeo, 2011). Multiple RCTs comparing the duct-to-mucosa and invagination techniques have been published. A systematic review and meta-analysis by Hua et al. included five RCTs of 654 patients, and did not find any difference in POPFs or other pancreatic resection-associated complications (Hua et al., 2015). Also, a more recent Cochrane review by Hai et al., which included 11 RCTs and 1,969 patients, did not find significant differences between the duct-to-mucosa or invagination PJ techniques (Hai et al., 2022).

There are also numerous ways to reinforce the suture line in PJ or PG to reduce the POPF. The PJ may be reinforced with a synthetic mesh wrapped around the body of the pancreas, and the PJ anastomosis sutures are brought through this mesh to prevent a cut-through. A retrospective study of 126 patients compared this mesh reinforcement to standard PJ and a reduction of POPFs from 34% to 15% was seen (Zhong et al., 2018). Also, wrapping the PJ with the patient's own mobilised falciform ligament has been described in the literature, but no comparative studies have been published (Zizzo et al., 2018). The PANDA trial showed that wrapping the gastroduodenal artery with falciform ligament reduced PPHs (Welsch et al., 2022). Also, wrapping the transection line in DP with falciform ligament has been shown to decrease the risk of clinically relevant POPFs after DP, so it would be truly an interesting research setting to see whether or not wrapping the PJ with falciform ligament might also diminish the rate of POPF after PD (Hassenpflug et al., 2016). Also, a stent may be introduced across the PJ to further reinforce the pancreaticoenteric anastomosis. Both internal and externalised stents have been studied. A recent systemic review and meta-analysis by Sun et al. included 12 RCTs and 1,117 patients with no stent placement, internal stent or externalised stent. The authors concluded that, in patients with a non-dilated pancreatic duct, the stent may be beneficial and the externalised stents seem to reduce POPF more than the internal stents (Sun et al., 2024).

2.6.1.2 Pylorus preserving pancreatoduodenectomy

The most commonly used modification of PD is PPPD where the proximal transection line of the GI-tract is couple of centimetres distal to the pylorus and, in the reconstruction phase, the continuity of the GI-tract is restored by anastomosing this short duodenal stump to a jejunum loop (Traverso & Longmire Jr, 1978; Itani et al., 1986). It has been thought that, by preserving the whole stomach in PPPD contrary to a standard PD where the distal stomach is resected, the patients' nutritional status would be better and there would be less dumping. Also, the operative time is shorter in PPPD and PPPD has gained a stable place in pancreatic surgery (Iqbal et al., 2008; Klaiber et al., 2017). Retrospective studies have shown that the pylorus-resecting PDs have less DGE than PPPD, which is somewhat contradictory to the assumption of what benefits pylorus preservation could have (Hackert et al., 2013; Nanashima et al., 2013; Zhou et al., 2015). However other studies have shown that there are no or only minimal differences between the postoperative complications of PPPD and PD. Two randomised trials (QUANUPAD and PROPP) have compared PPPD and PD and they did not find any differences in outcomes including DGE (Hackert et al., 2018; Busquets et al., 2022) Also, a review in the Cochrane Database of Systematic Reviews stated that these two operations are equal in terms of postoperative morbidity, mortality and survival (Hüttner et al., 2016). There is still an ongoing randomised trial comparing PPPD and PD (PyloResPres trial), which may give more insight into the debate about whether there is a difference between PPPD and PD or not (Renz et al., 2021).

2.6.1.3 Closure of pancreatic stump in distal pancreatectomy

The site for POPF after DP is the transection line. Different ways of transecting and reinforcing the resection site have been studied. The pancreas may be transected and closed either by cutting through the parenchyma with a scalpel or with an energy instrument such as ultrasound or bipolar scissors, and then the pancreatic stump is closed with handsewn sutures, or it can be completely divided with a stapler. A retrospective study of 2,026 DPs showed a lower risk of POPF if the pancreas was transected with a stapler versus other methods. However, the authors stated that data on the thickness of the pancreas were not available and hence there may be a selection bias since the riskiest pancreases for POPF are the thick ones and these may be technically impossible to even divide with a stapler (Ecker et al., 2019). There are also other studies of smaller cohort sizes that likewise showed no difference between the rate of POPF whether the pancreatic stump was closed handsewn or with a stapler (Maggino et al., 2019; Hiyoshi et al., 2020; Shen et al., 2020). If the pancreas was divided with an energy instrument and no additional sutures were placed in the pancreatic stump, the risk of POPF was significantly higher (Ecker et al., 2019; Pulvirenti et al., 2019). The staple line may also be reinforced with a biological material applied between the jaws of a stapler and the staples go through it. These kinds of reinforced staplers have been shown to be effective in reducing POPF after DP when compared to standard staplers (Jensen et al., 2013; Oweira et al., 2022).

In the DISCOVER trial, the pancreatic stump was closed with sutures or staples and then covered with the patient's own falciform ligament patch. The falciform ligament patch reduced the incidence of clinically relevant POPFs from 32.9% to 22.4% and, after multivariate analysis of the different possible risk factors, the risk reduction was statistically significant (OR 95%CI, 0.30

(0.12-0.79), p=0.015) (Hassenpflug et al., 2016). Other biological and synthetic materials such as fibrin glue and patches have also been studied. Applying fibrin glue to the pancreatic stump did not seem to affect the rate of POPF in any way (Carter et al., 2013). Likewise a randomised trial studying the effects of covering the pancreatic stump with a Hemopatch, a pad containing bovine-derived collagen, did not find any difference in the incidence of a POPF when compared to just suturing or staple closure of the pancreatic stump (Uranues et al., 2021). Recently a meta-analysis was published, which included the studies by Hassenpflug et al., Carter et al. and Uranues et al., as well as nine other RCTs studying different ways to cover the pancreatic stump after DP. The results of this meta-analysis suggested a significant risk reduction for POPF if the stump was just covered - either with autologous or artificial material (OR 0.69, 95%CI 0.51-0.94, p=0.02) (Walber et al., 2024).

Based on the current literature, it seems as that, in a DP, the pancreas needs to be divided with a stapler and preferably with a reinforced one. Additionally, it seems to be beneficial to cover the pancreatic stump somehow - for example with the patient's own falciform ligament or with some artificial material.

2.6.1.4 Use of intra-abdominal drains

Intra-abdominal drains are used in pancreatic surgery to diagnose and mitigate possible postoperative complications such as POPF or bile leakage. Early recognition and treatment of these complications is thought to lead to better results (Fisher, 2018). The use of drains has been shown to be insignificant in many major abdominal surgical procedures and, in 2001, Conlon et al. published the results of a randomised trial where they compared the use of drains in patients who underwent either a PD or DP. The authors did not find any difference between major complications in patients with or without intra-abdominal drainage and suggested that there is no need to use drains routinely after pancreatic resection (Conlon et al., 2001). Since then, there have been a few trials with the same setting but concerning only either PD or DP, and the results are somewhat confusing. George Van Buren et al. terminated their randomised trial comparing drainage versus no drainage in patients undergoing pancreatic head resections (mostly PD or its modification) since, in an the interim analysis, there were significantly more major complications and mortality in the no-drainage group (George Van Buren et al., 2014). Also, a large retrospective registry-based study reported higher postoperative morbidity and mortality if no drains were placed during PD compared to routine drainage, but this difference was seen only in high-risk pancreas cases (soft texture and small pancreatic duct) (Zaghal et al., 2019). On the other hand, the results of the PANDRA trial comparing intra-abdominal drainage after PD reported no difference or even a slightly increased risk of postoperative complications after intra-abdominal drainage after pancreatic head resections (Witzigmann et al., 2016). Later a systemic review and meta-analysis involving ten trials and 2,419 patients concluded that the results with or without intra-abdominal drainage were comparable in both PD and DP (Lyu et al., 2020). Even though there is quite strong evidence supporting the omission of routine intra-abdominal drainage, especially in patients with a low-risk pancreas, most of the pancreatic surgeons seem to be unwilling to stop the use of intra-abdominal drainage, especially after PD where the GI- and biliary tracts are transected allowing the operative field to be contaminated with gut bacteria (Demir et al., 2020).

Recently, the results of an anticipated RCT (PANDORINA) comparing no-drain policy to routine drainage after DP were published. In this non-inferiority trial of 282 patients undergoing DP, the rate of major complications (CD ≥ 3) was non-inferior in the no-drain group compared to the drain group, and clinically relevant POPFs (grade B or C) were more commonly seen in patients in the drain group. The authors of this trial suggested omitting routine drainage after DP since the major morbidity was the same and fewer clinically relevant POPFs were detected in the no-drain group (van Bodegraven et al., 2024).

2.6.1.5 Minimally invasive surgery

The technical aspects of different types of pancreatic resections have led to variances in the adaptation processes of minimally invasive techniques for each of these operations. DP is a more straightforward operation compared to PD with no reconstruction phase. Laparoscopic DP has been shown to reduce length of stay, blood loss and overall postoperative complications, and to promote faster recovery and it has become a routine technique for DP (DiNorcia et al., 2010; Suman et al., 2013; de Rooij et al., 2019). Recently, the results of the DIPLOMA trial even showed similar oncological results after minimally invasive DP compared to open DP in cancer patients, which further cements minimally invasive DP as the gold standard in left-sided pancreatic resections (Korrel et al., 2023).

The same cannot be said for laparoscopic PD. The reconstruction phase of PD makes it technically demanding to be performed in a minimally invasive way, and this has hindered the adaption of minimally invasive techniques in PD (Khachfe et al., 2022). The learning curve for laparoscopic PD is long, and the centres excelling in this technique have not previously reported the results of the early phase of adaptation of laparoscopic PD (Speicher et al., 2014; Wang et al., 2016). As an exception to this, a randomised trial LEOPARD-2 comparing laparoscopic PD to open PD was conducted in the Netherlands but was terminated after the enrolment of 105 patients due to higher mortality in the laparoscopic group (10% vs. 2%) without any difference in other postoperative complications or functional recovery (Van Hilst et al., 2019).

After the technical difficulties of a laparoscopic PD have been overcome, some studies suggest that laparoscopic PD is be superior in reduced postoperative complications, length of stay and blood loss, and in increasing survival rates after malignant diseases when compared to open PD (Feng et al., 2021). However, there are studies reporting the opposite such as the LEOPARD-2 trial (Van Hilst et al., 2019) and a recent prospective cohort study by Stauffer et al., which consisted of 347 open and 242 laparoscopic PDs. This study showed that, in their cohort, POPF and DGE were in fact significantly higher after laparoscopic PD compared to open PD (Stauffer et al., 2024).

Robot-assisted laparoscopic pancreatic surgery has been shown to be safe and feasible (Yan et al., 2020; Kim et al., 2022), the learning curve of younger surgeons seems to be flatter than in laparoscopic PD and they are achieving the plateau earlier (Rice et al., 2020; Chan et al., 2021). Compared to open PD and similar to laparoscopic PD, robot-assisted laparoscopic PD results in less blood loss, shorter length of stay, less SSIs but higher costs and longer operating time (Aiolfi et al., 2021; de Graaf et al., 2024).

Recently, the results of two RCTs comparing robot-assisted laparoscopic PD to open PD were published (Klotz et al., 2024; Liu et al., 2024). In the RCT by Klotz et al. (EUROPA-trial), the authors found that there was significantly less DGE after open PD compared to robot-assisted laparoscopic PD (34% vs. 6%), but the overall complication burden measured by 90-day CCI was comparable (Klotz et al., 2024). In the RCT conducted by Liu et al., there was no difference in postoperative morbidity between open and robot-assisted laparoscopic PD (Liu et al., 2024). Also, the preliminary results of the DIPLOMA-2 trial comparing minimally invasive PD (n=190) to open PD (n=98) reported significantly less CR-POPF in patients who underwent minimally invasive PD compared to open PD (22.6% vs 35.7%, p=0.03). These as yet unpublished results were presented at the International Hepato-Pancreato-Biliary Association's congress in Cape Town in May 2024 (Emmen et al., 2024).

Based on the current literature, it seems that minimally invasive PD has advantages over open PD, but conventional laparoscopic PD seems to have conflicting results. Robot-assisted laparoscopic PD seems to be rather equal or maybe even better than open PD.

2.6.2 PHARMACOLOGICAL INTERVENTIONS

2.6.2.1 Somatostatin and its analogues

Somatostatin analogues such as octreotide and pasireotide are the most studied pharmacological regimens for the mitigation of postoperative complications and especially POPF after pancreatic surgery. The rationale for using these regimens is the known fact that most POPFs are due to the exocrine enzymes the remnant that the pancreas produces, and somatostatin and its analogues reduce the secretion of these proteolytic enzymes (Raptis et al., 1978; Li-Ling & Irving, 2001; Allen et al., 2014; Adiamah et al., 2019).

Somatostatin itself has a short half-life of approximately 2 minutes and thus these analogues with longer half-life have been developed (Raptis et al., 1978).

Octreotide is a relatively weak somatostatin analogue binding to only two of five somatostatin receptors, whereas pasireotide has a high affinity in four of the five receptors (Schmid, 2008). The benefit of octreotide in reducing POPF has not been shown consistently (Volk et al., 2016; Adiamah et al., 2019), but there are some data supporting the use of pasireotide or lanreotide, the latter being a long-lasting somatostatin analogue. Studies looking specifically into pasireotide in the mitigation of postoperative complications after pancreatic resection are summarised in the Table 10.

In 2014 Allen et al. published the results of an RCT where they compared perioperatively administered pasireotide to placebo in patients undergoing pancreatic surgery. Patients who received pasireotide (n=152) had significantly fewer clinically relevant POPFs compared to patients who received placebo (n=148) [9% vs. 21%; RR, 0.44; 95%(CI), 0.24 to 0.78; P=0.006] and the findings were consistent in patients undergoing PD or DP and in high-risk and low-risk pancreases (Allen et al., 2014). Since the RCT by Allen et al., the benefit of pasireotide has not been shown consistently. However, the majority of these later studies have been retrospective-cohort studies and no other RCT after Allen et al., has been published (Table 10). Another somatostatin analogue with possibly beneficial effects for reducing POPF is long-lasting, single-dosed lanreotide. There are only few published studies concerning lanreotide, and more evidence would be needed to assess the possible benefits of lanreotide (Bootsma et al., 2022; Pillarisetty et al., 2022).

The side-effects of somatostatin analogues are nausea, vomiting and hyperglycaemia but, other than that, they are fairly well tolerated and the side-effects are rather mild compared to the postoperative complications a pancreatic surgery may cause (de Herder & Lamberts, 2002). However, one aspect hindering the use of somatostatin analogues may be their relatively high cost. A prophylaxis with pasireotide for one week costs approximately €700 in Europe, but several thousands of dollars in the United States of America (Welsch et al., 2016; Ma et al., 2017). For octreotide the costs are significantly lower being few hundred euros for prophylactic administration (Welsch et al., 2016).

Table 10. Studies looking into pasireotide in the mitigation of postoperative complications after pancreatic resection.

Author	Year	Country	Study design	Study drug(s) Number of patients (I / C)	Type of surgeries	The risk profile for POPF of the included patients	Main findings
Allen *et al.* (Allen et al., 2014)	2014	USA	Randomized controlled trial	pasireotide vs. placebo n=300 (152 / 148)	PD and DP	High and low risk	The rate of CR-POPF was lower with pasireotide vs. placebo (9% vs. 21%; RR, 0.44; 95% CI, 0.24 to 0.78; P=0.006)
Dominguez-Rosado *et al.* (Dominguez-Rosado et al., 2018)	2018	USA	Propensity score-matched prospective cohort study	pasireotide vs. control n=459 (127 / 332)	PD	High and low risk	The rate of POPF was similar between the patients who received pasireotide and the patients who did not receive pasireotide (12.5% vs 17%, p=0.346). The overall complication rate was lower in patients who received pasireotide, but this difference was not statistically significant (51.8% vs 62.5%, p = 0.105)
Young *et al.* (Young et al., 2018)	2018	USA	Prospective cohort study	pasireotide vs. control n=116 (43 / 73)	PD and DP	High and low risk	The rate of CR-POPF was similar between patients who received and who did not receive pasireotide (25.6% vs. 30.1%, P = 0.599)
Elliot *et al.* (Elliott et al., 2018)	2018	USA	Prospective cohort study	pasireotide vs. historical cohort n=279 (111 / 168)	PD and DP	High and low risk	The rate of CR-POPF was similar between patients who received pasireotide compared to historical cohort who did not receive pasireotide (15.5% control versus 17.1% pasireotide, p = 0.72)
Kunstman *et al.* (Kunstman et al., 2019)	2019	USA	Prospective cohort study	pasireotide vs. historical cohort n=800 (652 / 148)	PD and DP	High and low risk	The risk for CR-POPF was lower in patients who received pasireotide compared to the historical cohort of patients who had not receive pasireotide (OR 0.58; 95% CI, 0.37 to 0.92; p = 0.020)
Vuorela *et al.* (Vuorela et al., 2020)	2020	Finland	Retrospective cohort study	pasireotide vs. historical cohort n=153	PD	High and low risk, but pasireotide administered only to high risk	The incidence of CR-POPF was lower in the study cohort (2.6%) compared to historical cohort of PD patients before the use of pasireotide (7 %).
Peng *et al.* (Peng et al., 2020)	2020	USA	Retrospective cohort study	pasireotide vs. control n=300 (99 / 201)	PD and DP	High and low risk	The rate of CR-POPF was comparable between the patients who received pasireotide and a historical cohort of patients who had not received pasireotide (19.2% vs. 14.9%, p=0.347). The rates were similar even when patients were stratified by fistula risk score.
Vuorela *et al.* (Vuorela et al., 2021)	2021	Finland	Retrospective cohort study	pasireotide vs. octreotide vs. control n=258 (47 / 31 / 180)	DP	High and low risk	Patients receiving pasireotide or octreotide had similar rates of CR-POPF compared to the patients who did not receive either one of the study drugs (15% vs. 10% vs 17%, p=0.739). Also, the incidence of major complications (CD grade ≥ 3) was similar between the groups.

I/C, intervention / control; CR-POPF, clinically relevant postoperative pancreatic fistula; PD, pancreatoduodenectomy; DP, distal pancreatectomy; RR, relative risk; CI, confidence interval; CD, Clavien-Dindo; BMI, body mass index

2.6.2.2 Corticosteroids

Hydrocortisone has been shown to reduce postoperative complications and POPFs after partial pancreatectomy (Laaninen et al., 2016; Antila et al., 2019). Laaninen et al. conducted a randomised trial comparing perioperatively administered hydrocortisone to placebo in high-risk patients undergoing PD. They found that, in patients with a high risk of POPF, the hydrocortisone significantly reduced the overall complications and there was a tendency towards a lower incidence of POPF, DGE and PPH. The authors hypothesised that the hydrocortisone suppressed the postoperative inflammation leading to a reduction in pancreatic resection associated complications (Laaninen et al., 2016). Likewise, Antila et al. showed a reduction in relevant POPF after perioperative administration of hydrocortisone when compared to placebo (Antila et al., 2019). Other than these two studies, there are only a few other studies reporting results of perioperative corticosteroids usage in the reduction of postoperative complications in pancreatic surgery, and they have not been able show the benefit of corticosteroids. Studies looking into corticosteroids in the mitigation of postoperative complications after pancreatic resection are summarised in the Table 11.

Table 11. Studies looking into corticosteroids in the mitigation of postoperative complications after pancreatic resection.

Author	Year	Country	Study design	Study drug(s) Number of patients (I / C)	Type of surgeries	The risk profile for POPF of the included patients	Main findings
Laaninen *et al.* (Laaninen et al., 2016)	2016	Finland	Randomized controlled trial	hydrocortisone vs. placebo n=62 (28 / 34)	PD	High and low risk	The rate of major complications (CD grade ≥ 3) was lower in patients receiving hydrocortisone (18% vs. 41%, p<0.05). The rate of CR-POPF, DGE and PPH was lower in patients receiving hydrocortisone, but the differences were not statistically significant (11% vs 27% for CR-POPF; 29% vs. 44% for DGE; 14% vs. 24% for PPH).
Sandini *et al.* (Sandini et al., 2018)	2018	USA	Prospective cohort study	dexamethasone vs. control n=679 (117 / 562)	PD	High and low risk	Overall morbidity was similar between the patients who had received dexamethasone and the patients who had not received dexamethasone. However, there was fewer SSIs in patients receiving dexamethasone (18.8% vs. 28.5%, p=0.032)
Antila *et al.* (Antila et al., 2019)	2019	Finland	Randomized controlled trial	hydrocortisone vs. placebo n=40 (20 / 20)	DP	High and low risk	The rate of CR-POPF was significantly lower in pasireotide group (5.9% vs 42.9%, p=0.028). Also, the rate of major complications (CD grade ≥ 3) was lower in pasireotide group (5.9% vs. 21.4%, p=0.034).
Newhook *et al.* (Newhook et al., 2021)	2021	USA	Prospective cohort study	dexamethasone vs. control n=373 (223 / 150)	PD, DP, TP	High and low risk	Patients who received dexamethasone had similar rate of major complications (CD grade ≥ 3) compared to those who did not receive dexamethasone (21.1% vs 19.3%, p=0.68).
Kant *et al.* (Kant et al., 2024)	2024	India	Randomized controlled trial (n=105)	hydrocortisone vs. indomethacin vs. placebo	PD	High risk	Major complications were comparable between the study groups. Also, the rates of CR-POPF, DGE, PPH and SSIs were similar between the study groups.

I/C, intervention / control; PD, pancreatoduodenectomy; CD, Clavien-Dindo; CR-POPF, clinically relevant postoperative pancreatic fistula; DGE, delayed gastric emptying; PPH, postpancreatectomy hemorrhage; SSI, surgical site infection; DP, distal pancreatectomy; TP, total pancreatectomy

2.6.2.3 Trypsin inhibitors

Ulinastatin is a trypsinogen inhibitor used to treat acute and chronic pancreatitis. It suppresses the excretion of many of the exocrine pancreatic enzymes and a variety of inflammatory mediators (Chen et al., 2007). Based on these pharmacological features, a randomised trial was conducted to find out if ulinastatin would also decrease POPF after PD. Zhang et al. randomised 106 patients in a ratio of 1:1 to receive perioperatively either ulinastatin or placebo. Interestingly, they reported a statistically significant reduction in clinically relevant POPFs in patient who received ulinastatin compared to placebo (7% vs. 24%, p=0.045) and the effect was even stronger in a high-risk pancreas (Zhang et al., 2016). Other than this study, there is only one rather small study of 42 patients undergoing PD, which showed significant reduction in postoperative pancreatitis after ulinastatin administration (Uemura et al., 2008), but no other studies have been published.

2.6.3 ENHANCED RECOVERY AFTER SURGERY PROTOCOLS

ERAS protocols take all the aspects of perioperative care into consideration, and they are weighted based on current scientific evidence. The ERAS pathway is best established in colorectal surgery where it is shown to reduce both postoperative complications and recovery time (Pędziwiatr et al., 2018; Grieco et al., 2020). There is also a detailed ERAS protocol for PD and it has been tested in both the setting of randomised trials and retrospective series (Takagi et al., 2019; Melloul et al., 2020). The results of a randomised trial by Takagi et al. showed a significant reduction in postoperative complications, length of stay, readmissions and an increase in quality of life if the patients undergoing PD who were treated with the ERAS pathway compared to standard care (Takagi et al., 2019). Also, recently a large systematic review and meta-analysis of ERAS pathways in PD showed strong correlation between the ERAS pathway and a reduction in postoperative complications, length of stay and mortality rates, also leading to significant cost reductions (Noba et al., 2023). In other types of pancreatic resections, the ERAS pathways have been studied less. The results of a rather small retrospective cohort of 83 patients showed encouraging results after implementing the ERAS pathway with patients undergoing DP. The patients with high compliance to the ERAS pathway after DP had a significantly shorter length of stay and a significant risk reduction in postoperative complications (Majid-Jarrar et al., 2022). There seems to be a clear association with better outcomes after PD and DP if the ERAS pathways are implemented in perioperative care.

2.7 ROLE OF ANTIBIOTICS AND MICROBIOME IN PANCREATIC SURGERY

2.7.1 PREOPERATIVE ANTIBIOTIC PROPHYLAXIS

Timely administered preoperative prophylactic antibiotic has been shown to reduce SSIs in all major abdominal surgery and is a standard of care (Mangram et al., 1999; Bratzler et al., 2013; Purba et al., 2018). There are several guidelines recommending what antibiotics to use and when to administer them. If the patient has an ongoing infection or is allergic to recommended antibiotics, the prophylactic antibiotic may not be what the guidelines recommend.

In the setting of pancreatic surgery, the joint guidelines for antimicrobial prophylaxis in surgery by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society and the Society for Healthcare Epidemiology of America recommend a single dose of first-generation cephalosporin 60 minutes before incision in order for the concentrations to reach an effective level at the operative site (Bratzler et al., 2013). The ERAS society follows these same recommendations, so it is safe to assume that cephalosporins are the most widely used prophylactic antibiotics in pancreatic surgery (Melloul et al., 2020).

Basically, all studies looking into the antibiotic prophylaxis in pancreatic surgery are most likely concentrating on PD due to the fundamental differences between possible intraoperative contamination in PD and DP. In PD, both the biliary and the GI-tract are transected, which makes the operative field exposed to contamination with the respective fluids and bacteria they may contain. DP, on the other hand, is essentially a sterile operation.

2.7.1.1 Narrow- or broad-spectrum antibiotics in prophylaxis?

The recommended prophylactic antibiotic in pancreatic surgery has been the narrow-spectrum cephalosporins (Melloul et al., 2020). Until recently, there had not been that much data to question whether these first-generation cephalosporins were adequate in the surgical prophylaxis. Some retrospective studies have shown better outcomes with fewer SSIs when the prophylactic antibiotic has been a broader-spectrum one such as piperacillin/tazobactam (Donald et al., 2013; Sano et al., 2019; De Pastena et al., 2021). Recently also, a randomised trial comparing second-generation cephalosporin to piperacillin/tazobactam at prophylaxis in patients undergoing PD showed the superiority of piperacillin/tazobactam (D'Angelica et al., 2023). This trial was terminated at interim analysis after patients who received piperacillin/tazobactam had not only significantly fewer SSIs but interestingly also fewer POPFs. In the post hoc analysis, this difference was seen especially in patients who had undergone PBD (D'Angelica et al., 2023). Several studies - including a study using the same cohort of patients as in D'Angelica et al.'s trial - have shown that the most prevalent bacteria found in the patients' bile at the time of transecting the biliary tract during PD are *enterococcus* spp, *klebsiella* spp and *enterobacter* spp (Limongelli et al., 2007; Maxwell et al., 2020; Ellis et al., 2023). All these species are naturally resistant or have the ability to turn resistant to cephalosporins (Cheng et al., 2017; Nepal et al., 2017; Rello et al., 2020). In the study by Ellis et al., the cephalosporin-resistant species were found significantly more frequently in the biliary cultures of patients who had undergone PBD compared to those who had not undergone it (61.7% vs. 19.5%, $p<0.001$). This may be the main reason why, in the trial by D'Angelica et al., the significant reduction in SSIs when using broader-spectrum antibiotics in prophylaxis was seen especially in patients who had undergone PBD (D'Angelica et al., 2023; Ellis et al., 2023). The results of a recent meta-analysis further question the role of narrow-spectrum antibiotics in the prophylaxis of patients undergoing PD. A meta-analysis by Kumar et al. included more than 2,000 patients undergoing PD and showed that the patients who had received piperacillin/tazobactam in the prophylactic setting had significantly fewer SSIs and CR-POPFs compared to patients who had received traditional prophylactic antibiotics (Kumar et al., 2024).

Based on these recent findings, it seems that at least the patients who undergo PBD prior to PD could benefit from broader-spectrum antibiotics. There is no data available as to whether the cephalosporins recommended by the guidelines are still adequate in types of pancreatectomies other than PD.

2.7.2 GUT MICROBIOME AND POPF

Gut microbiome and its association with anastomotic leakage has been an interest of research in colorectal surgery. In rat models, it has been suggested that *Enterococcus faecalis* and *Pseudomonas aeruginosa* have an association with anastomotic leakage and these same bacteria are most commonly found in bacterial cultures of the leakage site after dehiscence of a colorectal anastomosis (Lee et al., 2015; Guyton & Alverdy, 2017). However, the association of gut microbiome and POPF – which is essentially an anastomotic leakage of PJ or PG – has not been a topic of research. There are some indirect findings that suggest the microbiome could also play a role in the development of POPF. The same species and especially *enterococcus* spp that has been associated with colorectal anastomotic leakage has also been shown to associate with POPFs (Ellis et al., 2023).

In past few years the role of the gut microbiome in anastomotic leakage has been an active topic of interest in colorectal surgery. Now there are also some findings suggesting that the microbiome may also have a role in the development of POPF. It could be that in near future we are going see more studies looking into the role of microbiome in POPFs.

2.7.3 ANTIBIOTIC RESISTANCE

Antibiotic resistance is a growing problem worldwide. The World Health Organization (WHO) states that antibiotic resistance is one of the biggest threats to global health, food security and development (WHO, 2021). The resistant bacteria cause severe complications, increase the costs of healthcare and even mortality. The liberal use of antibiotics has accelerated the resistance problem, and the resistant pathogens are nowadays found circulating in the community whereas previously they were restricted to healthcare and agricultural settings (Cook & Wright, 2022). There are also cultural differences in the use of antibiotics, which is reflected in the prevalence of resistant bacteria. For example, in Northern Europe the consumption of antibiotics is much lower than in Southern Europe and many parts of Asia (Llor & Bjerrum, 2014; WHO, 2022).

The reduction in antibiotic consumption has also been shown to reduce resistance, and the use of antibiotics should always be reasoned and targeted if possible (Llor & Bjerrum, 2014). Liberal consumption of empiric broad-spectrum antibiotics will lead to worse resistance problems, and will be a disservice to future generations (WHO, 2022).

3 AIMS OF THE STUDY

The aims of the specific studies were as follows.

I. To compare the short-term outcomes of perioperatively administered pasireotide and hydrocortisone in mitigating postoperative complications after partial pancreatectomy in patients with a high risk of postoperative pancreatic fistula (HYPAR trial) (Study I).

II. To report the long-term outcomes of the HYPAR trial and to assess the safety of both pasireotide and hydrocortisone in the long term in patients who were at a high risk of postoperative pancreatic fistula and underwent a partial pancreatectomy (Study II).

III. To study the incidence of bacterobilia at the time of biliary tract transection in pancreatoduodenectomy, the risk factors for resistant bacteria in bile and their correlation to surgical site infections (Study III).

IV. To assess the diagnostic challenges of a rare groove pancreatitis, its natural course and the outcomes of different treatment strategies (Study IV).

4 MATERIALS AND METHODS

4.1 STUDY HOSPITAL

This research was conducted at Helsinki University Hospital, Meilahti Tower Hospital, which functions both as a secondary and tertiary referral centre. Meilahti Tower Hospital is a high-volume centre of pancreatic surgery with 140 to 160 elective pancreatic resections scheduled per year, serving a population of 2.2 million people. All patients in **Studies I-III** underwent a pancreatic resection at Meilahti Tower Hospital.

Patients included in **Study IV** were treated at Meilahti Tower Hospital and six regional hospitals in Southern Finland, all part of the Helsinki and Uusimaa Hospital District with a population base of 1.7 million. The hospitals were at Jorvi, Peijas, Hyvinkää, Porvoo, Lohja and Raasepori.

4.2 STUDY DESIGN

Study I was a randomised controlled trial (the HYPAR trial), **Study II** a prospective long-term follow up study to the HYPAR trial and **Studies III** and **IV** retrospective cohort studies.

4.3 PATIENTS

Studies I and **II** consisted of 126 randomised patients with a high risk of POPF and who were scheduled for partial pancreatectomy between 19 May 2016 and 17 December 2018.

Study III consisted of 361 patients who underwent PD between 23 May 2016 and 29 October 2019. All included patients had to have an intraoperative biliary culture (IBC) taken at the time of the transection of the biliary tract in PD. Also, if the patient had had PBD before the surgery, the date of the PBD had to be known to assess the possible effects of the time delay between PBD and PD on the bacterial growth in bile.

Study IV consisted of 67 patients who had had a suspicion of GP and had been treated in the study hospitals between January 2005 and December 2015. The eligible patients were screened from the electronic medical records via a computerised search. The search included the keywords “groove*” and “paraduod*”, the latter referring to “paraduodenal pancreatitis”, which is one of the most common synonyms for GP. The asterisk (*) means that any character chain after the initial word is included in the search results. All patients brought up in the search results were then manually reviewed and only the patients with the keywords used in the context of pancreas were included.

4.4 DEFINITIONS, DATA COLLECTION, INCLUSION CRITERIA AND INTERVENTIONS

4.4.1 DEFINITIONS

In all studies, the comorbidities were recorded according to the Charlson Comorbidity Index (Charlson et al., 1987). In **Studies I-III,** the postoperative complications were recorded using CD classification and a CCI score was calculated for each patient (Dindo et al., 2004; Slankamenac et al., 2014). CD class 2 or worse was considered clinically significant and CD class 3b or worse as a major complication. Pancreatic resection-associated complications (POPF, DGE, PPH, bile leakage, chyle leakage) were classified based on ISGPS and the International Study Group of Liver Surgery's consensus statements (Wente et al., 2007; Wente et al., 2007; Koch et al., 2011; Bassi et al., 2017; Besselink et al., 2017). The updated ISGPS definition for POPF was published after the beginning of **Study I,** hence the POPFs are reported as grades A, B and C in **Study I**. In **Study III,** the updated definition of POPF was used and only grades B and C were noted. In **Studies I-III,** the risk of POPF was calculated during the analysis of the data using the Fistula Risk Score by Callery et al., the Modified Fistula Risk Score by Kantor et al. or the updated alternative Fistula Risk Score (ua-FRS) by Mungroop et al. (Callery et al., 2013; Kantor et al., 2017; Mungroop et al., 2019).

For the long-term outcomes reported in **Study II,** the status of adjuvant chemotherapy, recurrences of cancers and pNENs and the cause and date of death were recorded. In **Study II,** the overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS) of the patients randomised in the HYPAR trial were reported. For OS, the possible death of any cause of a patient during the 5-year period after the operation was recorded. For DFS, the time between surgery and recurrence was recorded and, for DSS, the deaths caused by the condition needing pancreatic surgery in the first place were recorded and other causes of deaths were censored. All follow-up data were gathered from the electronic medical records. If the medical records were unavailable, incomplete or unclear, a study nurse contacted the patients to complete the follow-up data. If the 5-year follow-up was still not obtainable, the patient was censored from the respective survival analysis.

4.4.2 INTERVENTIONS

The pancreatic resections in all the studies were performed by experienced pancreatic surgeons at Helsinki University Hospital. It was intended that all patients would receive preoperative antibiotic prophylaxis 30-60 minutes before the incision. A routinely used antibiotic was second-generation cephalosporin if there were no contra-indications for this drug. All PDs were performed openly, DPs and enucleations either openly or laparoscopically (including robot-assisted laparoscopy) and other operations openly (median pancreatectomy, transduodenal papillectomy). Two drains were routinely left after PD and one after other types of pancreatectomies. The removal of drains was based on the amylase level of the drain output on the 3rd postoperative day and the quantity of drain output. All patients underwent an ERAS pathway, which was deviated from if needed based on the patient's postoperative course.

The eligible patients in **Studies I** and **II** were randomised by a study nurse and the study drug was blinded from the treating surgeons and researchers until the primary outcomes had been analysed. The included patients received either pasireotide or hydrocortisone in a ratio of 1:1. They received the first dose of the study drug on the morning of the operation. The patients receiving pasireotide were administered 900 µg subcutaneously twice a day until the evening of the 6th postoperative day (14 doses), and the patients receiving hydrocortisone were administered 100 mg of hydrocortisone intravenously three times per day until the evening of the 2nd postoperative day (9 doses). The dosages of the study drugs were based on previously published trials comparing these study drugs to placebo (Allen et al., 2014; Laaninen et al., 2016).

4.4.3 INCLUSION CRITERIA AND DATA COLLECTION

In **Studies I** and **II,** only patients with a high risk of POPF were included. If the patient underwent PD, the risk of POPF was considered to be high if the pancreas was soft and the pancreatic duct not dilated at the site of the transection of the pancreatic parenchyma. All other types of pancreatic resections (DP, enucleation, median pancreatectomy) were always considered a high-risk operation for POPF. Preoperative exclusion criteria were an atrophic pancreas or dilated pancreatic duct of 4 mm or more at the transection site of the pancreas in the preoperative imaging studies of patients undergoing PD, since these indicate a low risk of POPF. Other preoperative exclusion criteria were a planned TP, a patient's contraindication to either of the study drugs (i.e. allergy), age younger than 18 years or if written informed consent had not been obtained. In addition, intraoperative exclusion criteria were set because the patients were randomised preoperatively since they received the first dose of the study drug before surgery. These intraoperative exclusion criteria were: a TP was performed despite the original plan of partial pancreatectomy or no pancreatic resection was performed (i.e. disseminated cancer). Also, if a randomised patient undergoing PD was found to have a firm pancreas or the width of the pancreatic duct was 4 mm or more at the transection site, the patient was intraoperatively excluded due to low risk of POPF.

The primary outcome of **Study I** was CCI within 30 postoperative days, and the secondary outcomes were clinically significant complications (CD class ≥ 2), POPF, DGE, PPH, length of stay and readmissions during the first 30 postoperative days. For a subgroup analysis of **Study I,** the patients were divided into those who had undergone PD or DP. For the subgroup analysis of **Study II,** the patients were further divided into subgroup of malignancies to assess the effect of study drugs in survival of cancer patients.

In **Study III,** all patients undergoing PD were included regardless of the risk of POPF. However, since this study analysed the bacterial growth in IBC and its risk factors, patients were excluded if an IBC was not obtained. All data on pre- and postoperatively administered antibiotics were gathered. IBCs were obtained during the PD at the time of the transection of the biliary tract. All the bacteria in IBCs and their resistance and sensitivity profiles were recorded. The 30-day postoperative morbidity and mortality was gathered including all SSIs, and all further bacterial cultures from fluid collections and SSIs during the postoperative course were obtained. All bacterial species obtained from the culture reports were categorised as either resistant or sensitive to second-generation cephalosporins based on the known resistance profiles of these bacteria or based on the bacterial cultures' sensitivity and resistance reports. SSIs were classified according to Centres for Disease Control and Prevention criteria into superficial, deep or organ/space SSIs (CDC, 2021).

For the analysis of the risk factors for resistant bacterial growth in IBC, the status of the patients' PBD was recorded. In **Study III,** the patients were divided into two groups based on whether or not they had undergone PBD. For further analysis of the time delay between the PBD and surgery, the patients who had undergone PBD were divided into those who eventually underwent PD in the following two months after PBD and those who underwent PD later than two months after PBD.

The retrospective study cohort of **Study IV** was formed after a computerised search as previously described in chapter 4.3 "Patients". There were two main focuses in **Study IV** of which the first was to assess the diagnostic challenges of a GP and the second to assess the natural course and treatment outcomes of GP. For the first part, the medical imaging studies of the patients' with a suspicion of GP were screened blindly (without the knowledge of the final diagnosis) by two experienced radiologists specialised in gastrointestinal imaging who had oriented in the radiological criteria of GP described previously (Kalb et al., 2013; Arora et al., 2014). Based on the previously described features of GP they categorised the patients in three groups: 1) "certain GP", 2) possible GP and 3) "other". This data combined with the patients' known final diagnosis was then used to analyse the radiological diagnostic challenges of GP.

For the second part of **Study IV**, four criteria were determined of which at least one had to be met for a patient who had had a suspicion of GP to be considered to have actually had GP. These criteria were as follows: GP confirmed 1) from a histopathological specimen by a pathologist, 2) by a multidisciplinary team with a statement in the patient's medical records, 3) by both of the radiologists classifying the imaging studies as "certain GP" and the patient had signs of pancreatitis and 4) by one radiologist stating "certain GP" and the other "possible GP" and an experienced surgeon had confirmed the possibility of GP in the patient's medical records. The laboratory parameters, the development of the symptoms, the treatments and their outcomes in this group of patients were then analysed to form an understanding of GP as a disease.

4.5 STATISTICAL ANALYSES

All statistical analyses were done with SPSS versions 25 to 29 (IBM, Armonk, NY). In all studies, the categorical variables were always presented as frequencies and proportions (%). Continuous variables were presented as mean and standard deviations (SD), if the variable was normally distributed or as medians and interquartile ranges (IQR) if the variable was non-normally distributed. Chi-square and Fischer's exact tests were used to test differences between the categorical variables. For testing the differences between continuous variables, either an independent T-test or Mann-Whitney U-test was used if there were two groups, and a Kurskal-Wallis test if there were more than two groups. A two-sided p-value of <0.05 was considered statistically significant in all the aforementioned tests.

Study I was a non-inferiority trial with the primary outcome of CCI. The threshold for non-inferiority was set at 9 points of CCI, since a 10-point increase in CCI equals one CD grade difference in the complication burden. SD was estimated to be 20 based on previously published data (Slankamenac et al., 2014) and 124 patients were calculated to have 80% power to show the non-inferiority of hydrocortisone with a one-sided α level of 0.05. Non-inferiority was met if the lower limit of 90% two-sided confidence interval (CI) (equal to 95% one sided CI) of the CCI mean differences between the study drug groups was not lower than -9 when hydrocortisone was compared to pasireotide. Non-inferiority was tested only against the primary outcome.

In **Study II,** the Kaplan-Meier survival analysis was used to report OS, DFS and DSS and the differences between the groups were tested with a log rank test. A two-sided p-value of <0.05 was considered statistically significant.

In **Study III,** the risk factors for second-generation cephalosporin resistance and SSIs were analysed by logistic regression analysis. First, a univariable logistic regression was performed and then a multivariate analysis with all variables having a p-value less than 0.20 in univariable analysis, and some previously described risk factors for the respective study variable were added in a multivariate logistic regression. All variables with possible collinearity were screened before the multivariate analysis and only one of these risk factors was included in the multivariate analysis. The risk factors were presented as an odds ratio with a 95% two-tailed CI. A two-sided p-value of <0.05 was considered statistically significant.

The **Study IV** had more of a descriptive nature with no other special statistical method than described in the first paragraph of this chapter.

4.6 ETHICAL APPROVALS AND STUDY PERMISSIONS

All studies were reviewed and approved by Helsinki University Hospital's institutional review board, which was sufficient for **Studies III** and **IV** due to their retrospective natures. In addition to that, **Studies I** and **II** were approved by the Finnish National Committee on Medical Research Ethics, the Finnish Medicines Agency, and Helsinki University Hospital's ethical committee, since the HYPAR trial was a randomised trial comparing different study drugs. All randomised patients gave written consent in **Studies I** and **II** and the HYPAR trial was also registered with clinicaltrials.gov (identifier: NCT02775227) and The EU Clinical Trials Register (identifier: 2016-000212-16).

5 RESULTS

5.1 STUDIES I AND II

5.1.1 PATIENT AND OPERATIVE CHARACTERISTICS

In the HYPAR trial, a total of 281 patients were assessed for eligibility and 168 were randomised to receive perioperatively either pasireotide or hydrocortisone. Forty-two of the randomised patients were further excluded intraoperatively based on predetermined exclusion criteria. Twenty-five of these 42 patients were excluded since they had not undergone pancreatic resection, 14 were deemed to be at low risk of pancreatic fistula (firm pancreas and/or dilated pancreatic duct), one due to concomitant somatostatin analogue use and two for logistic reasons. The final study groups consisted of 126 patients, 63 of whom were in the pasireotide group and 63 in the hydrocortisone group. As a randomised trial should be, the patient and operative characteristics were similar between the study groups. All patients were at least at intermediate risk of POPF, and the mean fistula risk scores indicated that most were at a high risk of POPF as was meant to be. These characteristics are summarised in Tables 12 and 13.

Table 12. Patient characteristics in **Studies I** and **II**.

	Pasireotide (n=63)	Hydrocortisone (n=63)
Median age, years (IQR)	64 (56-70)	67 (56-73)
Sex, male, no. (%)	35 (55.6)	25 (39.7)
Mean Body Mass Index (SD), kg/m^2	27.3 (3.6)	26.8 (4.3)
ASA physical status, no. (%)		
1	2 (3.2)	2 (3.2)
2	30 (47.6)	29 (46.0)
3	29 (46.0)	29 (46.0)
4	2 (3.2)	3 (4.8)
Charlson Comorbidity Index, no (%)		
Mild (0-2)	45 (71.4)	37 (58.7)
Moderate (3-4)	15 (23.8)	18 (28.6)
Severe (5->)	3 (4.8)	8 (12.7)
Mean Charlson Comorbidity Index (SD)	2.0 (1.4)	2.4 (1.9)
No comorbidities	7 (11.1)	11 (17.5)

SD, standard deviation; ASA, American Association of Anesthesiologist

Table 13. Operative characteristics of patients in **Studies** I and **II**.

	Pasireotide (N=63)	Hydrocortisone (N=63)
Resection type, no. (%)		
Pancreatoduodenectomy	30 (47.6)	27 (42.9)
Distal pancreatectomy	30 (47.6)	30 (47.8)
Open distal pancreatectomy	8 (26.7)	4 (13.3)
Laparoscopic distal	16 (53.3)	22 (73.3)
Laparoscopic distal - converted	6 (20.0)	4 (13.3)
Other[a]	3 (4.8)	6 (9.5)
Blood loss, ml, mean (SD)	550 (545)	572 (757)
Pancreatic duct width, mm, mean (SD)[b]	2.7 (1.3)	2.7 (1.6)
Pathology, no. (%)		
Pancreatic ductal adenocarcinoma	14 (22.2)	13 (21%)
Cholangiocarcinoma	4 (6.3)	5 (7.9)
Papilla adenocarcinoma	5 (7.9)	3 (4.8)
Duodenal adenocarcinoma	3 (4.8)	1 (1.6)
IPMN	5 (7.9)	7 (11.1)
MCV	4 (6.3)	4 (6.3)
PNEN	10 (15.9)	17 (27.0)
SPN	4 (6.3)	0
Serous cystadenoma	1 (1.6)	3 (4.8)
Papilla adenoma	2 (3.2)	1 (1.6)
Dysplasia (excl. papilla)	5 (7.8)	6 (9.5)
Metastasis of another carcinoma	2 (3.2)	2 (3.2)
Other[c]	4 (6.3)	1 (1.6)
Fistula Risk Score, mean (SD)[b]	6.2 (1.7)	6.4 (1.8)
Modified Fistula Risk Score, mean (SD)[b]	8.3 (1.1)	7.8 (1.4)
ua-FRS, mean (SD)[b]	29.3 (10.9)	27.3 (11.3)

IPMN, intraductal papillary mucinous neoplasia; MCN, mucinous cystic neoplasia; PNEN, pancreatic neuroendocrine tumour; SPN, solid pseudopapillary neoplasm; ua-FRS, updated alternative Fistula Risk Score

[a]3 enucleations in the pasireotide group and 3 enucleations, 2 median pancreatectomies and 1 transduodenal papillectomy in the hydrocortisone group.

[b] Only for patients undergoing pancreatoduodenectomy

[c] 1 pancreatic cystadenocarcinoma, 1 poorly differentiated pancreatic cancer, 1 benign choledochal cyst and 1 lymphoepithelial cyst in the pasireotide group. 1 adenosquamous carcinoma of the pancreas in the hydrocortisone group.

5.1.2 PRIMARY AND SECONDARY OUTCOMES OF THE HYPAR TRIAL

The primary and secondary outcomes are described in Table 11. Briefly the mean CCI (SD) was 23.94 (17.06) in the pasireotide and 30.11 (20.47) in the hydrocortisone group. The mean difference was -6.16 (95% CI (-12.81 to 0.48), p=0.07) and the two-tailed 90% CI was -11.73 to -0.60. The lower limit of the two-tailed 90% CI crossed the prespecified -9 point threshold for non-inferiority, which meant that the non-inferiority could not be demonstrated. Secondary outcomes were similar between the groups with the exception of PPH grades B or C, which were significantly more prevalent in the hydrocortisone group (0 vs. 6 (9.5%), p=0.01) (Table 14).

Table 14. Primary and secondary outcomes of the HYPAR trial

	Pasireotide (n=63)	Hydrocortisone (n=63)	p-value
Primary outcome			
CCI, mean (SD)	23.94 (17.06)	30.11 (20.47)	0.07
Mean difference (95% CI)	-6.16 (-12.81 to 0.48)		
Secondary outcomes			
CD ≥ 2 complications, n (%)	43 (68.3)	44 (70.0)	0.85
CD ≥ 3b complications, n (%)	5 (7.9)	10 (15.9)	0.17
POPF, grade B/C, n (%)	13 (20.6)	14 (22.2)	0.83
DGE, grade B/C, n (%)	6 (9.5)	5 (7.9)	0.75
PPH, grade B/C, n (%)	0	6 (9.5)	**0.01**
Length of stay, median (IQR), days	8 (7-13)	10 (6-14)	0.95
Readmission, n (%)	7 (11.1)	10 (15.9)	0.46

CCI, comprehensive complication index; SD, standard deviation; CI, confidence interval; CD, Clavien-Dindo; POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying; PPH, postpancreatectomy haemmorhage; IQR, interquartile range

In the subgroup analysis of PD and DP, there was no difference in CCI in the subgroup of PDs. In PDs, the mean difference of CCI between the groups was -5.51 (95% CI (-15.46 to 4.12), p=0.28). However, there was a statistically significant difference in CCI in the subgroup of DPs, where the mean difference of CCI was -10.25 (95% CI (-19.34 to -2.12), p=0.03) (Table 15).

Table 15. Primary outcomes in the subgroup analysis.

PD (N=57)	**Pasireotide (n=30)**	**Hydrocortisone (n=27)**	**p-value**
Primary outcome			
CCI, mean (SD)	32.39 (17.83)	37.90 (17.56)	0.28
Mean difference (95% CI)	-5.51 (-15.46 to 4.21)		
DP (N=60)	**Pasireotide (n=30)**	**Hydrocortisone (n=30)**	
Primary outcome			
CCI, mean (SD)	16.04 (11.94)	26.28 (21.76)	**0.03**
Mean difference (95% CI)	-10.25 (-19.34 to -2.12)		

PD, pancreatoduodenectomy; CCI, comprehensive complication index; SD, standard deviation; CI, confidence interval; DP, distal pancreatectomy

5.1.3 LONG-TERM OUTCOMES OF THE HYPAR TRIAL

The tertiary outcomes of the HYPAR trial were determined as OS, DFS and DSS at 1, 5 and 10 years. In **Study II,** the 1- and 5-year results were reported. The 10-year results are not yet obtainable. Eleven (8.7%) of the 126 study patients were lost during the follow-up period of five years. There were more patients lost in the pasireotide group (9 (14.3) vs. 2 (3.2), p=0.027).

In the whole study population, there were no differences between the pasireotide and hydrocortisone groups in the OS, DFS or DSS during the first five years after surgery (Figure 6). In the subgroup analyses of the patients who had a malignancy, OS, DFS and DSS were also convergent (Figure 7). The number of different malignancies in both groups are displayed in the Table 16.

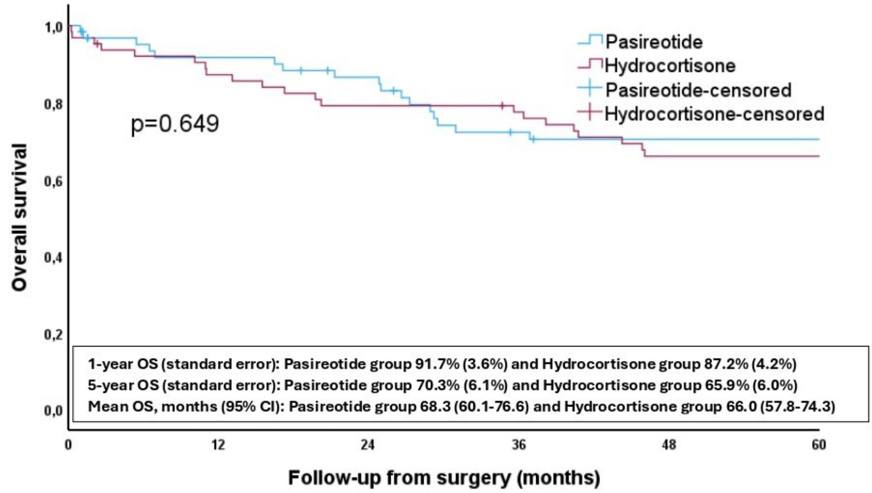
Table 16. Malignancies in **Study II**

Malignancies (N=84)	Pasireotide (n=41)	Hydrocortisone (n=43)
PDAC	14	13
Cholangiocarcinoma	4	5
Papilla adenocarcinoma	5	3
Duodenal adenocarcinoma	3	1
Mucinous adenocarcinoma originating IPMN	1	1
PNEN	10	17
Metastasis of another cancer	2	2
Pancreatic cystadenocarcinoma	1	0
Poorly differentiated pancreatic cancer	1	0
Adenosquamous carcinoma of the pancreas	0	1

PDAC, pancreatic ductal adenocarcinoma; PNEN, pancreatic neuroendocrine neoplasm.

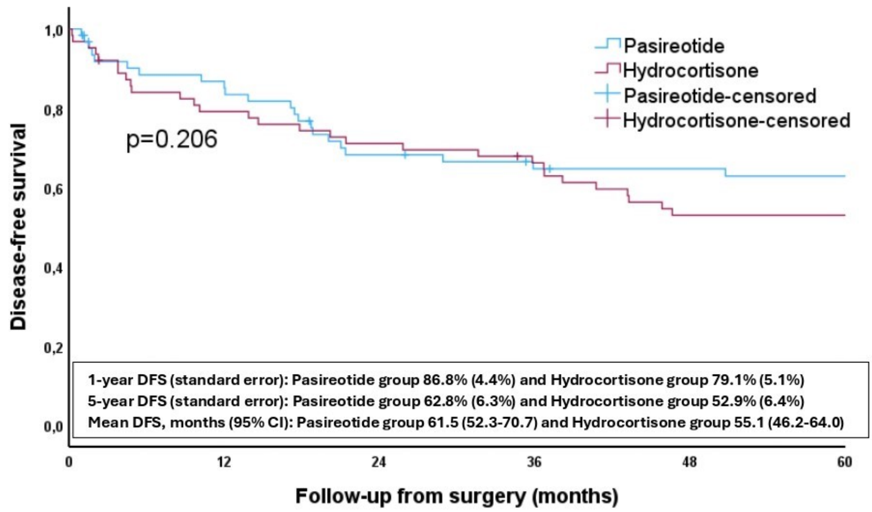
Figure 6. OS, DFS and DSS of all patients in the HYPAR trial

All patients (n=126)



Number at risk – Overall survival

Pasireotide	63	54	49	39	37	37
Hydrocortisone	63	54	49	47	40	40
Time in months	0	12	24	36	48	60

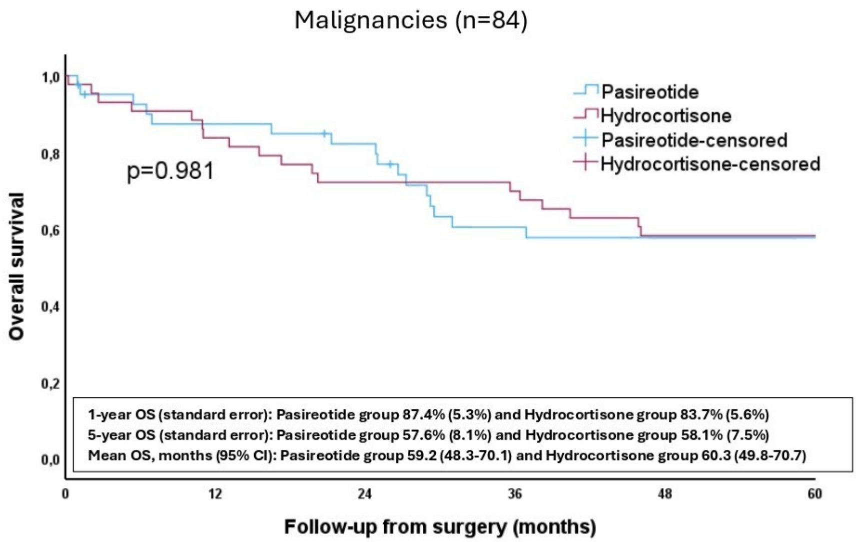


Number at risk – Disease-free survival

Pasireotide	63	52	40	36	35	34
Hydrocortisone	63	49	44	40	32	32
Time in months	0	12	24	36	48	60

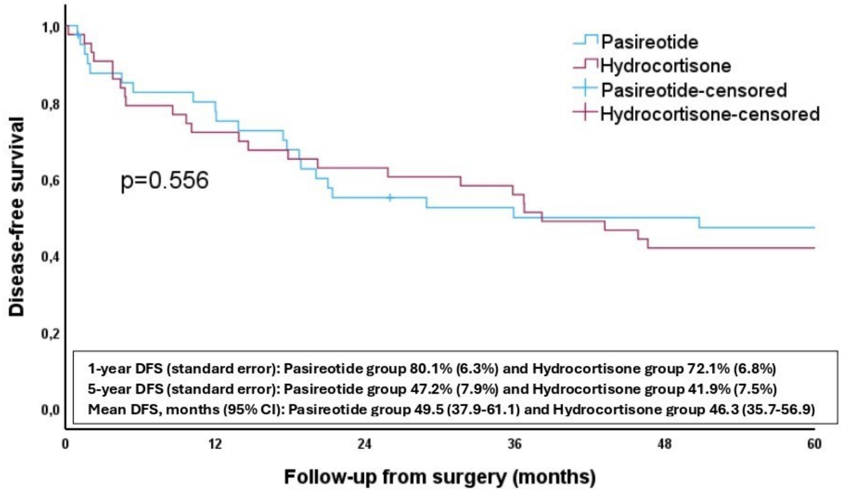
OS, overall survival; DFS, disease-free survival.

Figure 7. OS, DFS and DSS of patients with malignancies in the HYPAR trial



Number at risk – Overall survival

Pasireotide	41	34	31	22	21	21
Hydrocortisone	43	36	31	30	25	25
Time in months	0	12	24	36	48	60



Number at risk – Disease-free survival

Pasireotide	41	32	22	19	19	18
Hydrocortisone	43	31	27	24	18	18
Time in months	0	12	24	36	48	60

OS, overall survival; DFS, disease-free survival.

Based on these results, the patients in both of the study drug groups of the HYPAR trial had similar long-term outcomes.

5.2 STUDY III

5.2.1 PATIENT CHARACTERISTICS

A total of 376 patients were assessed for eligibility for this study. Fifteen patients were excluded from the analyses due to missing data on IBC (n=13) or the date of PBD (n=2). The remaining 361 patients were divided into two groups based on whether or not they had undergone PBD. One-hundred-and-seven patients had not undergone PBD forming the “no PBD” group and 254 patients had undergone PBD and formed the “PBD” group. For the analysis of the effects of the time delay between PBD and PD, the “PBD” group was further divided into subgroups of patients undergoing PD within two months (“PBD < 2 months” group) and two months or later after PBD (“PBD ≥ 2 months” group). The patient characteristics are shown in Table 17. The only difference between the “no PBD” and “PBD” groups were that there were more malignancies in the “PBD” group.

Table 17. Patient characteristics in **Study III**.

	no PBD (n=107)	**PBD** (n=254)	**p-value**
Age, median (IQR), y	67 (60-73)	68 (61-73)	0.755
Sex, male (%)	57 (53.3)	148 (58.3)	0.381
BMI, median (IQR), kg/m²	26.5 (24.2-28.7)	25.3 (22.9-28.1)	0.061
Smoking, n (%)*	23 (24.0)	58 (22.8)	0.078
Cancer	76 (71.0)	250 (98.4)	**<0.001**
Local	73 (68.2)	244 (96.1)	
Metastatic	3 (2.8)	6 (2.4)	
Charlson Comorbidity Index category, N (%)			0.204
Mild (0-2)	61 (57.0)	132 (52.0)	
Moderate (3-4)	33 (30.8)	101 (39.8)	
Severe (≥5)	13 (12.1)	21 (8.3)	
ASA physical status, - N (%)			
1	1 (0.9)	4 (1.6)	
2	38 (35.5)	79 (31.1)	
3	56 (52.3)	162 (63.8)	
4	12 (11.2)	9 (3.5)	
ASA physical status score, median (IQR)	3 (2-3)	3 (2-3)	0.097

PBD, preoperative biliary drainage; IQR, interquartile range; BMI, body mass index; ASA, American Association of Anesthesiologist

The operative characteristics of the patients are presented in Table 18. In the “PBD” group, there were more vascular resections, blood loss and a longer operative time. The median ua-FRS was statistically significantly higher in the "no-PBD" group (38.1 vs. 19.8, p<0.01) and there were more clinically relevant POPFs in the "no PBD" group (14 (13.1%) vs. 21 (8.3%)), but this difference did not reach statistical significancy (p=0.16). The "No PBD" group also had statistically significantly more postoperative bile leakages (p<0.001) and more frequently antibiotics during the postoperative course (p=0.04).

Table 18. Operative and postoperative characteristics of patients in **Study III**.

	no PBD (n=107)	**PBD** (n=254)	**p-value**
Neoadjuvant therapy, n (%)	18 (16.8)	63 (24.8)	0.097
Preop. antibiotic prophylaxis, n (%)			0.305
2nd gen. cephalosporin only	93 (86.9)	217 (85.4)	
other	14 (13.1)	37 (14.6)	
Procedure – n (%)			
Vascular resection	22 (20.6)	90 (35.4)	**0.005**
Blood loss, median (IQR), mL	550 (300-900)	700 (400-1250)	**0.002**
Operative time, median (IQR), minutes	317 (278-372)	342 (286-408)	**0.037**
ua-FRS, median (IQR)[a]	38.1 (23.9-54.1)	19.8 (11.7-41.6)	**<0.001**
SSI, n (%)	36 (33.6)	64 (25.2)	0.101
CCI, median (IQR)	30.8 (20.9-39.5)	29.3 (20.9-37.2)	0.127
POPF, grades B or C, n (%)	14 (13.1)	21 (8.3)	0.158
DGE, any grade, n (%)	36 (33.6)	85 (33.5)	0.974
PPH, any grade, n (%)	7 (6.5)	17 (6.7)	0.958
Postop. bile leak, any grade, n (%)	12 (11.2)	6 (2.4)	**<0.001**
Postop. chyle leak, any grade, n (%)	16 (15.0)	47 (18.5)	0.417
90 days postoperative mortality, n (%)	3 (2.8)	4 (1.6)	0.427
Postop. antibiotic treatment - n (%)			
Any	92 (86.0)	194 (76.4)	**0.040**
Only 2nd gen. cephalosporin	43 (40.2)	96 (37.8)	0.670
Other[d]	47 (43.9)	95 (37.4)	0.247

2nd gen, second-generation; IQR, interquartile range; ua-FRS, updated alternative Fistula Risk Score (Mungroop et al., 2021); SSI, surgical site infection; CCI, comprehensive complication index; POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying; PPH, postpancreatectomy haemorrhage

[a]1 patient's data on ua-FRS was missing in "no PBD" and 2 patients' in "PBD" group.

5.2.2 BACTERIAL ANALYSIS OF INTRAOPERATIVE BILIARY CULTURES

There was bacterial growth in the IBC of 281 (79%) of the patients. Positive bacterial culture was much more prevalent if the patient had undergone PBD. In the "PBD" group, almost all patients had bacterial growth in IBC compared to only a third of patients in the "no PBD group (251/254 of the patients (99%) vs 34/107 (32%) of the patients). Interestingly, only ten patients of 34 who had bacterial growth in IBC in the "no PBD" group had undergone a prior cannulation of the common bile duct without a stent placement, meaning that 24 of these 34 patients had spontaneously unsterile bile. The most common bacteria in all the patients' IBC were *Enterococcus* spp, *Enterobacter* spp and *Klebsiella* spp, all of which are or have the ability to turn into second-generation cephalosporin resistant.

Second-generation cephalosporin resistance was found in half of the patients IBCs [183 out of 361 patients (51%)] and the proportion of patients with second-generation resistant bacteria in IBC was markedly higher in the "PBD" group (67%) than in the "no PBD" group (12%). If the time delay between PBD and surgery extended, the probability of second-generation cephalosporin-resistant bacteria in IBC increased being 58% in the "PBD < 2 months" group and 74% in the "PBD ≥ 2 months" group.

5.2.3 RISK FACTORS FOR SECOND-GENERATION CEPHALOSPORIN RESISTANCE

The risk factors for second-generation cephalosporin resistance were analysed with univariable and multivariate logistic regression analyses. In univariable analysis, the risk of second-generation cephalosporin resistance was 14 times higher if the patient had undergone a PBD. The risk of resistance increased even further if the time delay between PBD and surgery got longer, being more than 20-fold if the time delay was two months or more. After the multivariate analysis, PBD remained as the only statistically significant risk factor for second- generation cephalosporin resistance (OR 22.58 (95% CI (9.61-53.01), $p<0.001$) (Table 19).

Table 19. Risk factors for second-generation cephalosporin resistance.

Second-generation cephalosporin resistance in IBC (n=183)			
Univariable analysis			
	n (%)	**OR (95% CI)**	**p-value**
PBD (n=254)	170 (66.9)	**14.63 (7.75-27.64)**	**<0.001**
Neoadjuvant (n=81)	46 (56.8)	1.37 (0.83-2.26)	0.214
Sex, male (n=205)	109 (53.2)	0.80 (0.52-1.21)	0.795
Age, median (IQR)	68 (61-72)	1.01 (0.99-1.03)	0.495
no PBD (n=107)	13 (12.1)	reference	
PBD < 2 months (n=109)	63 (57.8)	**9.90 (4.95-19.81)**	**<0.001**
PBD ≥ 2 months (n=145)	107 (73.8)	**20.36 (10.23-40.51)**	**<0.001**
Second-generation cephalosporin resistance in IBC (n=183)			
Multivariate analysis			
	n (%)	**OR (95% CI)**	**p-value**
PBD (n=254)	170 (66.9)	**22.58 (9.61-53.01)**	**<0.001**

IBC, intraoperative biliary culture; OR, odds ratio; PBD, preoperative biliary drainage

5.2.4 SURGICAL SITE INFECTIONS AND THE RISK FACTORS

A total of 100 patients (28%) had an SSI and the organ/space SSIs were the most common SSIs occurring in 79 patients. Organ/space SSIs were more prevalent in "no PBD" group [30/107 (28%)] than in the "PBD" group [49/254 (19%)] while the other SSIs had similar prevalence between the groups. In univariable analysis, the risk factors for SSIs were male sex and overweight, and the patients in the "PBD ≥ 2 months"-group were at lower risk of SSIs (Table 20). In the whole study population, the second-generation cephalosporin resistance was not a risk factor for SSIs (Table 20) but, in the subgroup analyses, the second- generation cephalosporin resistance stood out as a risk factor for SSIs in the "PBD ≥ 2 months" group (OR 4.14 (95% CI, 1.18-14.51), p=0.027) (Table 21).

Table 20. Risk factors for SSIs.

Pancreatoduodenectomies (n=361)			
SSI (n=100)			
Univariable analysis			
	n (%)	**OR (95%)**	**p-value**
2nd generation CR (n=183)	51 (27.9)	1.02 (0.64-1.61)	0.942
Neoadjuvant treatment (n=81)	16 (19.8)	0.57 (0.31-1.05)	0.072
PBD (n=254)	64 (25.2)	0.66 (0.41-1.09)	0.103
Sex, male (n=205)	71 (34.6)	**2.32 (1.41-3.81)**	**0.001**
Age, median (IQR)	67 (61-72)	0.99 (0.97-1.02)	0.494
Diabetes, (n=78)	16 (20.5)	1.64 (0.89-3.00)	0.111
no PBD (n=107)	36 (33.6)	reference	
PBD < 2 months (n=109)	33 (30.3)	0.86 (0.48-1.52)	0.596
PBD ≥ 2 months (n=145)	31 (21.4)	**0.54 (0.31-0.94)**	**0.030**
BMI, n (%)			
20-25 kg/m2 (n=128)	23 (18.0)	reference	
<20 kg/m2 (n=24)	3 (12.5)	0.65 (0.18-2.37)	0.516
25-30 kg/m2 (n=158)	58 (36.7)	**2.65 (1.52-4.61)**	**0.001**
>30 kg/m2 (n=51)	16 (31.4)	2.09 (0.99-4.29)	0.053
Multivariate analysis			
	n (%)	**OR (95%)**	**p-value**
Sex, male (n=205)	71 (34.6)	**2.36 (1.40-3.96)**	**0.001**
BMI, n (%)			
20-25 kg/m2 (n=128)	23 (18.0)	reference	
<20 kg/m2 (n=24)	3 (12.5)	0.74 (0.20-2.75)	0.656
25-30 kg/m2 (n=158)	58 (36.7)	**2.59 (1.47-4.56)**	**0.001**
>30 kg/m2 (n=51)	16 (31.4)	**2.57 (1.19-5.57)**	**0.016**

SSI, surgical site infection; OR, odds ratio; CR, cephalosporin resistance; PBD, preoperative biliary drainage; BMI, body mass index

Table 21. Risk factors for SSIs in the subgroups based on the time delay between PBD and surgery.

Univariable analysis of the subgroups			
	No PBD (n=107)		
	SSI (n=36)		
	n (%)	**OR (95%)**	**p-value**
2nd generation CR (n=13)	6 (41.2)	1.83 (0.57-5.91)	0.313
	PBD < 2 months (n=109)		
	SSI (n=33)		
	n (%)	**OR (95%)**	**p-value**
2nd generation CR (n=63)	17 (27.0)	0.69 (0.30-1.58)	0.382
	PBD ≥ 2 months (n=145)		
	SSI (n=31)		
	n (%)	**OR (95%)**	**p-value**
2nd generation CR (n=107)	28 (26.2)	**4.14 (1.18-14.51)**	**0.027**

SSI, surgical site infection; PBD, preoperative biliary drainage; OR, odds ratio; CR, cephalosporin resistance;

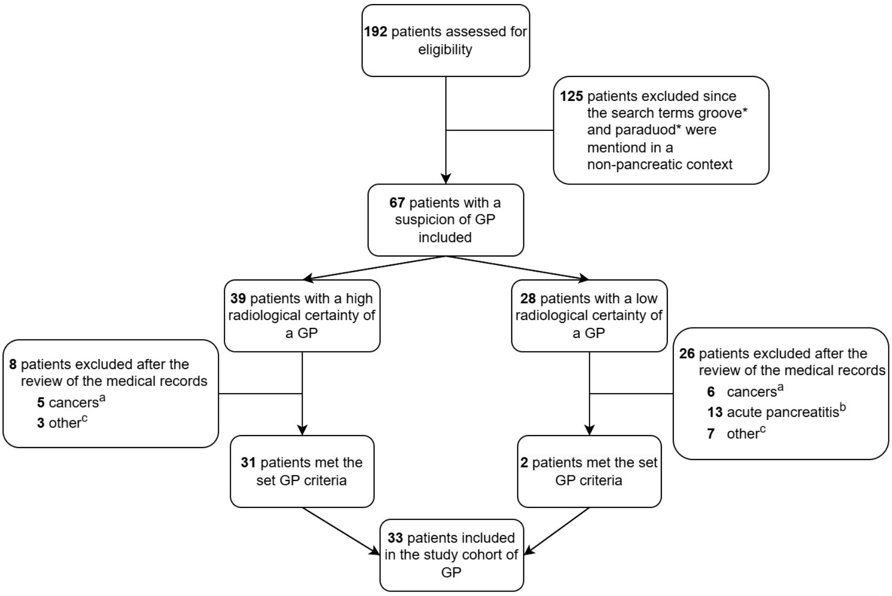
5.3 STUDY IV

5.3.1 PATIENT CHARACTERISTICS

The computerised search from the electronic medical database brought up in total of 192 patients. In 125 patients' medical records, the term "groove*" or "paraduod*" was mentioned in a context that was unrelated to the pancreas and was excluded. The remaining 67 patients formed the study population of patients with a suspicion of GP.

The radiological imaging of these 67 was then reviewed blindly by the two experienced radiologists. They categorised the patients into three categories ("certain GP", "possible GP" or "other"). If both radiologists considered the patient as "certain GP" or one considered the patient "certain GP" and the other "possible GP", the certainty of GP was considered high. A high certainty for radiological GP diagnosis was set in 39 patients and the remaining 28 were considered as low certainty for GP. After reviewing the medical records, eight of these 39 patients with a high radiological certainty for GP did not meet the set criteria for GP (paragraph 4.4 "Definitions, data collection and interventions"). Five of these eight patients whom the radiologists categorised as high certainty for GP, but did not meet the set criteria for GP, did in fact have a histologically confirmed pancreatic cancer. In addition to the remaining 31 patients with a high radiological certainty for GP and who met the set criteria for GP, two patients of low radiological certainty for GP were considered as GP by the set criteria. These 33 patients were considered to have had GP, and they formed the study group of GP patients (Figure 8).

Figure 8. Flow chart of patient inclusion in **Study IV**



GP, groove pancreatitis

[a] Ten pancreatic ductal adenocarcinomas and one gastric cancer

[b] Excluding groove pancreatitis

[c] Three chronic pancreatitis', three peptic ulcer diseases, two biliary infections, one abdominal trauma and one spontaneous bacterial peritonitis

The basic characteristics of these 33 GP patients are shown in Table 22. The typical GP patient was a middle-aged male with only a few or no comorbidities and a habit of smoking and moderate to heavy use of alcohol.

Table 22. Basic characteristics of GP patients.

	GP (n = 33)
Median age, years (IQR)	55 (42 – 62)
Sex, male, n (%)	26 (78.8)
Mean Body Mass Index (SD), kg/m^2	24,9 (4,3)[a]
No comorbidities, n (%)	17 (51.5)
Charlson Comorbidity Index	
Mild (0-2)	29 (87.9)
Moderate (3-4)	2 (6.1)
Severe (>5)	2 (6.1)
Mean Charlson Comorbidity Index, (SD)	1.0 (1.7)
Alcohol and tobacco, n (%)	
Heavy alcohol consumption[a]	22 (66.7)
Moderate alcohol consumption	11 (33.3)
Total abstinence from alcohol	0
Smoker	28 (84.8)
Previous pancreatitides, n (%)	
Any	13 (39.4)
1	3 (9.1)
2	4 (12.1)
3	3 (9.1)
4 or more	3 (9.1)

GP, groove pancreatitis; IQR, interquartile range; SD, standard deviation
[a]The limit between a heavy drinker and a moderate one was set at 24 consumed units of alcohol per week. If no exact data was available, the patient was considered a heavy user if there were signs of harmful alcohol consumption (i.e. cerebellar degeneration or multiple rehabilitation episodes).

5.3.2 DIAGNOSTIC CHALLENGES OF GROOVE PANCREATITIS

The symptoms of the GP patients varied a lot, and the only more frequent symptom was abdominal pain, which was present in 29 of 33 patients (88%). All other symptoms such as nausea, vomiting, jaundice or weight loss appeared in less than half of the patients. Also, there were no distinct laboratory parameters in GP patients, but almost all had elevated CRP and blood leukocyte levels (97% and 81% of the patients) and two thirds (22 of 33) had elevated serum alanine aminotransferase (ALAT). Elevated tumour markers, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were observed in one third of the patients. The median abnormal level of CEA was 6.7 (IQR, 5.7 – 10.6) and for CA19-9 it was 86 (IQR, 40 – 314).

The radiological findings were also quite dispersed. The only more frequent finding was cystic lesions in the groove area, which were present in 26 of the 33 patients (79%). Other findings such as thickening of the duodenal wall or obstruction of the biliary, pancreatic or GI tract was seen in one third or fewer of the patients. In the primary clinical radiology report, a pancreatic cancer as a possible differential diagnosis had been stated in 14 of the 33 GP patients.

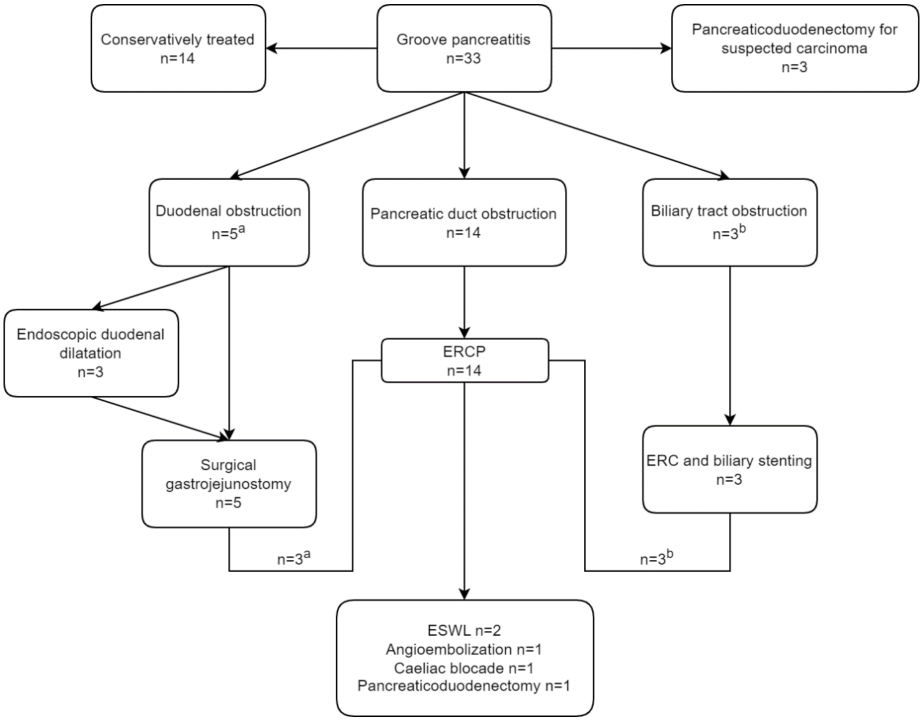
5.3.3 TREATMENT OUTCOMES OF GROOVE PANCREATITIS

Nearly half of the patients (14 of 33) did not require any sort of invasive intervention during the course of GP. Primarily, PD was needed only in three patients and one patient underwent PD after prior endoscopic interventions. All PDs were done due to a suspicion of PDAC, but the final histopathological report revealed GP. The remaining 16 patients underwent a number of endoscopic or surgical interventions due to the obstructive symptoms of GP (Figure 9).

In the case of duodenal obstruction (n=5), the endoscopic duodenal dilatation or stenting was never enough, and all five patients eventually needed a surgical gastrojejunostomy (Figure 9). Patients with biliary and/or pancreatic tract obstruction underwent multiple endoscopic interventions with a mean of 3.9 interventions per patient.

After five years from the onset of GP, the overall symptoms of the patients decreased regardless of the given treatment and approximately 75% of the patients were symptomless. However, all the patients who were treated conservatively were asymptomatic at five years whereas only 10 of 16 patients (63%) treated either endoscopically or surgically were free of symptoms at five years. Deceased patients and patients lost during follow-up (n=7) were excluded from these long-term analyses.

Figure 9. Treatment strategies of GP patients.



[a]3 patients had both duodenal and pancreatic duct obstruction.
[b]3 patients had both biliary and pancreatic duct obstruction.

6 DISCUSSION

Patients undergoing partial pancreatectomy are at high risk of postoperative complications and POPF is the leading factor for a major part of this postoperative morbidity (Schoellhammer et al., 2014; Karim et al., 2018). Countless ways to mitigate POPF and other postoperative complications after pancreatic surgery have been studied. This thesis aimed to bring new knowledge to the perioperative care of patients undergoing pancreatic surgery, which may help to mitigate the postoperative complications. In addition, new insights into the natural course and treatment strategies of rare GP are presented.

6.1 PERIOPERATIVE PHARMACOTHERAPY TO MITIGATE POSTOPERATIVE PANCREATIC FISTULA (STUDIES I AND II)

Studies I and **II** of this thesis compared the short- and long-term outcomes of the patients at high-risk of POPF, who received perioperatively either pasireotide or hydrocortisone. The HYPAR trial was the first ever published trial comparing pasireotide and hydrocortisone against each other in this setting. The study design was a non-inferiority trial, and it failed to show the non-inferiority of hydrocortisone compared to pasireotide in the whole study population. Also, the long-term outcomes were convergent between the study drug groups. However, in the short term, pasireotide may be beneficial compared to hydrocortisone in the subgroup of patients undergoing DP, but these favourable short-term results were not reflected in improved long-term outcomes.

Based on the current literature, the role of pasireotide in the mitigation strategies of POPF and other postoperative complications after pancreatic surgery is still somewhat unclear and the use of pasireotide has not been widely implemented. In 2014, a well-known RCT by Allen et al. showed a significant reduction in the CR-POPF rate in patients receiving pasireotide when compared to placebo (Allen et al., 2014). Since the RCT by Allen et al., several studies looking into the role of pasireotide in reducing postoperative complications after pancreatic surgery have been published. The majority of them are retrospective cohort studies. These non-randomised studies report mixed results as to whether pasireotide is beneficial in reducing postoperative complications after pancreatic resection or not. In most of these retrospective studies, the control patients were from historical cohorts operated on before implementing pasireotide in perioperative care bundles (Dominguez-Rosado et al., 2018; Elliott et al., 2018; Young et al., 2018; Peng et al., 2020). In addition to the status of the administration of pasireotide, the patients treated at different time periods may also have had some other non-reported differences in their perioperative care. These non-reported differences in care may also have had an impact on the outcomes and affected the reported results. In contrast to these studies failing to show the benefits of pasireotide, there are a couple of non-randomised studies also reporting the beneficial results of pasireotide (Kunstman et al., 2019; Vuorela et al., 2020). However, the study cohort by Kunstman et al. consisted partly of the same patients as in the Allen et al. study, so these results cannot be considered an external verification (Kunstman et al., 2019).

The superiority of pasireotide shown by Allen et al. has not yet been reliably externally verified. However, most of the studies have not been randomised and their results need to be assessed accordingly. **Study I** of this thesis has been the only RCT since the RCT by Allen et al., which has used pasireotide, and was able to show the possible benefit of pasireotide in subgroup of patients undergoing distal pancreatectomy. Based on the current literature, the studies able to show the benefit of pasireotide are more often randomised trials or prospective cohort studies, while the studies reporting zero outcomes are retrospective series.

Hydrocortisone or other corticosteroids have been far less studied than pasireotide and other somatostatin analogues in the prevention of postoperative complications after pancreatic surgery. Two RCTs carried out at Tampere University Hospital, Finland, have shown the benefit of hydrocortisone compared to placebo in patients undergoing PD or DP (Laaninen et al., 2016; Antila et al., 2019). The authors of these RCTs hypothesised that the mechanism by which hydrocortisone reduces postoperative complications is the suppression of the inflammatory response at the site of the pancreatic resection. Other studies looking into corticosteroids have not been able to replicate the results by Laaninen et al. and Antila et al. However, these negative studies are methodologically inferior. Two of these three studies were retrospective cohort studies (Sandini et al., 2018; Newhook et al., 2021), and the last and most recent one was a small three-armed RCT with a low number of patients in each arm (n=35) (Kant et al., 2024). The study by Kant et al. may have limited power, as the sample size calculations appear to be based on higher-than-reported values for major complications. Specifically, Kant et al. referenced the RCT by Laaninen et al. but used a major complication incidence rate of 50% for the placebo arm, while the actual rate reported by Laaninen et al. was 41% (Laaninen et al., 2016; Kant et al., 2024). Employing the reported values would indicate a need for a substantially larger sample size.

Since the RCTs by Laaninen et. al. and Antila et. al., the impact of PPAP has been shown to be an important risk factor for postoperative complications after partial pancreatectomy (Bonsdorff et al., 2022). The anti-inflammatory features of hydrocortisone are an interesting subject of study in mitigating postoperative complications after pancreatic resection. Whether hydrocortisone can reduce the rate of PPAP, which would then reduce POPFs and other complications, is a question needing attention in further studies.

When the HYPAR trial was conducted, all DP patients were considered at high risk of POPF. Since then, fistula risk estimators specific to DP have been published (Bonsdorff et al., 2022; De Pastena et al., 2023). HYPAR included all DP patients, based on historical POPF rates of approximately 20%, comparable to high-risk PD (Chong et al., 2021; Mungroop et al., 2021). If these risk scores had been available and lower-risk patients excluded, pasireotide's benefit in DP patients might have been even more pronounced.

In **Study II** of this thesis, we reported the long-term outcomes of the HYPAR trial. Five-year OS, DFS and DSS were all convergent between the pasireotide and hydrocortisone groups.

Postoperative adjuvant chemotherapy increases survival in patients with a resectable PDAC (Conroy et al., 2023). Postoperative complications may adversely affect the patient such that they are not fit for the intended adjuvant chemotherapy in the optimal time frame, which then leads to poorer long-term outcomes (Merkow et al., 2014; Henry et al., 2023). A recent nationwide registry study from Netherlands including over a thousand patients who had undergone a pancreatic resection due to a PDAC reported risk factors for poorer long-term outcomes. Patients who had had one or more major complications (CD grade ≥ 3) [150 out of 305 patients (49%)] received significantly less adjuvant chemotherapy than those who had not had any major complication [511 out of 763 patients (67%)] ($p<0.001$). Patients who had had major complications also had significantly lower disease-free interval and OS compared than those who had not had major complications. After running the causal mediation analysis, the authors stated that the omission of adjuvant chemotherapy was the main mediator for poorer survival in patients who had had major complications after pancreatic resection for PDAC (Henry et al., 2023). Improved short-term outcomes seem to be a significant factor in better long-term results in PDAC patients undergoing pancreatic resection.

In **Study II,** OS, DFS and DSS were all convergent between the pasireotide and hydrocortisone groups in a sub-group of patients with malignancies. Patients with malignancies were analysed as one group due to a low number of patients if divided into disease-specific groups. For example, the largest group would have been PDAC with only 14 patients in the pasireotide group and 13 patients in the hydrocortisone group. Analysing the whole group of malignancies leads to a rather heterogenous group of diseases, which all have different biological features and prognosis. Also, analysing such a small group of patients with PDAC as in the HYPAR trial may lead to false negative or positive findings.

Animal studies have shown that inflammation increases the dissemination of pancreatic cancer cells, which can then be suppressed with the use of dexamethasone (Rhim et al., 2012). There are also some clinical studies suggesting that the risk of recurrence after PDAC resection could be reduced by the administration of corticosteroids (Sandini et al., 2018; Zhang et al., 2021). In these retrospective studies, the patients received either dexamethasone or methylprednisolone mostly to prevent postoperative nausea and vomiting. However, there is also a study showing no benefit of perioperative corticosteroids in the long term after pancreatic cancer resection (Newhook et al., 2021). Also, a systematic review and meta-analysis looking into different types of cancers did not find any differences in long-term outcomes after the use of perioperative corticosteroids (Rosenkrantz Hölmich et al., 2019). Studies report mixed results with regard to the long-term effects of perioperatively administered hydrocortisone. More studies looking into this are warranted.

To sum up, in the long term, the patients participating in the HYPAR trial showed no significant differences. Based on subgroup analysis, in short term pasireotide may be superior to hydrocortisone in patients undergoing DP. This finding compounded with the previously published results showing that major complications worsen overall survival, leads one to think that pasireotide may also have a beneficial role to play in the longer term. The HYPAR trial had a low number of cancer patients and even lower number of patients with PDAC, which is why it lacked the power to show this difference. Also, the immunological aspect that hydrocortisone has and its role in long-term outcomes remains unclear. Further studies are needed to assess not only the short-term benefits of both the study drugs, but also the long-term advantages they may have.

6.2 PREOPERATIVE ANTIBIOTIC PROPHYLAXIS IN PATIENTS UNDERGOING PD (STUDY III)

In **Study III** of this thesis, PBD was found to be strongly associated with second-generation cephalosporin-resistant bacteria in IBC at the time of surgery. Patients who had undergone a PBD had more than a 20-fold risk of cultivating second-generation resistant bacteria in their bile at the time of PD. The risk of second-generation cephalosporin-resistant bacteria further increased if the time between the PBD and surgery got longer. Three of four of the patients who had a time delay of two months or more between PBD and surgery had second-generation cephalosporin-resistant bacteria in their IBC. The risk of SSI in these patients was more than four times higher than those who did not have second-generation cephalosporin-resistant bacteria in their bile.

The association of PBD to SSIs has been widely studied but there are conflicting findings. Some studies show an increased risk of SSIs after PBD (van der Gaag et al., 2010; De Pastena et al., 2018) while a large registry-based study of nearly 6,000 patients who had undergone a PBD did not find PBD as a risk factor for SSIs (Hamidi et al., 2021). Also, in our study PBD was not an independent risk factor for SSIs. However, the resistant bacteria in IBC were a risk factor for SSIs in patients who had at least two months' time delay between PBD and PD. The time delay between PBD and PD was also shown to drastically increase the risk of resistant bacteria in bile. The findings of **Study III** suggest that it is not PBD itself but the time delay between PBD and surgery that increases the risk of resistant bacteria in IBC, which further seems to increase the risk of SSIs.

The results of a few retrospective cohort studies and most importantly the results of a recent RCT further enchance our findings that some patients undergoing PD might benefit from broader spectrum antibiotics in the prophylactic setting (Donald et al., 2013; Sano et al., 2019; De Pastena et al., 2021; D'Angelica et al., 2023). The results of the RCT by D'Angelica et al. suggested that broader spectrum antibiotic piperacillin/tazobactam was superior to second-generation cephalosporins in the prophylaxis of PD. Patients receiving piperacillin/tazobactam had significantly fewer SSIs, and interestingly also fewer POPFs. In post-hoc analyses, this difference was especially seen in patients who had undergone PBD. The benefit of piperacillin/tazobactam was so significant that the study was stopped at the interim analysis (D'Angelica et al., 2023). The results of **Study III** are in line with these findings. Based on our results, patients who have had a time delay of two months or more between PBD and surgery seem to be the ones who might benefit from broader spectrum antibiotics in the prophylactic setting. Interestingly, these patients are the ones who have the lowest overall risk of POPFs and SSIs. Patients who had undergone PBD had a lower risk of POPF, which is shown in the data of **Study III** as a significantly lower ua-FRS score in PBD groups compared to no-PBD group. Also, patients who had undergone PBD had fewer SSIs than the no-PBD group, but the rate of SSIs was still rather high in the PBD group. In **Study III,** one fifth of the patients in the "PBD ≥ 2 months" group developed an organ/space SSI, so the reduction of SSIs also in this group of patients has clinical significance for overall morbidity.

The results of a recent meta-analysis further support the use of broader-spectrum antibiotics in the prophylaxis of patients undergoing PD. In this meta-analysis, which included eight studies and 2,382 patients who had undergone PD, piperacillin/tazobactam was superior in the prophylactic setting compared to traditional prophylactic antibiotics, which were mostly cephalosporins. In this meta-analysis, the use of piperacillin/tazobactam was seen to significantly reduce SSIs (OR 0.43 (95%CI, 0.30-0.62); $p<0.001$) and major complications (CD grade ≥ 3) (OR 0.61 (95%CI, 0.45-0.81); $P<0.001$) compared to traditional antibiotics (Kumar et al., 2024). This difference in SSIs and major complications was seen in all patients undergoing PD, and not just those who had undergone PBD. The findings of **Study III** of this thesis and the RCT by D'Angelica et al. suggest that it may be the patients who have undergone PBD who would benefit the most from broader spectrum antibiotics. This group of patients may have been the one, which also shifted the results of the meta-analysis by Kumar et al. towards the benefit of piperacillin/tazobactam over traditional antibiotics. However, no subgrouping of patients based on PBD status was done in this meta-analysis by Kumar et al, and this reasoning remains speculation.

In **Study III,** the most common bacteria in IBC were *Enterococcus* spp, *Enterobacter* spp and *Klebisella* spp, which all have intrinsic resistance or the ability to turn resistant to cephalosporins and this most likely explains most of the resistance found in IBCs (Cheng et al., 2017; Nepal et al., 2017; Rello et al., 2020). These bacteria species are also commonly found in other studies reporting the bacterial analysis of IBCs (Limongelli et al., 2007; Fong et al., 2016; Goel et al., 2019; Maxwell et al., 2020; Ellis et al., 2023). In other words, our findings are not just limited to our geographical area of Northern Europe but may also be adapted in other regions as well.

Antibiotic resistance is a growing and worldwide concern. It would be important to find which groups of patients would need broad-spectrum antibiotics and which could still be adequately treated with narrow-spectrum antibiotics. The guidelines recommend the use of cephalosporins in the prophylaxis of pancreatic surgery but, based on the results of **Study III** of this thesis and other recently published studies with good methodology (D'Angelica et al., 2023; Kumar et al., 2024), this recommendation seems to be outdated in patients undergoing PD. Patients undergoing PD seem to benefit from broader spectrum antibiotics, at least if they have undergone PBD. According to the current literature, the recommended antibiotic should be piperacillin/tazobactam for these patients. At the moment, there is no data available to assess if the cephalosporins are still a valid option for other types of pancreatic resections.

6.3 GROOVE PANCREATITIS: A CHALLENGE FOR PHYSICIANS (STUDY IV)

Study IV of this thesis reinforced previously shown perceptions of the diagnostic challenges of GP and brought new insights to the treatment strategies of this rare disease. GP remains a difficult disease to diagnose and especially to differentiate from pancreatic malignancies, but a major proportion of GP patients become asymptomatic without extensive pancreatic surgery such as PD – an operation entailing a high burden of postoperative morbidity and formerly described to be the gold standard in the treatment of GP.

GP is a rare disease with no estimates of its incidence. In **Study IV**, we were able to identify retrospectively only 33 patients over a 10-year period of time from a population base of 1.7 million. Even though the absolute number of GP patients in the cohort of **Study IV** was relatively low, there are only a few studies concerning GP with larger cohorts (Ukegjini et al., 2023). GP can mimic pancreatic malignancies, and the radiological diagnosis of GP is also difficult for experienced radiologists (Lekkerkerker et al., 2016; Mittal et al., 2017). In **Study IV,** two experienced radiologists specialised in gastrointestinal imaging diagnosed GP with a high certainty in 31 of the 33 GP patients. Even though the proportion of true diagnoses was substantial in GP patients, they also diagnosed five patients with a high certainty of GP, but who eventually had histologically verified PDAC. It is safe to assume that the radiological diagnostic challenges are even more evident in clinical work where most of the abdominal CT scans are reviewed by radiologists who are not as specialised as those in our study.

Laboratory parameters do not add much to the diagnosis of GP. In **Study IV**, the only somewhat consistently abnormal values were CRP and blood leukocytes reflecting an unspecified inflammatory process. It has been suggested that elevated CA19-9 levels help in differentiating GP from PDAC (Lekkerkerker et al., 2016). However, in **Study IV,** one third of the GP patients had elevated CEA and CA19-9 levels making them practically non-usable in the differential diagnosis between GP and PDAC.

Some authors favour pancreatic resection as the first-line treatment for GP (Rahman et al., 2007; Casetti et al., 2009; Egorov et al., 2014; Egorov et al., 2021), even though high rates in symptom resolution after conservative treatment were already reported almost two decades ago (Rebours et al., 2007). In recent years, the results of a conservative approach have been increasingly reported and the role of pancreatic resections has seemed to decrease. However, the efficacy of endoscopic treatment in GP has been far less studied. Based on the studies reporting endoscopic treatment in GP, it seems that there are some patients who do not achieve satisfactory symptom relief after conservative or endoscopic treatment and are eventually operated on (Arvanitakis et al., 2014; Vujasinovic et al., 2022). There are no studies giving straight answers as to whether these patients with obstructive symptoms would need a pancreatic resection, or if an operation where the obstruction was only bypassed could be sufficient enough. This is most likely due to the fact that GP is a rare disease, and the study cohorts are small ranging from case studies to a maximum of a little more than 100 patients, and not all patients have obstructive symptoms as shown in the data of **Study IV**. In the case of duodenal obstruction, it seems that bypassing the duodenum with gastrojejunostomy is sufficient for to relieve the symptoms. In our study, all patients with a duodenal obstruction (n=5) were operated on, either after failed endoscopic stenting or as first-line treatment. A gastrojejunostomy was sufficient for all of the patients with a duodenal obstruction and there was no need for pancreatic resection for these patients. However, in the case of biliary or pancreatic duct obstruction, the achievability of ERCP nowadays has most likely reduced the need for bypass operations, but surgery may still be needed after failure in endoscopic treatment for biliary or pancreatic duct obstruction in GP (Arvanitakis et al., 2014; Vujasinovic et al., 2022).

In recent years, some authors have still suggested pancreatic resection as first-line treatment for GP (Egorov et al., 2021; Teo et al., 2022). The findings of **Study IV** heavily question this concept. In **Study IV,** only four patients underwent PD and all of them due to a suspicion of PDAC. Nevertheless, 75%

of the GP patients were asymptomatic at five years, regardless of treatment strategy, which is the same success rate as previously described after PD (Casetti et al., 2009; Egorov et al., 2014). Invasive interventions were needed if the inflammation process of GP obstructed the pancreatic, biliary or GI tract, but these were present in only half of the patients. All the patients who had no obstructive symptoms and did not require invasive intervention (endoscopic or surgical), were asymptomatic at five years. Based on the results of **Study IV**, the treatment strategy of GP should be led by the obstructive symptoms and not by the diagnosis itself, and a step-up approach seems justified.

6.4 STRENGTHS AND LIMITATIONS

6.4.1 STRENGTHS

The strengths of this thesis are that the studies were conducted at a high-volume centre for pancreatic surgery with 140-160 elective pancreatectomies per year, and all pancreatic resections were performed by a limited number of experienced pancreatic surgeons giving all surgeons a sufficient number of resections annually. Both of the study drugs in **Study I** had previously been shown to be beneficial against placebo in RCT settings, so the comparison of these two drugs against each other can be considered a valid study design. However, neither one of these drugs has widely established their place in a routine perioperative care bundle, and their use is limited only to some centres. Most likely, more randomised trials would be needed to convince the surgeons of the benefits of pasireotide or hydrocortisone in mitigating postoperative complications after pancreatic surgery. **Study I** was also the first ever published study comparing hydrocortisone and pasireotide in any setting, and no other study comparing these two drugs against each other have since been published. **Study II** also had a high number of patients with complete follow-up for five years [115 of 126 (91%)] giving more power to the long-term outcomes.

Study III had a large cohort of consecutive PDs with only 15 of 376 (4.0%) excluded due to a missing IBC or date of PBD, meaning that all indications for elective PDs were covered, minimising the selection bias. Also, the bacterial analysis of the IBCs in **Study III** were in line with previously reported findings, as the most prevalent bacteria found in IBCs were the same, which have been reported in other studies conducted in different parts of the world. Based on these findings, the results of **Study III** may also be applied outside Finland.

Lastly, even though the absolute number of GP patients was rather low in **Study IV**, the study cohort of this rare disease was one of the biggest in the literature at the time when the results were published. Prior to **Study IV,** one could find only four studies with a larger cohort of GP patients. Also, the GP patients in **Study IV** were screened from the medical records and not from the histopathological specimens, as in some of the historical studies. This way, patients without the need of surgery were also found and included, which then gave a more complete perception of this disease.

6.4.2 LIMITATIONS

There are also limitations to the studies of this thesis. **Studies I** and **II** lacked a placebo arm. A three-armed trial with pasireotide, hydrocortisone and placebo would have brought more strength to the study. With such a setting, however, twice the number of patients would have been needed for an appropriate sample size. This would have naturally doubled the time to finish the RCT or, alternatively, a multi-centre approach would have been required. Implementing fistula risk scores for DPs in the inclusion phase could have also given more strength to the study, but these fistula risk calculators were not available at the time of **Study I**. A limitation of **Study II** was the insufficient statistical power to assess the true effects on long-term survival due to a heterogenous group of malignancies and low number of PDACs. However, the primary aim was to provide descriptive data from the long-term follow-up of the HYPAR trial.

The main limitations of **Studies III** and **IV** are that they were retrospective observational studies possessing all the restrictions that such study design entails. Also, the findings of **Study III** also have a somewhat geographical limitation even though the most common bacteria found in IBCs were comparable with other studies. Antibiotic resistance differs around the world and the same species may have different resistance profiles in other regions. Lastly in **Study IV**, due to the rarity and under-recognition of GP, the criteria for patients considered as GP had to be retrospectively determined. This may have excluded some eligible patients, but on the other hand most likely did not include false positives.

6.5 FUTURE PROSPECTS

In the literature, both pasireotide and hydrocortisone have conflicting findings as to whether they reduce POPF and other postoperative complications after partial pancreatectomy, and future studies are still needed. We were not able to show the non-inferiority of hydrocortisone but, since the publication of our results, some new insights into PPAP as a risk factor for POPF and other postoperative complications have been published. This brings up the question of whether corticosteroids could be beneficial in reducing PPAP, which then would work in favour of mitigating POPF. So even though we could not demonstrate the non-inferiority of hydrocortisone, this drug remains an interesting subject of study. Concerning pasireotide, our results showed that it may be beneficial at least in patients undergoing DP. At the time of **Study I,** all DPs were considered to be at high risk of POPF. A few years after publishing our results, POPF risk estimators for DPs were also published. In future studies, these risk estimators for POPF after DP should be implemented in the study protocols to exclude the DPs that are at lower risk of POPF. Lastly, a three-armed randomised trial with pasireotide, hydrocortisone and placebo or even a four-armed trial where the fourth arm might be pasireotide and hydrocortisone together would be an interesting study design and most likely would bring new insight into this topic. The combination of pasireotide and hydrocortisone would be interesting, since the mechanism by which these two drugs mitigate postoperative complications differ, and they might possibly even have a synergistic effect. These types of study designs, however, would need a multicentre approach since the number of patients needed to complete the study would be significantly higher, and it is not practical to conduct a randomised trial taking up to five years or more. The HYPAR trial alone took two and half years to complete, even at a high-volume centre.

SSIs and especially organ/space SSIs are a significant source of postoperative morbidity after PD. Contamination with bile is inevitable at the time of transection of the biliary tract in PD. By targeting prophylactic antibiotics to the bacteria found in bile, one may prevent some of the organ/space SSIs. However, antibiotic resistance is a real threat and, with the liberal use of broad-spectrum antibiotics, one could cultivate multidrug-resistant bacteria, and broad-spectrum antibiotics should be reserved only for those who would benefit the most from them. Based on the current literature, it seems that broader-spectrum antibiotics are beneficial in the prophylactic setting in patients who undergo PD, but whether this benefit is for all PD patients or only for patients who have undergone PBD still remains somewhat unclear. The results of **Study III** and the post-hoc analysis of the RCT by D’Angelica et al. (D’Angelica et al., 2023) suggest that the patients who have undergone PBD could be the ones who benefit the most from broader-spectrum antibiotics, and perhaps the cephalosporins could still be adequate for other patients. More studies would be needed to confirm this hypothesis and, for now, piperacillin/tazobactam seems to be advisable for all patients undergoing PD.

7 CONCLUSIONS

I. Hydrocortisone was not non-inferior to pasireotide in mitigating the postoperative complication burden after partial pancreatectomy in all patients at a high risk of POPF.

II. The long-term outcomes were comparable between the study drug groups.

III. The incidence of bacterobilia at the time of biliary tract transection was 32% in the no-PBD group and 99% in the PBD group. Second-generation cephalosporin resistance in IBC is common after PBD and the resistance is more prevalent when the time delay from PBD to PD increases. Second-generation cephalosporin resistance increases the risk of SSIs significantly in patients who have undergone PBD at least two months prior to PD.

IV. The radiological diagnosis of GP is difficult with a high risk of misdiagnosing it as a cancer and vice versa. The majority of patients do not need any invasive intervention. The treatment strategies should be based on patients’ obstructive symptoms and a step-up approach may be advisable.

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