**Postoperative fistula and other complications in pancreatic surgery:**

**A retrospective analysis of 255 pancreatic resections**

Nick De Wever

Student number: 01309484

Supervisor: Prof. dr. Frederik Berrevoet

A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Medicine in Medicine

Academic year: 2017 – 2018

**Postoperative fistula and other complications in pancreatic surgery:**

**A retrospective analysis of 255 pancreatic resections**

Nick De Wever

Student number: 01309484

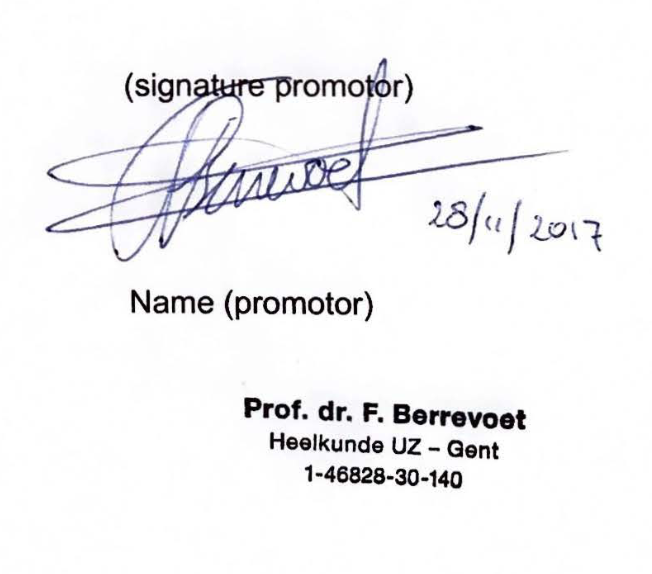
Supervisor: Prof. dr. Frederik Berrevoet

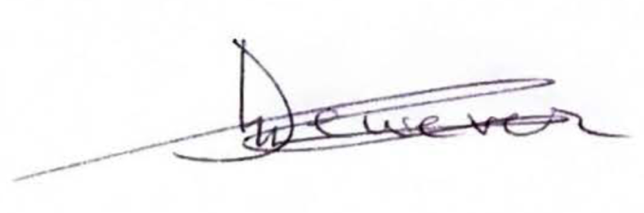
A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Medicine in Medicine

Academic year: 2017 – 2018

*“The author and the promotor give the permission to use this thesis for consultation and to copy parts of it for personal use. Every other use is subject to the copyright laws, more specifically the source must be extensively specified when using results from this thesis.”*

../../../Desktop/Schermafbeelding%202017-11-29%20om%2016.29.07.pngDate



(signature student) (signature promotor)

Name (student) Name (promotor)



Preface

I am proud to present this dissertation which was written to fulfill the requirements for the degree of Master of Medicine in Medicine at Ghent University. I was engaged in the process of data acquisition, data analysis and writing of this dissertation from March 2016 until December 2017.

First and foremost, I would like to thank my promotor Professor Frederik Berrevoet (MD, PhD, Associate Professor General and HPB Surgery at Ghent University Hospital) for his guidance and constructive support during this research process. I am also thankful to have had the chance to observe some of the pancreatic surgeries live.

Although this dissertation was written individually, the experimental part of the research including data acquisition and statistical analysis was performed together with my colleague Sybren Vanwynsberghe. I would like to thank him for his enthusiasm and efforts throughout the research process. Discussing the results with you has been helpful in formulating conclusions.

Finally, my parents also deserve special thanks for reading this dissertation, providing helpful comments and suggestions. Thank you for giving me the opportunity to complete my medical education and pursue a career as a healthcare professional.

I hope you enjoy reading this dissertation.

Nick De Wever

Contents

[1 Abstract 1](#_Toc500220042)

[2 Samenvatting 3](#_Toc500220043)

[3 Introduction 5](#_Toc500220044)

[3.1 Research question and aim 5](#_Toc500220045)

[3.2 Problems in pancreatic surgery 6](#_Toc500220046)

[3.2.1 Mortality 6](#_Toc500220047)

[3.2.2 Morbidity 7](#_Toc500220048)

[3.3 Background 16](#_Toc500220049)

[3.3.1 Pancreatic Surgery 16](#_Toc500220050)

[3.3.2 Pancreatic cancer 17](#_Toc500220051)

[4 Patients and methods 21](#_Toc500220052)

[4.1 Study design 21](#_Toc500220053)

[4.2 Patients and data collection 22](#_Toc500220054)

[4.3 Database construction and variable selection 22](#_Toc500220055)

[4.4 Specific variable definition 24](#_Toc500220056)

[4.5 Surgical approach 26](#_Toc500220057)

[4.6 Postoperative care 27](#_Toc500220058)

[4.7 Statistical analysis 28](#_Toc500220059)

[4.8 Literature search 28](#_Toc500220060)

[5 Results 29](#_Toc500220061)

[5.1 Database descriptive statistics 29](#_Toc500220062)

[5.2 Postoperative pancreatic fistula (popf) 29](#_Toc500220063)

[5.2.1 Patient characteristics by grade of fistula 30](#_Toc500220064)

[5.2.2 Univariate analysis of risk factors for clinically relevant POPF 30](#_Toc500220065)

[5.2.3 Univariate analysis of risk factors for all grades of POPF 33](#_Toc500220066)

[5.3 Management of POPF 35](#_Toc500220067)

[5.4 Other postoperative complications 35](#_Toc500220068)

[6 Discussion 36](#_Toc500220069)

[6.1 Database and patient characteristics 36](#_Toc500220070)

[6.2 Postoperative pancreatic fistula (POPF) 36](#_Toc500220071)

[6.2.1 Incidence of POPF after PD and DP 36](#_Toc500220072)

[6.2.2 Risk factors for POPF 39](#_Toc500220073)

[6.3 Other postoperative complications (DGE & PPH) 45](#_Toc500220074)

[7 Conclusion 46](#_Toc500220075)

[8 References 48](#_Toc500220076)

[Appendix 1: List of abbreviations i](#_Toc500220077)

# Abstract

**Background and aim:** Pancreatic surgery is the only potentially curative treatment for pancreatic cancer. However, morbidity of these operations remains high with complications in 30-50% of all patients. Postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and postpancreatectomy hemorrhage (PPH) are the most important complications as they are associated with mortality, delay in adjuvant therapy and impaired quality of life. POPF is the most feared as it is the one most frequently associated with catastrophic consequences making it the leading risk factor for postoperative death and longer hospital stay with increased hospital costs. Analyzing the series of pancreatic surgeries performed at Ghent University Hospital gives the opportunity to compare incidences and outcomes of these complications with literature data, which provides feedback to the surgeons as it could potentially indicate aspects of care needing specific attention. Secondly, investigating the associations between patient or surgery related risk factors and the occurrence of POPF could help to identify high risk patients, serving as a future guidance for directing strategies to reduce complication rates. The main research question and goal can be summarized as the evaluation of the incidence of POPF, the determining risk factors and the therapeutic measures in relation to morbidity and mortality.

**Methods:** Between January 2010 and November 2015, 255 pancreatic resections for benign or (pre)malignant lesions were performed at Ghent University Hospital. This included 198 (pylorus-preserving) pancreaticoduodenectomies (PD) and 57 distal pancreatectomies (DP). A large database with variables including the occurrence of POPF, DGE, PPH and many others was constructed retrospectively, using the data that were available in the electronic patient records. A selection of variables from this database was made, based on literature review and current evidence concerning the association between these variables and the occurrence of POPF. Statistical analysis was then performed on those possible risk factors or protective factors for POPF.

**Results:** Fifty-three patients (20.8%) developed a fistula after pancreatic surgery, including 18 patients (7.1%) with a clinically relevant grade B or C fistula (CR-POPF). Twenty-four patients (12.1%) developed POPF after PD, including 8 patients (4%) with CR-POPF. Twenty-nine patients (50.9%) developed POPF after DP, including 10 patients (17.5%) with CR-POPF. There was a significant difference in the occurrence of POPF as well as the occurrence of CR-POPF in the group of patients who had undergone PD compared to those who had undergone distal pancreatectomy (P<0.001 and P=0.002 for POPF and CR-POPF respectively).

Univariate analysis showed that soft pancreatic texture was a significant risk factor for any grade of POPF after PD (P<0.001), but not for CR-POPF. Age, gender, BMI, diabetes, neoadjuvant therapy, drain perdu, DGE and PPH showed no significant association with POPF after pancreaticoduodenectomy.

Univariate analysis of the same variables in the group having undergone DP, showed that diabetes was a significant protective factor for any grade of POPF after DP (P=0.034), but not for CR-POPF. All other variables showed no significant association with POPF after DP, although there was a trend towards significance for delayed gastric emptying (P=0.062).

Altogether, 25.6% of all patients undergoing pancreatic surgery developed at least one of the three major complications. There were 47 cases (18.5%) of DGE, with no significant difference between the PD group (18.8%) and the DP group (17.5%). PPH occurred in 12 patients (4.7%) with no significant difference between the PD group (5.6%) and the DP group (1.8%).

**Discussion:** Our study shows a low rate of POPF and CR-POPF after PD compared to other published series. This may be attributable to high surgeon experience and the invariable use of the same anastomotic technique. On the other hand, the incidence of POPF after distal pancreatectomy was high compared to other institutions, but the majority of these were grade A biochemical leaks and thus not clinically relevant. The incidence of CR-POPF after DP was indeed comparable to current literature data. Closure of the pancreatic remnant with a stapler is used which is the best method based on current evidence. The fact that lipase levels were used instead of amylase levels to detect POPF, does not jeopardize the observation that CR-POPF rate in this series is low compared to other published data.

Soft pancreatic texture was found to be a significant risk factor for POPF after PD, supporting the use of this variable in fistula risk scores. DGE was present in 40% of the patients suffering from CR-POPF after DP, but it is not a significant risk factor according to our analysis. High BMI was found to be a significant risk factor for POPF after DP, but this result needs careful interpretation as there is a high risk for confounding influences. Future studies might benefit from measuring serum albumin to clarify the seemingly contradictive effects of BMI and serum albumin on POPF rate as they are both markers for nutritional status. Diabetes showed to be a significant protective factor against POPF after DP. The percentage of diabetic patients was higher in the group of patients without POPF after both PD and DP. Our results therefore support the suggested protective effect of diabetes in pancreatic surgery, but further research is still required.

The incidence of DGE in Ghent University Hospital was comparable to other reported single-center studies, and the occurrence of PPH was a little lower than in most series. These findings suggest that no major flaws in surgical technique or postoperative care are present.

# Samenvatting

**Achtergrond en doelstelling:** Pancreaschirurgie blijft tot op vandaag de enige potentieel curatieve behandeling bij pancreaskanker. Chirurgische resecties van de pancreas gaan echter nog steeds gepaard met een hoge incidentie aan complicaties (30-50%). Pancreasfistels (POPF), vertraagde maaglediging (DGE) en postoperatieve bloeding (PPH) vormen daarbij de belangrijkste complicaties gezien ze geassocieerd zijn met oponthoud van verdere behandeling, verminderde levenskwaliteit en toegenomen sterfte. Vooral POPF is een gevreesde complicatie omdat het de belangrijkste risicofactor is voor sterfte, verlengde hospitalisatieduur en toegenomen kosten. Het analyseren van een reeks pancreasoperaties in het UZ Gent laat ons toe de incidentie van deze complicaties na te gaan en te vergelijken met andere ziekenhuizen, wat een feedback geeft naar de chirurgen en eventuele aandachtspunten in de zorg kan identificeren. Verder heeft het onderzoeken van patiënt of operatie gerelateerde risicofactoren voor fistels tot doel om mensen met een verhoogd risico te identificeren, zodoende een leidraad te verschaffen voor eventuele preventieve maatregelen. De doelstelling van dit onderzoek bestaat dus vooral uit het evalueren van de incidentie van complicaties na pancreaschirurgie in het UZ Gent, alsook het bepalen van de risicofactoren en de therapeutische strategieën.

**Methoden:** Tussen januari 2010 en november 2015 ondergingen 255 patiënten een pancreasoperatie in het UZ Gent omwille van een benigne of (pre)maligne letsel. Dit omvatte 198 (pylorussparende) pancreaticoduodenectomieën (PD) en 57 kop- en/of staartresecties (DP). Een grote database met gegevens van deze patiënten werd retrospectief opgesteld op basis van de gegevens in het elektronisch patiëntendossier. Na literatuuronderzoek werden een aantal variabelen uit deze database opgehaald, waarvan gedacht werd dat zij potentiële risicofactoren of beschermende factoren kunnen zijn voor fistels. Vervolgens werd statistische analyse van deze variabelen verricht om hun associatie met fistels na te gaan.

**Resultaten:** Drieënvijftig patiënten (20,8%) ontwikkelden een fistel na de operatie, waarvan 18 patiënten (7,1%) een klinisch relevante graad B of C fistel (CR-POPF). Vierentwintig patiënten (12,1%) ontwikkelden en fistel na PD, waaronder 8 patiënten (4%) een CR-POPF. Negenentwintig patiënten (50;9%) ontwikkelden een fistel na DP, waaronder 10 patiënten (17,5%) een CR-POPF. Er was dus een significant hoger aantal fistels en ook CR-POPF na DP in vergelijking met PD (P<0,001 en P=0,002 voor POPF en CR-POPF respectievelijk).

Univariate analyse toont aan dat een zachte textuur van het pancreasweefsel een significante risicofactor is voor het ontwikkelen van een fistel na PD (P<0,001), maar niet voor het ontwikkelen van CR-POPF. Leeftijd, geslacht, BMI, neoadjuvante therapie, drain perdu, DGE en PPH waren niet significant geassocieerd met POPF na PD.

Univariate analyse voor dezelfde variabelen na DP toont dat diabetes een significant beschermende factor is voor fistels (P=0,034), maar niet voor CR-POPF. Alle andere variabelen toonden geen significante associaties met de incidentie van fistels na DP, hoewel vertraagde maaglediging wel een trend naar significantie toonde (P=0,062).

In totaal ontwikkelden 25,6% van alle patiënten tenminste één van de drie hoofdcomplicaties na hun operatie. Er waren 47 gevallen (18,5%) van vertraagde maaglediging, waarbij geen significant verschil tussen PD (18,8%) en DP (17,5%) werd vastgesteld. Bloedingen kwamen slechts bij 12 patiënten (4,7%) voor, waarbij ook geen significant verschil werd vastgesteld tussen PD (5,6%) en DP (1,8%).

**Discussie:** Deze studie toont een lage incidentie van POPF en CR-POPF na PD in vergelijking met andere series. Dit is waarschijnlijk te verklaren door de uitgebreide ervaring van de chirurgen en het systematisch toepassen van dezelfde anastomosetechniek. De incidentie van POPF na DP is daarentegen wel hoog ten opzichte van andere series, maar de meerderheid bedroeg de klinisch weinig relevante graad A fistels. De incidentie van CR-POPF was wel vergelijkbaar met literatuurgegevens. Bij DP werd de pancreasrest gesloten met een stapler, wat op basis van de huidige evidentie de beste methode lijkt. Het feit dat lipase in plaats van amylase gebruikt werd om POPF aan te tonen, doet geen afbreuk aan de observatie dat de incidentie CR-POPF in onze serie laag is ten opzichte van andere data.

Een zachte textuur van de pancreas blijkt een significante risicofactor te zijn voor POPF na PD, wat het gebruik van dit kenmerk in risicoscores voor fistels ondersteunt. Veertig procent van de mensen met een CR-POPF na DP hadden ook last van DGE, maar dit was geen significante risicofactor volgens onze analyse. Een hoog BMI blijkt wel een significante risicofactor te zijn voor POPF na DP, maar dit resultaat moet met de nodige omzichtigheid geïnterpreteerd worden gezien het hoge risico op verstorende variabelen. Toekomstig onderzoek dient naast BMI ook albuminespiegels in het serum te bepalen gezien er tegenstrijdige resultaten worden gepubliceerd over deze twee factoren, terwijl beide merkers van de nutritionele toestand zijn. Diabetes bleek een significant beschermende factor te zijn voor fistels na DP. Het percentage diabetici was steeds hoger in de groep zonder fistels ten opzichte van de groep met fistels en dit zowel na PD als na DP. Deze resultaten ondersteunen dus het gesuggereerde protectieve effect van diabetes, maar verder onderzoek is nog steeds nodig.

De incidentie van DGE in deze studie was vergelijkbaar met andere monocentrische studies en de incidentie van PPH was zelfs iets lager dan in de meeste series. Dit toont aan dat er geen duidelijke tekortkomingen zijn in de gebruikte chirurgische techniek en de postoperatieve zorg.

# Introduction

## Research question and aim

Pancreatic surgery is the domain which is responsible for the surgical treatment of pancreatic disease including cancer, pancreatitis and trauma. The importance of this surgical field is illustrated by some epidemiological data concerning the indications for which surgery is performed. Pancreatic cancer accounts for an estimated global death toll between 200 000 and 330 000 persons per year and it is the fourth leading cause of cancer deaths in the developed countries (1-3). Surgical resection of the tumor remains the only potentially curative treatment for this global health issue.

The second major indication for pancreatic surgery is acute pancreatitis, which is one of the most frequent causes for hospital admission for gastrointestinal problems, implying a significant impact on hospitalization costs. Acute pancreatitis has an annual incidence between 13 and 45 per 100 000 persons with an observed increase of 20% over the past 10 years (4, 5). Overall mortality of acute pancreatitis is 2%, but it approaches 30% among patients with severe forms and persistent organ failure (5). This last category often requires surgical interception. The third major indication for pancreatic surgery is chronic pancreatitis. The incidence of this disease in Europe is estimated to be 4-13 per 100 000 per year, with an increased incidence reported in several studies (6-8). Surgery is one of the basic treatment strategies in chronic pancreatitis as nearly 50% of the patients undergo surgery at some point during the disease progression (8).

These epidemiologic data clearly prove that the three main indications for pancreatic surgery are important and prevalent diseases with a high impact on general population health. However morbidity after these operations remains high with reported complications in about 30% to 50% of the patients in most large series (9-14). This indicates the importance of a better understanding of these complications and their prevention and management options as they are responsible for delay in adjuvant therapy and result in increased hospital costs and length of hospital stay (10, 14, 15). Most importantly, they negatively impact the quality of life in patients who frequently already have a limited life expectancy. It is therefore that this study aims to investigate these postoperative complications. Analysis of a series of pancreatic surgeries that have been performed at Ghent University Hospital will enable us to compare outcomes and postoperative complications with literature data and identify potential flaws in the perioperative care and management of these complications. This is a good feedback to the surgeons as it can indicate aspects needing specific attention in the multidisciplinary management of these complex patients. Secondly, we want to investigate the correlations between patient or surgery related risk factors and the occurrence of certain complications in order to identify high risk patients. In time, this can serve as a guidance for directing future strategies to reduce complication rates in these high risk individuals. As postoperative pancreatic fistula remains one of the most frequent and most feared complications after pancreatic resections, the study focusses on the risk factors, occurrence and management of this complication in particular.

The main research question and goal of this dissertation can therefore be summarized as the evaluation of the incidence of different types of pancreatic fistula after pancreatic resection, the determining risk factors and the therapeutic measures in relation to morbidity and mortality. Secondary goals were to evaluate the incidence of delayed gastric emptying and postpancreatectomy hemorrhage.

The contribution of the two students to this study consisted of completing the missing data in a large database of patients that underwent pancreatic surgery in Ghent University Hospital based on electronic patient records. They subsequently identified relevant variables for analysis, based on current literature data and performed statistical analysis for the entire patient cohort. All steps in the research process were performed under the supervision and guidance of Professor F. Berrevoet (Associate Professor General and HPB Surgery at Ghent University Hospital).

## Problems in pancreatic surgery

### Mortality

Historically, the mortality rates of pancreatic surgery, and more specific pancreatic resections, were very high. Until the 1960s, mortality rates after Whipple surgery were more than 25%. Only relatively recently have these mortality rates dropped to <5% and even <2% in high-volume centers (9, 16, 17). This significant decrease in mortality rates only started from the 1980s onwards, and can be explained by centralization of these procedures in specialist high-volume centers, accurate indications, improvements in surgical technique and progress in perioperative care (13, 18-20). Although there is large variation among studies considering the term ‘high-volume’, the relationship between hospital and surgeon volume and the outcomes of pancreatic resections has now been well proven (9, 21). Nowadays, pancreatic resections are relatively safe procedures in terms of mortality.

Of course, the eventual goal of surgery for pancreatic cancer is to obtain a curative resection and thus cure the patient. However, despite the advances in the safety of these procedures, the 5-year survival rate for pancreatic cancer is still only approximately 20% within this selected group of patients that qualify for surgery (22, 23). On top of these poor survival outcomes, only 20% of the patients are eligible for surgery at the time of diagnosis (9, 10, 24). Thus we can conclude that on this day pancreatic surgery is still not able to cure pancreatic cancer and that early diagnosis remains the largest obstacle in improving survival rates.

### Morbidity

#### Complications after pancreatic surgery

Although mortality has improved drastically over the last decades, morbidity still remains high with reported complications in about 30% to 50% of the patients in most large series (9-14). However, postoperative complications are influenced by the type of surgery, as well as the underlying indication for pancreatic resection and this has to be taken into account when comparing different studies. Not only do postoperative complications negatively influence quality of life for these patients, they also delay adjuvant therapy and result in increased hospital costs and length of hospital stay (10, 14, 15). Morbidity remains a very important problem and a challenge within the field of pancreatic surgery, even in large-volume specialist centers (25, 26).

The postoperative complications can be divided into general surgical complications and pancreas-specific complications. General complications that are a risk in all types of major abdominal surgery include sepsis, surgical site infection and respiratory complications. The most important pancreas-specific complications on the other hand include pancreatic fistula, bleeding and delayed gastric emptying. It is known that pancreas-specific complications can also induce secondary general complications such as sepsis and wound infection. In the past decades, lack of standardized definitions compromised the reporting of these surgical complications, making it difficult to compare studies. Therefore, the International Study Group of Pancreatic Surgery (ISGPS) has constructed definitions for pancreatic leaks (27), bleeding (28) and delayed gastric emptying (29).

##### Postoperative pancreatic fistula (POPF)

Postoperative pancreatic fistula (POPF) is one of the most frequent and most feared complications after pancreatic surgery. In 2005, the International Study Group for Pancreatic Fistula (ISGPF) defined POPF as a failure of healing/sealing of a pancreatic-enteric anastomosis or a parenchymal leak not directly related to an anastomosis such as one originating from the raw pancreatic surface (27). This internationally accepted definition was created with the intention to solve the problems in comparison of studies because of the large heterogeneity in the definitions of POPF which resulted in large variations in reported incidences, ranging from 2% to more than 35%. The all-inclusive definition of POPF is a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the upper normal serum value. The study group also proposed a grading system for POPF, based on the clinical impact of the complication (Grade A, B or C) (9, 27). The parameters used for POPF grading can be seen in table 1. (For further information on the ISGPF definition for POPF, see ‘patients and methods’). Despite the advantages of a uniform grading system that allows the comparison of data, the ISGPF grading has also been a subject of criticism. Some authors argue that the practical implications are limited, as grade A POPF has no clinical implications and the distinction between clinically relevant grade B and grade C fistula may be artificial (30).

Table 1 Parameters for POPF grading (ISGPF classification)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Criteria** | **No fistula** | **Grade A fistula** | **Grade B fistula** | **Grade C fistula** |
| Drain amylase | <3 times normal serum amylase | >3 times normal serum amylase | >3 times normal serum amylase | >3 times normal serum amylase |
| Clinical condition | Well | Well | Often well | Bad/ill appearing |
| Specific treatment\* | No | No | Yes/No | Yes |
| US/CT (if obtained) | Negative | Negative | Positive/negative | Positive |
| Persistent drainage (>3 weeks) | No | No | Usually yes | Yes |
| Sepsis | No | No | No | Yes |
| Readmission | No | No | Yes/No | Yes/No |
| Reoperation | No | No | No | Yes |
| Death related to POPF | No | No | No | Yes |
| Signs of infection | No | No | Yes | Yes |
| US, ultrasonography; CT, Computed tomography; \* partial or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage. Adapted from Bassi et al. (27) and from Callery et al. (14). | | | | |

POPF is feared because it is the complication most frequently associated with catastrophic consequences such as sepsis, hemorrhage and intra-abdominal abscesses making it the leading risk factor for postoperative death, longer hospital stay and increased hospital costs (13, 15, 31). It is also linked with the other important complications such as delayed gastric emptying, wound infection and ileus. Surprisingly the rate of POPF has not declined significantly in the last decades, even in high-volume centers (14). It is clear that POPF remains one of the most important problems in pancreatic surgery and has a large impact on the quality of life of these patients. It is for these reasons that the focus of this study lies on pancreatic fistula as this clearly indicates the importance of more research addressing this issue.

###### Clinical aspects:

The presence of a postoperative pancreatic fistula can usually be suspected based upon nonspecific clinical features such as unexplained fever, nausea and vomiting, abdominal pain, constipation, infected wound dehiscence with erythema and swelling, and delayed gastric emptying. Actually, every deviation from the expected postoperative course should raise suspicion for the presence of POPF (30, 32). Another important clinical sign is an effluent appearance of the drain fluid, which allows for the diagnosis of POPF to be made by analysis of the amylase or lipase levels. Observation of the drain fluid is also important because large drain volumes or abnormal coloration may indicate the presence of a fistula and demand further attention. The importance of the drain fluid in the early detection of POPF is illustrated by Traverso and Colleagues (33), who showed that a drainage volume of more than 30ml after postoperative day 5 together with a high amylase content had a 59% positive predictive value for clinically relevant POPF. A daily drainage volume of more than 200ml increased the predictive value to 84%, clearly indicating the impact of a large drainage volume (14, 30, 32).

###### Imaging:

Routine imaging after pancreatic surgery to screen for POPF is not recommended as the ISGPF definition is based on the amylase levels of the drain fluids. Furthermore, cross-sectional imaging can be false-positive in patients lacking any clinical signs suggestive of POPF. If there is a deviation from the expected postoperative course however, cross-sectional imaging is commonly used to detect peripancreatic fluid collections, which are significantly correlated with POPF (32). Contrast-enhanced CT is the preferred technique as it has a sensitivity of 63% and a specificity of 83% for the diagnosis of POPF by identifying undrained fluid collections around the pancreaticojejunostomy site (34). Detecting these abdominal fluid collections is important to allow for percutaneous drainage in the management of the POPF (see ‘management’). Fistulography has also shown to be a useful imaging technique as it is readily available and cost-effective, limiting the radiation dose to which the patient is exposed (30, 32).

###### Management

Nutritional support:

Most patients with POPF have an increased catabolic status and above normal basal energy consumption. In addition, the high exocrine excretion through the fistula causes additional loss of electrolytes and nutritional components resulting in deficiencies (35). As a result, it is not surprising that nutritional support is an important element in postoperative care and conservative therapy for POPF (32).

However, as oral feeding triggers pancreatic exocrine secretion, it is obvious that this is not desirable in patients who suffer from POPF. Patients after pancreatic resection therefore receive total parenteral nutrition (TPN) or enteral nutrition (EN). The rationale for the use of TPN is that it is shown to inhibit pancreatic exocrine secretion. However, it also eliminates the release of gastrointestinal hormones, which attributes to the negative long-term effects of TPN on the gastrointestinal tract, including negative functional and morphological changes (36-38). It has also been shown that TPN increases the incidence of wound infection and sepsis. Enteral nutrition on the other hand does not show these negative effects because it inhibits pancreatic excretions while at the same time possibly stimulating the release of gastrointestinal hormones which further contributes to the pancreatic inhibition (37). Klek and colleagues (39) showed that EN more than doubled the probability of fistula closure, shortened the closure time and led to faster recovery and lower costs as compared to TPN, making it a more favorable strategy.

Somatostatin analogues:

Somatostatin is a natural peptide that, among other functions, inhibits pancreatic exocrine secretion. It was therefore suggested that it could enhance POPF closure and reduce closure time (40). Due to the very short half-life of somatostatin, synthetic analogues such as octreotide and lanreotide were developed. Many studies have analyzed the effects of these somatostatin analogues on the occurrence and closure of POPF. A recent meta-analysis by Gans SL et al. (40) concluded that no significant advantage could be observed in terms of fistula closure rate.

Interventional techniques:

Interventional radiology has shown increased applications in the management of POPF by image-guided percutaneous or EUS-guided transmural drainage of peripancreatic fluid collections associated with POPF (41-43). Percutaneous drainage was able to manage 85% of the POPF patients successfully, implying no need for reoperation (44, 45). However, this technique shows some obvious disadvantages compared to EUS-guided drainage, including the need for catheter monitoring, skin irritation, infections and prolonged hospital stay (46). Possible advantages of EUS-guided drainage include the feasibility to create a precise cyst-gastrostomy and allow rapid evacuation resulting in quicker symptom resolution. Multiple studies have shown equal effectiveness between the two techniques, although it should be noted that these are retrospective studies with a substantial risk of selection bias, as is remarked by Malleo and colleagues (32, 46-49).

Surgical treatment:

Luckily, surgical treatment is only required in a minority of severe postoperative fistula which cannot be managed adequately using non-surgical and supporting care. The indications for reoperation include inaccessible, septic fluid collections, peritonitis, and necrosis (30, 32). Several different management strategies for the pancreatic stump are used, depending on the intraoperative findings and the patient’s clinical condition (50-52). These include debridement of the peripancreatic region, repair of the leakage, construction of a new anastomosis, resection of the anastomosis or completion pancreatectomy. However, anastomotic revision or completion pancreatectomy should be avoided if possible (30, 32). Occasionally, an enterocutaneous fistula with wound infection can develop, requiring the diversion of pancreatic secretions from the wound and the use of negative pressure therapy (30).

###### Risk factors

Considering the importance of POPF, a lot of effort has gone into identifying possible risk factors for this complication, which is key to successful prevention and management strategies in high risk patients. In general, risk factors for POPF development can be divided into three categories: patient-related factors, disease-related factors and operative risk factors (14). As disease-related and patient-related risk factors are non-modifiable, most prevention strategies have focused on identifying operative risk factors and subsequently develop surgical techniques associated with a lower risk for POPF development.

These surgery-associated factors, including the management of the pancreatic remnant, the type of pancreatic anastomosis, the use of a stent across the anastomosis and the use of somatostatin analogues and/or fibrin sealants are further discussed in the paragraph on prevention. Another operative risk factor is large intraoperative blood loss (>1500ml) which was associated with higher POPF rates (14).

On the other hand, we have patient- and disease-related risk factors which allow for the identification of high risk patients. Disease-related risk factors include soft pancreatic parenchyma, small pancreatic duct size (<3mm) and the pathological diagnosis (14, 26, 53). Patient-related risk factors include high age (>70), male gender, history of coronary artery disease, jaundice and decreased creatinine clearance. A positive history for diabetes or neoadjuvant chemoradiotherapy on the other hand have shown to be protective against POPF (14, 53). These risk factors will be covered more extensively in the discussion of this dissertation.

###### Prevention

As noted before, somatostatin analogues showed no significant advantages in the treatment of existing POPF. Other studies however, have focused on the prophylactic use of somatostatin analogues in the prevention of POPF. The recently published position statement of the International Study Group of Pancreatic Surgery (ISGPS) (54) finally concludes that somatostatin and its analogues may reduce perioperative complications such as POPF but not mortality, as was also the conclusion of an earlier meta-analysis (55) and the Cochrane review of 2013 (56).

Secondly, a lot of research has focused on the relation between surgical strategies/techniques and the incidence of POPF. Recently, the ISGPS has published a position statement on the current evidence concerning the association between surgical techniques, the use of tissue sealants, stenting, prophylactic abdominal drainage,… and the occurrence of POPF. In this dissertation only a brief resume is provided but we refer to the ISGPS publication for a more detailed overview (54).

RCTs and meta-analyses comparing the anastomosis of the pancreas to the stomach (PG) versus the anastomosis to the jejunum (PJ) show varying results and conclusions regarding the risk of POPF. These conflicting results can be explained by the heterogeneity in the studies that were analyzed, as some studies for example did not yet apply the 2005 ISGPF definition for POPF. Not only the place of the pancreatic anastomosis is a subject of discussion, there is also no consensus on the technique best used to construct this anastomosis. Variations on the anastomotic technique such as duct-mucosa or end-to-side invagination haven’t shown a clear advantage to each other in PJ. However, this is largely the result of difficulties in the comparison of studies because of confounding variables and absence of standardization. Various techniques such as duct-to-gastric-mucosa and gastric partition have also been described for PG, but again there is no clear evidence showing superiority of one technique over the other which could also be attributed to the lack of standardization (54).

Another factor in the surgical management that has been analyzed for its potential to decrease the incidence of POPF, is stenting across the pancreatic anastomosis. Although there are multiple RCTs showing reduced rate of POPF, there is no high-quality evidence of it. Moreover, a recent Cochrane systematic review by Dong Z. and colleagues (57) shows uncertainty regarding the role of stenting in decreasing the rate of POPF.

Prophylactic postoperative drainage has been the subject of controversy for years with conflicting data concerning its benefits towards postoperative complications (58, 59). More recently however, the concept of selective drainage in high-risk patients was assessed and the ISGPS states that current evidence allows the avoidance of prophylactic drainage, with selective drainage and early drain removal in high-risk patients (54).

Finally, there has been a lot of research concerning the use of tissue sealants and patches. The ISGPS concluded that no advantages in the prevention of POPF could be supported by high-level evidence (54).

##### Delayed gastric emptying

Delayed gastric emptying (DGE) is one of the most frequent complications after pancreatic resections. The ISGPS defined delayed gastric emptying as the inability to tolerate a regular oral diet 1 week postoperatively (29). A large variability in incidences has been reported, ranging from 19% to 60% of the patients (9). Noorani and colleagues (60) reported an incidence of 40% of the patients undergoing pancreaticoduodenectomy. After distal resections of the pancreas, the reported incidence was lower, but still reached one quarter of the patients. Although it is a less serious complication than POPF and not life-threatening, it is still one of the most troublesome postoperative complications after pancreatic resections. This postoperative complication is important because it may lead to the prolonged need for a nasogastric drain and nutritional support, and results in longer hospital stay, compromising the quality of life (9, 60-62).

In analogy with the ISGPF grading system for POPF, the International Study Group of Pancreatic Surgery also proposed a definition and grading system for DGE which is displayed in table 2 (for further information see ‘patients and methods’). This classification was introduced to address the considerable variation in incidences of DGE that were presented by different surgical centers as a result of the absence of a uniform and universally accepted definition (29).

Table 2 definition and grading of DGE (ISGPS classification)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **DGE grade** | **NGT required** | **Unable to tolerate solid oral intake by POD** | **Vomiting/gastric distention** | **Use of prokinetics** |
| A | 4-7 days or reinsertion after POD 3 | 7 | ± | ± |
| B | 8-14 days or reinsertion after POD 7 | 14 | + | + |
| C | >14 days or reinsertion after POD 14 | 21 | + | + |
| DGE, delayed gastric emptying; NGT, nasogastric tube; POD, postoperative day  To exclude mechanical causes of abnormal gastric emptying, the patency of the gastrojejunostomy or the duodenojejunostomy should be confirmed by endoscopy or upper gastrointestinal gastrografin series. Adopted from Wente and Colleagues (29). | | | | |

Even though the ISGPS definition of DGE has most certainly had a positive impact promoting a uniform language for researchers examining this complication, there has also been some criticism regarding the inclusive criteria. As indicated by El Nakeeb and colleagues (63), the ISGPS classification does not include the etiology of the complication. This is important because two types of DGE can be distinguished. DGE is mostly associated with other postoperative complications such as POPF, which is referred to as secondary DGE. However, in the situation where DGE occurs without any associated complications, it is referred to as primary DGE. It is likely that these two types of DGE somewhat differ in etiology and require a different therapeutic approach.

Another point of criticism regards the inclusive design of the criteria of the ISGPS definition. Healy and colleagues (64) argue that these criteria might overestimate the true incidence of this complication. They therefore proposed to add exclusion criteria to the definition in order to more accurately characterize and research genuine DGE.

Since DGE is highly frequent and troublesome, there has been a lot of interest in identifying possible risk factors for the development of this postoperative complication. However, as is noted by Wu and colleagues (62), it is important to bear in mind that studies describing these risk factors are often biased and influenced by confounding factors such as the route of construction, the administration of prokinetic drugs and the postoperative care, which are not uniform among the published studies (65-67). Nevertheless, there is strong evidence for the association between certain risk factors and the occurrence of DGE.

First of all, DGE is associated with some preoperative risk factors including age, cholangitis, pancreatic fibrosis, diabetes mellitus and malnutrition. Also, it has been observed that preoperative drainage of the bile ducts reduced DGE, which could possibly be explained by the fact that preoperative hyperbilirubinemia is a general risk factor for postoperative complications (60, 61).

Secondly, there has been research on the association between operative factors and the incidence of DGE. It was shown that an antecolic construction of the jejunostomy played some role in decreasing the incidence of DGE (68-70). A possible explanation would be that an antecolic construction reduces the risk of obstruction and increases the mobility of the stomach, while at the same time posing a barrier from the pancreas (61). Another operative factor of possible influence is the impact of pylorus preservation. Results on this matter are inconclusive so far, as some studies indicate a higher incidence of DGE after pylorus-preserving pancreaticoduodenectomy than after a classical Whipple procedure, while others reported a lower incidence (69, 71-73). A meta-analysis by Wu and colleagues (62) showed no significant difference between pylorus-preserving and pylorus-resecting techniques.

Finally, DGE is most strongly associated with postoperative intra-abdominal complications. This is also referred to as secondary DGE. Postoperative pancreatic fistula, which is the most feared complication after pancreatic resection, remains the main cause of secondary DGE both in pancreaticoduodenectomy and in distal resections (60, 61, 74-76).

##### Postoperative hemorrhage

Postoperative hemorrhage is a third major complication after pancreatic surgery. Although it is less common than pancreatic fistula or delayed gastric emptying, it has a high mortality rate of up to 50%, emphasizing the importance of this complication. In analogy to POPF and DGE, the ISGPS proposed a definition for postpancreatectomy hemorrhage (PPH) as to reduce the variability in reported hemorrhage rates that were the consequence of differences in the definition used by the surgeons. PPH was defined by the use of 3 parameters: onset, location and severity. Additional grading was based upon the clinical impacts (grade A, B and C) (28). The incidence of PPH (using the ISGPS definition) is between 1 and 10% in most series, with high reported mortality rates ranging from 11 to 50% (77-79). The importance of this complication becomes evident when considering the fact that it is responsible for up to almost 40% of overall mortality after pancreatic resections (9, 28).

According to the ISGPS definition, PPH can be classified as early (≤24h after operation) or late (>24h after operation) (28). Early bleeding is mostly considered to be the result of technical failure during the surgery (inadequate hemostatic control and nonsecured vessels). Hemorrhage in the late postoperative phase is multifactorial and may be the result of tissue edema due to infection with vascular erosion, ulcers, pseudoaneurysms or failure of an anastomosis. Multiple factors predisposing to PPH have been identified, including POPF, bile leak, intraabdominal infections and abscesses (77, 80). Wellner et al. (81) found nine factors to be independently predictive for severe grade C PPH in all types of pancreatic resections. These included POPF, high age and BMI, male sex, portal vein resection, multivisceral resection and intraoperative transfusion.

Mild hemorrhage can usually be treated conservatively and often even remains unnoticed. Severe hemorrhage on the other hand requires more invasive interventions such as interventional endoscopy (for intraluminal bleeding), angiography (for extraluminal bleeding) or operative hemostatic control (80). Although a universally accepted treatment algorithm is not available, some algorithms have been proposed. For these algorithms, we refer to Wellner and colleagues (81) or Gao and colleagues (82).

## Background

### Pancreatic Surgery

#### Historical evolution and current trends

Pancreatic surgery is the domain which is responsible for the surgical treatment of pancreatic disease including cancer, pancreatitis and trauma. Historically, developments and advancements in pancreas surgery were mainly driven by the search for curative treatment for pancreatic cancer (10, 16). From 1940 to 1970 there were no improvements in the results of Whipple surgery and morbidity and mortality remained very high with 40-60% and 20-40% respectively and a 5-year survival rate of less than 5%. Only from the 1980s onwards outcomes following PD began to improve because of centralization of these complex procedures in large-volume centers (18-20). Today, mortality rates after Whipple surgery are less than 5% (even less than 2%) in high-volume centers, whereas this was still more than 25% in the 1960s. Significant improvement in postoperative morbidity has also been achieved with a decrease from <60% in the 1960s to under 35% nowadays (9, 10, 16, 17). However, it is clear that despite these advancements in pancreas surgery, the morbidity (and mortality) rates are still very high.

Current trends in pancreas surgery comprise the expansion of surgical indications. Patients that would previously have been classified as inoperable are now operated on (16, 24). There is also a movement towards minimally invasive surgery using laparoscopy and robotic techniques. The first laparoscopic pancreaticoduodenectomy was performed in 1994 by Gagner and Pomp for chronic pancreatitis. There is more experience with laparoscopic distal pancreatectomy because of its lack of anastomoses and lesser risk of damaging large vessels. Laparoscopic pancreaticoduodenectomy has a higher degree of technical difficulty and requires a long learning curve. However, it can be performed safely by specialized, experienced surgeons. Robotic-assisted pancreatectomy makes an easier transition from open surgery compared to laparoscopy. So far the limited experience with these minimally invasive techniques looks promising (16, 83, 84).

There are quite some advancements in the surgical technique. However, the main barrier and challenge for future pancreatic surgeons remains the difficulty of early diagnosis of pancreatic cancer (PC). Although PC was the main driver in the development of pancreatic surgery, it is not the sole indication for surgical intervention nowadays. Surgical treatment of acute and chronic pancreatitis are also part of the domain, as well as the approach of traumatic injuries of the pancreas (24, 85, 86).

#### Types of surgery and indications

There are many surgical procedures of the pancreas, depending on the specific indications. Pancreatic cancer and pancreatitis are the two main indications for pancreatic surgery nowadays.

For PC, the surgical technique is based on the location of the lesion. Pancreaticoduodenectomy (PD) is used for the treatment of lesions in the head, neck or uncinated process. This procedure, also known as the Whipple procedure, involves the removal of the pancreatic head, the gall bladder with the bile duct, the duodenum and the pylorus of the stomach. In a pylorus-preserving PD, the stomach is left intact (87). After the resection three reconstructions are made. These include a pancreaticojejunostomy, choledochojejunostomy and gastrojejunostomy (88). If the lesion is located in the body or tail of the pancreas, a distal or left partial pancreatectomy (sometimes accompanied by a splenectomy) is performed (87).

### Pancreatic cancer

#### Epidemiology

Having an understanding of the epidemiology and trends in pancreatic cancer (PC) can lead to clues on etiological factors and is therefore crucial in the development of prevention strategies (89). Pancreatic cancer is the 9th most common cancer in the United States and the fourth leading cause of cancer death (1, 10). According to Yabar et al. (17), it has even surpassed breast cancer and is therefore, as of 2016, the third leading cause of cancer deaths in the US. The amount of deaths due to pancreatic cancer is currently increasing and it is therefore predicted that in the next decade, PC will likely surpass colorectal cancer and become the second leading cause of cancer death (1, 17). Pancreatic cancer is a major health problem in North-America.

In Europe pancreatic cancer deaths are almost just as high and they are also increasing, making PC the fourth leading cause of cancer deaths in the developed countries altogether (1, 2). Malvezzi et al. made a European cancer mortality prediction for 2015, putting PC in the fourth place for cancer mortality in both men and women (90). Estimates of the global impact of pancreatic cancer on mortality differ, but with an estimated death toll between 200 000 and 330 000 persons per year, it can be stated that it is a global health issue (1, 3). The developed countries have the highest incidence and mortality rates for pancreatic cancer worldwide (89).

Incidence rates vary considerably between different parts of the world. The highest incidence is seen in Northern America and Western Europe (7,4 per 100 000 people per year), while the lowest incidence is almost ten-fold lower and is found in Middle Africa and South-Central Asia (1 per 100 000 per year). The largest part of this variation is attributed to differences in exposure to known and suspected environmental and lifestyle factors such as smoking. However, part of the variation can be explained by differences in diagnostic capacities. The same variation is seen for pancreatic cancer mortality rates, which can be explained by high fatality of these malignant tumors (89, 91, 92).

Pancreatic cancer incidence rates have increased from the 1950’s through the 1980’s, with a levelling off since then, which is most likely due to decreased smoking. However, recent increasing trends in the European Union indicate that other factors such as obesity, physical inactivity and dietary factors also play a role (89, 93).

#### Diagnosis

Early diagnosis is essential in the outcome of PC because of the malignant potential of this tumor, characterized by rapid invasion and metastatic spread, with surgical resection being the only possible curative treatment. However, most PC have no symptoms in early stage, making early detection a challenge (1, 10).

The initial clinical presentation of a patient with PC and the accompanying symptoms are related to the location of the tumor in the pancreas (10, 17). Tumors in the head, neck and uncinated process mostly lead to obstruction of the pancreatic and common bile duct. This results in obstructive jaundice in 75% of the cases. Obstruction also often leads to acute pancreatitis and steatorrhea because of the impaired exocrine pancreatic function. Tumors in the body and tail of the pancreas are most commonly associated with abdominal and back pain, new-onset diabetes and nausea (10, 17, 94). In general, there are about 12 alarm symptoms that should raise a doctor’s suspicion for PC. These include weight loss, abdominal pain, nausea, bloating, dyspepsia, new-onset diabetes, changes in bowel habit, pruritus, lethargy, back pain, shoulder pain and jaundice (95). Obstruction of the bile ducts can also lead to a palpable gallbladder, also known as Courvoisier’s sign, which is a classic sign in PC (1, 10).

If there is a clinical suspicion for PC, further diagnostic investigations will be performed to confirm this suspicion. First of all, tumor markers such as CA19-9, CA125 and CEA are used. However, these markers only have limited sensitivity and specificity (96). A lot of new tumor markers are currently being examined and will be introduced by genomic epigenetic and proteomic techniques. These markers include cytokines, chemokines, miRNA levels and even autoantibodies (94). Secondly, imaging techniques are extremely important for early detection, determination of the location and invasion of the tumor and for staging. Computed tomography (CT) is used for diagnosis, assessment of resectability and vascular invasion and for the diagnosis of metastatic lesions. It has a sensitivity of 83% and a specificity of 63-75%. However, endoscopic ultrasonography (EUS) is now considered the best method for diagnosing PC. Both retrospective and prospective studies reported superiority over CT with a sensitivity of 98-100%. EUS-guided fine needle aspiration has a high diagnostic accuracy of more than 85-90% (1, 94).

#### Staging and resectability

When the diagnosis of pancreatic cancer is made, the next step is to determine tumor size, location, local and distant spreading. This process is called staging and results in a TNM-based classification of the tumor. Conventional staging for pancreatic duct adenocarcinoma (PDA) is based on the American Joint Cancer Committee (AJCC) TNM-staging system (7th edition). This staging correlates with overall survival and thus provides prognostic information (97). However, in PC the ultimate goal of staging is to determine surgical resectability of the tumor. Therefore, the National Comprehensive Cancer Network (NCCN) published guidelines in 2015 for a surgically relevant staging system which divides nonmetastatic disease in three groups (resectable, borderline resectable and locally advanced). These NCCN guidelines have recently been updated (98). In pancreatic cancer this assessment is specifically critical since surgical resection is the only potentially curative therapy. The primary factor in determining if a patient qualifies for surgical resection is whether or not the surgery can result in a reasonable chance at microscopically negative resection margins. This implies that only 20% of the patients qualify for surgery at the time of diagnosis (9, 10, 24).

Staging is primarily accomplished by different imaging techniques. The most important elements that determine resectability are tumor size, location of the tumor within the pancreas, vascular involvement, lymphadenopathy, anatomic variations and presence of metastasis. Computed Tomography (CT) is most frequently used for staging but endoscopic evaluation using EUS is also used. Despite this extensive staging, 10-25% of the patients undergo an unnecessary laparotomy because unresectable disease (e.g. peritoneal or liver metastasis) is discovered upon exploration of the abdomen (99, 100).

#### Therapy

Treatment options for pancreatic cancer include surgery, neoadjuvant therapy, adjuvant chemotherapy, radiation therapy and palliative care. The choice for one therapy or another will largely depend on the stage of the tumor at diagnosis and the patient’s preferences (1).

Surgery is the cornerstone of therapy for PC because it is the only treatment leading to a potential cure and can result in significant longer survival as compared to other treatment options. However, less than 20 % of the patients qualify for surgery at the time of presentation, making patient selection critical (9, 10). Surgical resection largely consists of two distinct operations (and some variations), based on the anatomic location of the tumor in relation to the superior mesenteric vein/portal vein axis. A pancreaticoduodenectomy (Whipple procedure) is typically performed for cancers of the pancreatic head, neck and uncinated process. A variant on this procedure is the pylorus preserving pancreaticoduodenectomy. In this variant of the classical Whipple, the stomach as well as 3cm of the proximal duodenum are preserved. It has been shown that this would reduce complications such as dumping and delayed gastric emptying, but a recent meta-analysis shows no significant differences in morbidity and mortality (10, 101, 102). For cancers located in the body or tail of the pancreas, a distal pancreatectomy can be performed, which is sometimes combined with a splenectomy (9, 10, 17).

More recently, neoadjuvant therapy has found its access in the treatment of PC, because it has some possible advantages over adjuvant therapy. First, the chance of delivering a full chemo dose is bigger when given before surgery. Secondly, neoadjuvant therapy may be more effective because poor drug delivery to the tumor bed after resection is observed and it also has low sensitivity to radiation (1). This therapy is most commonly suggested for borderline resectable tumors, because it results in a greater percentage of patients eventually undergoing surgery and leads to a higher rate of R0 resections (1, 10, 17).

Metastatic disease is present in 50% of the patients at presentation. These patients can only be managed by chemotherapy and this treatment will be palliative (17). Current evidence suggests that both FOLFIRINOX and gemcitabine plus nab-paclitaxel are effective therapies, if the patient can tolerate them. Further research is needed to see if the combination of chemotherapy with radiotherapy shows additional benefits to chemotherapy alone (1).

New therapeutic strategies are on the horizon. Targeted therapies including small molecules and antibodies have already proven to be successful in the management of some other malignancies. The same applies to immunologic therapies. However, their efficacy in pancreatic cancer is yet to be proven (10, 17).

Last but not least, palliative care is extremely important. In this stage, the focus will be on the patient’s comfort. This is achieved through surgical and endoscopic therapies, but chemotherapy and radiotherapy are also used (1, 10).

# Patients and methods

## Study design

We conducted a retrospective analysis of a series of 255 pancreatic surgeries (classical Whipple, pylorus-preserving Whipple, distal pancreatectomy) performed for various indications at the department of general and hepatobiliary surgery of the Ghent University Hospital. All surgeries were performed between January 2010 and November 2015. The study protocol (EC/2016/0892) was approved by the Medical Ethics Committee of the Ghent University Hospital on 07/27/2016. The retrospective analysis of an existing database has the advantages of being relatively rapid and inexpensive. The database was not designed specifically for this research and contains many more variables than the ones we used in our analysis, allowing for other research questions to be investigated using the same data. Of course, this study design also shows some clear disadvantages, including the fact that many of the data were derived from electronic patient records leading to frequent missing values. Other disadvantages concerning this type of research are the predetermined selection of the study population and the way variables were recorded.

Before starting our analysis we reviewed whether all of the variables needed for answering our research question were available in the first place. Secondly, we revised the quality and accuracy of the data and, after completing the missing data through the electronic patient records, concluded that the quality and availability of these data was sufficient to obtain reliable and representative results. As the database included all patients who successively underwent pancreatic surgery between January 2010 and November 2015, we also assumed that the population selection of this database adequately represented the general population undergoing pancreatic surgery. In other words, despite the disadvantages and difficulties that are inherent to this study design, we ensured that this had only a minimal impact on the study results, thus supporting the reliability of our findings and conclusions.

## Patients and data collection

Between January 2000 and November 2015, 906 patients underwent pancreatic surgery at the Department of General and Hepatobiliary surgery at Ghent University Hospital. A large database was constructed using the data that were available in the electronic patient records. No additional investigations were performed and no extra contact with the patients was required. Since all of the information consisted of early perioperative data and no long-term follow-up data were used, there was no requirement to obtain informed consent.

## Database construction and variable selection

All data were initially collected in a database using Filemaker Pro. These included 906 surgeries performed between 2000 and 2015 for various indications such as pancreatic cancer, pancreatitis, benign lesions of the pancreas and trauma. We selected all cases from January 2010 until the end of November 2015, resulting in a database of 454 pancreatic surgeries. All cases before 2010 were excluded because of the substantial amount of missing data in these patients. The database was then converted into an Excel file and an SPSS file for further analysis.

More than 50% of the cases were (pylorus-preserving) Whipple procedures and almost 15% were body and/or tail resections. The remaining 34% included a variation of different surgical procedures that were each individually only performed a limited number of times. Among others, this group included necrosectomies for acute pancreatitis, drainage procedures (Frey, Partingon-Rochelle, Puestow) for chronic pancreatitis, enucleation of cystic lesions, explorative laparotomies for trauma and double derivations in a palliative setting. Because of the heterogeneity of this group and the fact that some of these procedures weren’t relevant for the aim of this study (e.g. palliative double derivation), we decided to exclude these cases. This resulted in a series of 288 patients who underwent a (pylorus-preserving or classical) Whipple procedure OR a body and/or tail resection. Nine more patients were excluded because of inconsistency between the database and the electronic patient record, leaving 279 cases. Finally it was decided to exclude surgeries performed for pancreatitis (n=24) and focus only on (pre)malignant pancreatic lesions, resulting in a final database of 255 patients. This series can be divided into 198 cases of (pylorus-preserving) pancreaticoduodenectomies and 57 pancreatic body and/or tail resections.

**N = 906**

All pancreatic resections performed between January 2000 and the end of November 2015

All pancreatic resections before January 2010 were excluded (452 cases).

**N = 454**

**N = 288**

All types of resections other than (pylorus-preserving) Whipple procedures and distal pancreatectomies were excluded (166 cases).

**N = 279**

Nine cases were excluded because of inconsistencies between the database and the electronic patient records.

**N = 255**

All resections for pancreatitis (both acute and chronic) were excluded (24 cases).

Thorough data cleaning in SPSS version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.) was performed prior to any statistical analysis of the database. First, the variable ‘CODEFORTYPEOFSURGERY’ was recoded into a dichotomous variable ‘CODEFORTYPEOFSURGERY\_dc’. This ensured that the different terms ‘classical Whipple, pylorus-preserving Whipple, PPPD, extended Whipple,…’ referring to the same type of surgery were all comprised by the same attribute ‘Whipple (pylorus-preserving + non pylorus-preserving + extended)’. In accordance, this also ensured that the terms ‘body + tail resection’ and ‘tail resection’ were comprised by the same attribute ‘Pancreatic corpus and/or tail resection’. Similarly, we recoded the variables ‘FistelEarly\_DC’ and ‘GENDER\_dc’ into dichotomous variables. The new variable ‘FistelEarlyMetTypeA\_DC’ included type A fistula. As type A fistula are shown to have no clinical impact, a second dichotomous variable was constructed, excluding type A fistula as to only withhold those which are clinically relevant (type B and C). Further data cleaning was performed using the ‘Codebook’ function in SPSS which allowed us to see the frequencies of all values for a particular variable. This enabled us to identify false or impossible values and correct or recode them. This method was used for the variables ‘Diabetes’, ‘Aspectpancreas’, ‘Drainperdu’, ‘neoadjuvantetherapie’, ‘postpancreatectomy hemorrhage’ and ‘DelayedGastricEmptying’, which were subsequently recoded into dichotomous variables as described before.

As mentioned in the introduction, the goal of this study was to analyze postoperative complications after pancreatic surgery in a high-volume institution, with the emphasis on postoperative pancreatic fistula as this is one of the major complications that still exists in pancreatic surgery. A second goal was to analyze the existence of correlations between certain risk factors (patient related risk factors, surgical risk factors and disease related risk factors) and the occurrence of these fistula, as well as other postoperative complications. Therefore, prior to the selection of any variables for statistical analysis, we conducted a literature search on the risk factors for postoperative pancreatic fistula.

Eventually, we made a selection of variables based on a number of studies that reviewed current evidence concerning the association between these possible risk factors and the occurrence of POPF (14, 31, 103, 104). The variables that were eventually selected for analysis included age, sex, type of surgery, presence of an early pancreatic fistula (within 1 month after surgery), presence of a late pancreatic fistula, type of POPF, pancreatic texture, pancreatic duct size, body mass index (BMI), T-stadium in the TNM classification, lymph node invasion, neoadjuvant therapy, Somatostatin use, operating time, weight loss, postoperative bleeding, (wound) infection, and delayed gastric emptying.

## Specific variable definition

##### Postoperative pancreatic fistula (POPF):

In most studies today, postoperative pancreatic fistula are defined, based on the definition proposed by the International Study Group for Pancreatic Fistula (ISGPF) (27). In 2005, ISGPF defined POPF as a failure of healing/sealing of a pancreatic-enteric anastomosis or a parenchymal leak not directly related to an anastomosis such as one originating from the raw pancreatic surface. The all-inclusive definition of POPF is a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the upper normal serum value. The study group also proposed a grading system for POPF, based on the clinical impact of the complication (Grade A, B or C). For more details on this definition, we refer to Bassi et al. (27). POPF grade A is a transient fistula with no clinical impact nor any delay in hospital discharge. POPF grade B are fistula that require additional management such as repositioning the drains and the continuation of parenteral nutrition. This grade of fistula usually delays hospital discharge, although patients can be sent home with the drains still in place. The most sever type of POPF is classified as grade C. These require major adjustment of the standard management, including invasive procedures and sometimes even re-exploration of the abdomen. This grading system is also summarized in table 1 (see introduction).

However, in this study the ISGPS definition of POPF was not strictly followed as lipase levels were used to identify POPF instead of amylase. In consultation with our clinical biologists, it was decided that the amylase levels determined on the drain fluid are also dependent on the drainage volume and are hence inaccurate. Therefore, lipase levels were measured on the drain fluid instead. A threshold lipase level of 1000 Units/liter in the drain fluid on postoperative day 3 was used to identify pancreatic fistula in our patient cohort. Grading of the POPF was performed according to the ISGPS grading system. Additionally, we subdivided the variable POPF into two distinct variables ‘early POPF’ and ‘late POPF’. In this study, ‘early’ was defined as the occurrence of POPF within the first 30 postoperative days. All fistula that occurred or still existed beyond this time were denoted as ‘late POPF’.

##### Postpancreatectomy hemorrhage (PPH):

Postoperative bleeding can be suspected clinically and is diagnosed by imaging techniques or reoperation. In this study, postpancreatectomy hemorrhage was defined, based on the definition proposed by the International Study Group of Pancreatic Surgery (ISGPS) in 2007 (28). Their definition of PPH is based on three aspects, being the time of onset, the location, and the severity of the bleeding.

1. The time of onset can be ‘early’ (≤24 hours after the end of the operation) or ‘late’ (>24 hours).
2. The location of the hemorrhage can be ‘intraluminal’ (e.g. pancreatic surface, anastomoses, gastric/duodenal ulcer/erosion, or hemobilia) or ‘extraluminal’ (e.g. arterial or venous vessel, operating field, external suture or staple line, or pseudoaneurysm).
3. The severity of the bleeding can be either ‘mild’ or ‘severe’. Mild bleeding is defined as a small or medium volume blood loss with no or minimal clinical impairment, no need for invasive intervention, and successful conservative treatment. Severe bleeding is a larger volume blood loss and potentially life threatening clinical impairment accompanied by tachycardia, hypotension, and/or oliguria. Treatment involves the need for blood transfusion and/or invasive treatment.

For more details on this definition we refer to Wente et al. (28).

##### Delayed gastric emptying (DGE):

In this study, delayed gastric emptying or gastroparesis was defined, based on the definition proposed by the International Study Group of Pancreatic Surgery (ISGPS) in 2007 (29). They state that “DGE is the inability to return to a standard diet by the end of the first postoperative week and includes prolonged nasogastric intubation of the patient”. Again, three different grades (A, B, and C) were proposed based on the clinical impact and the postoperative management. This grading system is summarized in table 2 (see introduction).

DGE is present if a nasogastric tube is required after 4 to 7 days postoperatively, or if a reinsertion of the nasogastric tube was necessary after removal of the tube by postoperative day 3, and the patient can’t tolerate a solid oral diet by postoperative day 7. This is defined as grade A DGE. “DGE is classified as grade B if the nasogastric tube is required from postoperative day 8 until 14, if reinsertion of the nasogastric tube was necessary after postoperative day 7, or if the patient cannot tolerate unlimited oral intake by POD 14. Finally, the most severe grade of DGE is grade C, which implies that nasogastric intubation cannot be discontinued or has to be reinserted after postoperative 14, or the patient is unable to maintain unlimited oral intake by postoperative day 21.”. For more details on this definition and clinical grading, we refer to Wente et al. (29).

##### Pancreatic texture:

Pancreatic texture is a subjective judgement made by the surgeon, based on palpation of the pancreatic tissue. In this study a distinction was made between ‘soft’ and ‘firm’ texture of the pancreatic parenchyma.

## Surgical approach

The 255 patients included in this study underwent different types of pancreatic resections: twenty-one patients underwent a classic Whipple procedure, 177 underwent a pylorus-preserving Whipple procedure and 57 underwent a body and/or tail resection. A general overview of the surgical technique will be described in the following section. However, it should be taken into account that a variation in surgical steps was used, depending on the indication or any difficulties that occurred during the procedures, or depending on anatomic variations in individual patients.

For a pylorus-preserving Whipple procedure, the patient was positioned in a dorsal decubitus fashion and a median laparotomy or a transverse incision was made. The omental bursa was opened to find the pancreas and a Kocher maneuver was performed. The hepatoduodenal ligament was dissected and isolated from the common bile duct, dividing it at the bifurcation of the left and right hepatic duct. Vascular structures were dissected free and the gastroduodenal artery was divided, followed by the transection of the duodenum just past the pylorus. The portal vein was mobilized above and below the pancreatic body. Then, the duodenojejunal flexure was made free and the pancreatic body was divided over a clamp. Prolene 5/0 sutures were used to ensure hemostasis. The jejunum was divided at this point and an omega loop was prepared. The jejunum was pulled under the vascular pedicle and the vascular structures were divided, dissecting the pancreatic head and the uncinated process. The resection piece was removed in one piece and sent to pathology. Reconstruction was started by performing a pancreaticojejuneostomy in two layers, using Prolene 4/0 single stitches and separate duct to mucosa stitches. Then, a hepaticojejuneostomy was performed at 35 cm with single stitches using PDS 5/0. Finally, the duodeno-enterostomy was performed in two layers with transmesocolic sutures using Vicryl 3/0 suturing material. Two Ch24 drains and a penrose drain were placed in a classical fashion, followed by the closure of the abdomen in a layered fashion using PDS 1 for the fascia, Vicryl 2/0 sutures for the subcutaneous tissue and Monocryl 3/0 for the intradermal closure of the skin. The classic Whipple procedure was performed in an analogous fashion, but instead of transecting the duodenum past the pylorus, an antrectomy was performed. By consequence, reconstruction was achieved by a gastro-enterostomy instead of a duodeno-enterostomy.

For a body and tail resection of the pancreas, the patient was positioned in a dorsal decubitus fashion and a subcostal incision extended to the left was made. The omental bursa was opened to find the pancreas and the splenic flexure of the colon was released. The pancreas was dissected free from adjacent structures and a tunnel was created, followed by the mobilization of the spleen. The splenic and hepatic artery were identified. The splenic artery and vein were then ligated using Prolene 4/0 and were subsequently divided. A linear stapler TL 60 was used to transect the pancreatic body and hemostasis was ensured using Prolene 4/0 sutures. The pancreas was further mobilized from medial to lateral and the short gastric arteries were divided proximal of the stomach. Resection of the pancreatic body and tail, together with the spleen was then completed. A penrose drain was placed under the pancreatic stump and a silicone drain was placed in the splenic compartment. Finally, the abdomen was closed in a layered fashion analogous as described for the pylorus-preserving Whipple procedure.

## Postoperative care

At Ghent University Hospital, the standard postoperative care protocol after pancreatic resections starts with total parenteral nutrition smofkabiven 12N on postoperative day 1. On postoperative day 3, the lateral drain on the right side is removed and the nasogastric tube is withdrawn 10 cm. Primperan was also started on this day (1 ampule of 10mg/2ml, 3 times a day) unless contraindicated. On postoperative day 5, lipase was measured on penrose and drain fluids. If the lipase was negative, indicating that no POPF was present, the right medial drain was removed and the penrose drain was mobilized. If lipase was positive however, the penrose was fixated and 30mg Sandostatine LAR was administered. The dose of somatostatine was divided in half on postoperative day 6 and stopped on postoperative day 7. From postoperative day 6, the patient was further mobilized and per oral feeding was started as soon as het nasogastric tube was removed. Food intake was build up in a stepwise fashion until the patient was ready for discharge.

## Statistical analysis

Statistical analysis was performed using IBM SPSS version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.). First, descriptive analysis of the entire database was performed using the ‘CODEBOOK’ function. Counts, percentages, means, standard deviations and quartiles were calculated for all relevant variables. The same process was then repeated separately for those patients who underwent (pylorus-preserving) Whipple surgery, and once more for patients who underwent a distal pancreatectomy. Finally, we also performed descriptive analysis on the patients who developed POPF, using the same method.

Secondly, univariate analysis of categorical variables was performed using a Chi-Square test (or Fisher’s Exact test when needed). Analysis of continuous variables such as ‘Age’ and ‘BMI’ was performed using the Mann-Whitney U test or an independent t-test. Normality tests such as the Kolmogorov-Smirnov and the Shapiro-Wilk test were first used to identify whether a parametric or a non-parametric test had to be used. Significance was defined as a p-value ≤0.05, implying that a 5% chance of a type 1 error was accepted (⍺ = 5%).

## Literature search

Before the start of this study, a literature search was performed to expand our background knowledge on pancreatic surgery, POPF, DGE, PPH, pancreatic cancer and so on. This information was used in the introduction of this dissertation. Throughout the rest of the study, additional searches were performed when needed. These literature searches were performed using Pubmed, Embase and Web Of Science, giving access to major biomedical databases including Embase, Medline, Science Citation Index Expanded, and others.

A first search was usually performed using Pubmed, because this allowed the identification of appropriate MeSH-terms for the intended literature search. A limited number of relevant publications was retrieved, using a combination of MeSH-terms and Major Subject Headings. These publications were scanned on relevance by reading the abstract and were then included or excluded accordingly. Additional searches were performed, both in Pubmed and the other search engines, using a free text-string to identify the most recent literature that hadn’t been indexed in Medline yet.

# Results

## Database descriptive statistics

A final database of 255 pancreatic surgeries for (pre)malignant pancreatic lesions was obtained (see flowchart patients and methods). This series consisted of 198 pancreaticoduodenectomies, of which 177 (89%) were pylorus-preserving. The other 57 surgeries were distal pancreatectomies, consisting of 29 (51%) tail resections and 28 (49%) body and tail resections. There were slightly more male patients (56.5%) compared to female patients (43.5%) and the mean age was 64.7 (± 11.17). Other baseline variables are shown in table 3. Statistical analysis did not reveal significant differences in these patient characteristics between the different types of surgery.

Table 3 Patient characteristics

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient characteristics and baseline variables** | **All patients**  **(n = 255)** | **(pylorus-preserving) pancreaticoduodenectomy (n = 198)** | **Body and/or tail resection (n = 57)** |
| Gender (male/female) | 144/111 (1.30) | 111/87 (1.28) | 33/24 (1.38) |
| Age (years) | 64.7 ± 11.2 | 65.3 ± 10.8 | 62.5 ± 12.2 |
| Body mass index (% >25kg/m2) | 47.9% | 45.8% | 54.3% |
| Diabetes (%) | 18% | 17.2% | 21.1% |
| Data are given as the mean ± standard deviation (SD) unless indicated otherwise. | | | |

## Postoperative pancreatic fistula (popf)

Table 4 shows the rate of postoperative pancreatic fistula in the complete study cohort, as well as in the group undergoing (pylorus-preserving) pancreaticoduodenectomy and the group undergoing distal pancreatectomy separately. Using the ISGPS criteria, 202 out of 255 patients (79.2%) did not develop a pancreatic fistula, and 35 patients (13.7%) only experienced a transient biochemical leak (grade A), whereas a clinically relevant fistula (grade B or C) occurred in 18 patients (7.1%). There were significantly more clinically relevant fistula in the distal resection group (17.5%) compared to the (pylorus-preserving) Whipple group (4.0%) (P = 0.002).

Table 4 Incidence of POPF

|  |  |  |  |
| --- | --- | --- | --- |
| **Postoperative pancreatic fistula** | **All patients**  **(n = 255)** | **(pylorus-preserving) pancreaticoduodenectomy (n = 198)** | **Body and/or tail resection (n = 57)** |
| All grades n(%) | 53 (20.8%) | 24 (12.1%) | 29 (50.9%) |
| Clinically relevant\* POPF n(%) | 18 (7.1%) | 8 (4.0%) | 10 (17.5%) |
| Grade A n(%) | 35 (13.7%) | 16 (8.1%) | 19 (33.3%) |
| Grade B n(%) | 17 (6.7%) | 7 (3.5%) | 10 (17.5%) |
| Grade C n(%) | 1 (0.4%) | 1 (0.5%) | 0 (0%) |
| \* Grade B and C POPF are considered clinically relevant whereas grade A fistula is only a biochemical leak. | | | |

### Patient characteristics by grade of fistula

Table 5 shows four patient characteristics of the 255 patients classified by the ISGPS grading system for POPF, grouping ‘no fistula’ and ‘grade A’ fistula together because only grade B and C POPF are considered clinically relevant. There were no significant differences in these patient characteristics between those developing clinically relevant POPF and those who did not.

Table 5 Patient characteristics by grade of fistula

|  |  |  |
| --- | --- | --- |
| **Patient characteristics** | **No fistula or grade A fistula  (n=237)** | **Clinically relevant fistula grade B or C (n=18)** |
| Gender (male/female) | 134/103 (1.30) | 10/8 (1.25) |
| Age (years) | 64.6 ± 11.35 | 66.1 ± 8.58 |
| Body mass index (kg/m2) | 24.7 ± 4.07 | 25.1 ± 2.23 |
| Diabetes (%) | 18.1% | 16.7% |
| Data are given as the mean ± standard deviation (SD) unless indicated otherwise. | | |

### Univariate analysis of risk factors for clinically relevant POPF

##### All pancreatic surgeries

Univariate analysis was performed to identify predictive risk factors for the development of clinically relevant (grade B or C) postoperative pancreatic fistula. Ten variables displayed in table 6 were tested, showing that there was a significant difference in clinically relevant fistula between the group of patients who had undergone (pylorus-preserving) pancreaticoduodenectomy, compared to those that had undergone distal resections (P = 0.002). For delayed gastric emptying, a trend towards significance could be observed, with almost 39% of the patients with grade B or C POPF having some degree of DGE compared to 17% in the group without clinically relevant POPF (P = 0.052). There was no significant difference in gender ratio between those with and without clinically relevant POPF. There was no significant difference between the group without POPF or with grade A POPF compared to the grade B/C group in terms of Body mass index, percentage with diabetes, age, neoadjuvant therapy, drain perdu, pancreatic texture or postpancreatectomy hemorrhage.

Table 6 univariate analysis of predictive risk factors for clinically relevant POPF

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictive factors** | **No fistula or grade A fistula (n=237)** | **Clinically relevant fistula grade B or C (n=18)** | **P value** |
| Gender (Male/Female)\* | 134/103 | 10/8 | 0.935 |
| Body mass index (kg/m2)‡ | 24.7 ± 4.07 | 25.1 ± 2.23 | 0.658 |
| Diabetes (%)\* | 18.1% | 16.7% | 1 |
| Age (years)‡ | 64.6 ± 11.35 | 66.1 ± 8.58 | 0.832 |
| Type of surgery (Whipple/distal resection)\* | 190/47 (4.04) | 8/10 (0.80) | **0.002** |
| Neoadjuvant therapy (%)\* | 4.3% | 0% | 1 |
| Drain perdu (%)\* | 19.2% | 11.1% | 0.539 |
| Pancreatic texture (hard/soft)\* | 82/74 (1.11) | 3/7 (0.43) | 0.203 |
| DGE (%)\* | 16.9% | 38.9% | **0.052** |
| PPH (%)\* | 5.1% | 0% | 1 |
| \* Chi-Square test or Fisher’s Exact test (where appropriate)  ‡ Mann-Whitney U test (after normality tests)  Data are given as the mean ± standard deviation (SD) unless indicated otherwise. | | | |

##### (pylorus-preserving) Whipple procedures

Univariate analysis was performed again with the same variables (except ‘type of surgery’) to identify risk factors for clinically relevant POPF after (pylorus-preserving) Whipple procedures only. No significant predictive factors for clinically relevant POPF after pancreaticoduodenectomy were found, as shown in table 7.

Table 7 Univariate analysis of risk factors for clinically relevant POPF after (pylorus-preserving) Whipple

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictive factors** | **No fistula or grade A fistula (n=190)** | **Clinically relevant fistula grade B or C (n=8)** | **P value** |
| Gender (Male/Female)\* | 107/83 (1.29) | 4/4 (1) | 0.739 |
| Body mass index (kg/m2) ‡ | 24.8 ± 4.15 | 24.7 ± 2.94 | 0.930 |
| Diabetes (%)\* | 17.4% | 12.5% | 1 |
| Age (years)‡ | 65.4 ± 10.86 | 63.2 ± 9.54 | 0.413 |
| Neoadjuvant therapy (%)\* | 4.3% | 0% | 1 |
| Drain perdu (%)\* | 24.1% | 25% | 1 |
| Pancreatic texture (hard/soft)\* | 75/69 (1.09) | 1/5 (0.2) | 0.114 |
| DGE (%)\* | 18.0% | 37.5% | 0.173 |
| PPH (%)\* | 5.8% | 0% | 1 |
| \* Chi-Square test or Fisher’s Exact test (where appropriate)  ‡ Mann-Whitney U test (after normality tests)  Data are given as the mean ± standard deviation (SD) unless indicated otherwise. | | | |

##### Body and/or tail resections

Univariate analysis was performed with the same variables to identify risk factors for clinically relevant POPF after distal pancreatectomies only. The variable ‘drain perdu’ was not analyzed in distal resections as it is not used in this type of surgery. No significant predictive factors for clinically relevant POPF after distal pancreatectomy were found. There was a trend towards significance for delayed gastric emptying (P = 0.062).

Table 8 Univariate analysis of risk factors for clinically relevant POPF after distal resection

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictive factors** | **No fistula or grade A fistula (n=47)** | **Clinically relevant fistula grade B or C (n=10)** | **P value** |
| Gender (Male/Female)\* | 27/20 (1.35) | 6/4 (1.5) | 1 |
| Body mass index (kg/m2)‡ | 24.6 ± 3.84 | 25.5 ± 1.38 | 0.654 |
| Diabetes (%)\* | 21.3% | 20.0% | 1 |
| Age (years)‡ | 61.3 ± 12.74 | 68.4 ± 7.42 | 0.131 |
| Neoadjuvant therapy (%)\* | 4.3% | 0% | 1 |
| Pancreatic texture (hard/soft)\* | 7/5 (1.4) | 2/2 (1) | 1 |
| DGE (%)\* | 12.8% | 40% | **0.062** |
| PPH (%)\* | 2.1% | 0% | 1 |
| \* Chi-Square test or Fisher’s Exact test (where appropriate)  ‡ Mann-Whitney U test (after normality tests)  Data are given as the mean ± standard deviation (SD) unless indicated otherwise. | | | |

### Univariate analysis of risk factors for all grades of POPF

##### All pancreatic surgeries

Univariate analysis was performed with the same ten variables to identify risk factors for postoperative pancreatic fistula of any grade. The results are shown in table 9. Again, there was a significant difference in the occurrence of POPF in the group of patients who had undergone (pylorus-preserving) pancreaticoduodenectomy, compared to those that had undergone distal resections (P<0.001). Though pancreatic texture did not prove to be a significant predictive risk factor for clinically relevant POPF, it is a significant factor in POPF when including all grades of POPF (P = 0.009). BMI showed to be significantly higher in the group with POPF (P = 0.041).

Table 9 Univariate analysis of risk factors for all grades of POPF

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictive factors** | **No fistula**  **(n=202)** | **Grade A, B or C POPF**  **(n=53)** | **P value** |
| Gender (Male/Female)\* | 113/89 (1.27) | 31/22 (1.41) | 0.739 |
| Body mass index (kg/m2) ‡ | 24.5 ± 4.17 | 25.8 ± 2.92 | **0.041** |
| Diabetes (%)\* | 19.3% | 13.2% | 0.304 |
| Age (years)‡ | 64.7 ± 11.46 | 64.6 ± 10.06 | 0.645 |
| Type of surgery (Whipple/distal resection)\* | 174/28 (6.21) | 24/29 (0.83) | **<0.001** |
| Neoadjuvant therapy (%)\* | 4% | 3.8% | 1 |
| Drain perdu (%)\* | 19.1% | 17.0% | 0.725 |
| Pancreatic texture (hard/soft)\* | 77/61 (1.26) | 8/20 (0.4) | **0.009** |
| DGE (%)\* | 16.9% | 24.5% | 0.204 |
| PPH (%)\* | 5.1% | 0% | 1 |
| \* Chi-Square test or Fisher’s Exact test (where appropriate)  ‡ Mann-Whitney U test (after normality tests)  Data are given as the mean ± standard deviation (SD) unless indicated otherwise. | | | |

##### (pylorus-preserving) Whipple procedures

Univariate analysis was performed within the cohort of (pylorus-preserving) Whipple procedures to identify predictive risk factors for all grades of POPF after this specific type of procedure. The results are presented in table 10. Soft pancreatic texture showed to be a significant risk factor for the development of any grade of POPF (P < 0.001). All other variables showed no significance as predictive factors.

Table 10 Univariate analysis of risk factors for all grades of POPF after (pylorus-preserving) Whipple

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictive factors** | **No fistula**  **(n=174)** | **Grade A, B or C POPF**  **(n=24)** | **P value** |
| Gender (Male/Female)\* | 98/76 (1.29) | 13/11 (1.18) | 0.842 |
| Body mass index (kg/m2)‡ | 24.6 ± 4.22 | 25.5 ± 3.18 | 0.392 |
| Diabetes (%)\* | 17.2% | 16.7% | 1 |
| Age (years)‡ | 65.3 ± 11.07 | 65.6 ± 8.72 | 0.747 |
| Neoadjuvant therapy (%)\* | 4.1% | 4.2% | 1 |
| Drain perdu (%)\* | 22.2% | 37.5% | 0.101 |
| Pancreatic texture (hard/soft)\* | 74/58 (1.28) | 2/16 (0.13) | **<0.001** |
| DGE (%)\* | 17.8% | 25% | 0.408 |
| PPH (%)\* | 5.8% | 0% | 1 |
| \* Chi-Square test or Fisher’s Exact test (where appropriate)  ‡ Mann-Whitney U test (after normality tests)  Data are given as the mean ± standard deviation (SD) unless indicated otherwise. | | | |

##### Body and/or tail resections

Univariate analysis was performed within the subgroup of patients that had undergone distal resections to identify predictive risk factors for the development of all grades of POPF after body and/or tail resections specifically. As can be seen in table 11, diabetes showed to be a significant protective factor for the development of any grade of POPF (P = 0.044). On the other hand, higher BMI showed to be a significant risk factor for POPF (P = 0.034). All other variables showed no significance as predictive factors.

Table 11 Univariate analysis of risk factors for all grades of POPF after distal resection

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictive factors** | **No fistula**  **(n=28)** | **Grade A, B or C POPF (n=29)** | **P value** |
| Gender (Male/Female)\* | 15/13 (1.15) | 18/11 (1.64) | 0.516 |
| Body mass index (kg/m2)‡ | 23.4 ± 3.84 | 26.1 ± 2.75 | **0.034** |
| Diabetes (%)\* | 32.1% | 10.3% | **0.044** |
| Age (years)‡ | 61.2 ± 13.35 | 63.8 ± 11.13 | 0.523 |
| Neoadjuvant therapy (%)\* | 3.6% | 3.4% | 1 |
| Pancreatic texture (hard/soft)\* | 3/3 (1) | 6/4 (1.5) | 1 |
| DGE (%)\* | 10.7% | 24.1% | 0.297 |
| PPH (%)\* | 2.1% | 0% | 1 |
| \* Chi-Square test or Fisher’s Exact test (where appropriate)  ‡ Mann-Whitney U test (after normality tests)  Data are given as the mean ± standard deviation (SD) unless indicated otherwise. | | | |

## Management of POPF

Out of 24 patients developing POPF after PD, only 8 had clinically relevant grade B or C POPF and needed specific treatment. All these patients with CR-POPF were given Sandostatine-LAR. Two patients required additional surgical reëxploration and drain placement on top of that. One month postoperatively, six patients still had persisting POPF.

The fistula rate after distal pancreatectomy was 50.9%, with 29 patients developing POPF. Ten of them had clinically relevant grade B or C POPF and required specific treatment. All these patients with CR-POPF were given Sandostatine-LAR. One patient required additional antibiotic treatment and one patient underwent surgical wound exploration and debridement of a wound infection caused by the presence of the fistula. Seven of these patients (70%) with CR-POPF still had persisting POPF one month postoperatively.

## Other postoperative complications

In total 25.6% of all patients undergoing pancreatic surgery had at least one of the three most common and most important complications, being clinically relevant POPF, DGE and PPH. This was not significantly different between the two surgical groups, with 29.8% of the patients in the PD group having at least one complication compared to 24.4% of the patients in the distal resection group (P = 0.406). In total there were 47 cases (18.5%) of delayed gastric emptying, with no significant difference between the PD group (18.8%) and the DP group (17.5%). Postpancreatectomy hemorrhage was the least frequent complication, occurring in 12 (4.7%) patients. Again, no significant difference in bleeding rate was observed between the PD group (5.6%) and the DP group (1.8%).

Table 12 Postoperative complication rates

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Postoperative complications** | **All patients (n=255)** | **(pylorus-preserving) pancreaticoduodenectomy (n=198)** | **Body and/or tail resections (n=57)** | **P value** |
| Complication\* n(%) | 65 (25.6%) | 17 (29.8%) | 48 (24.4%) | 0.406 |
| DGE n(%) | 47 (18.5%) | 37 (18.8%) | 10 (17.5%) | 0.832 |
| PPH n(%) | 12 (4.7%) | 11 (5.6%) | 1 (1.8%) | 0.310 |
| \* This variable comprises patients who developed clinically relevant POPF or DGE or PPH | | | | |

# Discussion

## Database and patient characteristics

As described in the paragraph on database construction, this study involved a series of 255 patients who underwent pancreatic surgery for the removal of benign and (pre)malignant tumors. All cases with pancreatitis as a surgical indication were excluded as to ensure that the patient sample was as homogeneous as possible. However, doing this reduced the sample size significantly. Furthermore, the absence of certain patient data, which is the primary disadvantage of any retrospective study design, resulted in missing values which further decreased sample sizes, thus increasing the risk of insufficient power for accurate statistical analyses. However, the sample sizes in our study are comparable to those of other single center studies such as the one by Gagnière et al. (105), including 191 patients and a study by Yang et al. (106) including 62 patients. This allows comparison with these studies to be made. Nevertheless, it is recognized that the limited sample size is one of the biggest limitations in this study, implying that values showing a trend towards significance are probably worth being further evaluated in larger patient cohorts.

Patient characteristics such as age, gender, mean BMI etc. were very similar in values compared to other published patient cohorts undergoing pancreatic surgery (such as the two mentioned above), which indicates that the potential confounding influence of these variables was reduced to a minimum.

## Postoperative pancreatic fistula (POPF)

### Incidence of POPF after PD and DP

One of the main aims of this study was to analyze the occurrence of POPF, which is the most important complication after pancreatic resections, in Ghent University Hospital and compare this to other literature data. However, it should be noted that in this study lipase levels were used instead of amylase levels to determine the presence of POPF. In other words, the ISGPS definition was not followed completely which could be a point of criticism. Nevertheless, lipase levels have shown a high correlation with amylase levels and are also a good method to identify pancreatic fistula. A study in 2012 by Facy and colleagues (107) compared the use of lipase for POPF detection with the use of amylase as described by ISGPS. They found that a threshold lipase level of 1000U/l yielded a sensitivity of 93% for the detection of clinically relevant POPF. By definition, the use of amylase has a 100% sensitivity. This could mean that some POPF were missed using lipase instead of amylase. However, in the same study a separate analysis was done identifying patients with CR-POPF based upon clinical and radiological finding, independent of their drain amylase levels. In this group, they found that “a lipase threshold of 1000U/l yielded a higher sensitivity and specificity than amylase” (107). These findings may suggest that the use of lipase instead of amylase in this study could be an advantage in detecting clinically relevant POPF, implying that our CR-POPF rates are overestimated compared to other studies using the ISGPS definition.

In our patient cohort (n=255), a total of 53 patients (20.8%) developed a POPF but only 18 patients (7.1%) developed a clinically significant (grade B or C) POPF. It has to be noted that this patient cohort consisted of 198 PD’s and 57 DP’s. The surgical techniques of these operations differ significantly, as patients undergoing PD end up with an anastomosis between the pancreatic remnant and the jejunum or stomach, while patients undergoing DP do not have such anastomosis and end up with a free distal remnant of the pancreas. It is clear that this has significant implications towards the mechanisms and risks of developing a pancreatic leak, which is reflected in the different POPF rates for these two types of surgery.

Following (pylorus-preserving) pancreaticoduodenectomy, 12.1% of our patients developed a fistula. A recent study by Gagnière et al. (105) reports a POPF rate of 36.6% (198 PD’s), Guilbaud et al. (108) report a POPF rate of 38.3% after PD (86 patients). A larger monocentric study by Hu et al. (109) including 539 PD’s had a POPF rate of 49.9%. There are also some larger studies that analyze POPF rate on pooled data, such as the study by McMillan et al. (110) describing a 27.2% POPF rate after PD (1533 patients). A large series of 2000 PD’s performed at Johns Hopkins Hospital describes a 16% POPF rate (111). Even though all of these studies use the ISGPF criteria for the definition of POPF, there is still a large variation in fistula rates. Our study shows a fairly low rate of POPF after Whipple surgery, but we have to acknowledge that no data considering the indications for surgery were analyzed. This could be of importance since a study by Aranha et al. (112) in 2006 showed that there is a significant difference in POPF rate following PD according to the nature of the pancreatic tumor. For example the POPF rate after PD for an ampullary neoplasm, a duodenal neoplasm or a serous cystic neoplasm was more than 30 percent, whereas the POPF rate was as low as 6% after PD for pancreatic cancer. Differences in the distribution of tumor types within the cohort could therefore influence the global POPF rate. Nevertheless, as patients were not included/excluded based upon the underlying pathology, the distribution of tumor types in this series is not expected to be significantly different from other series.

Within the group of 24 people who developed a POPF following (pylorus-preserving) PD, only 8 fistula (4%) were clinically relevant (grade B or C) and only 1 patient needed surgical reintervention (grade C POPF). These percentages are again lower than other reports such as the multicenter analysis by Kawai et al. (113) which reports a 14.4% clinically relevant POPF rate in a series of 1239 PD’s or the multicenter report of more than 4000 PD’s by McMillan et al. (114) reporting a clinically relevant POPF rate of 11.1%. In 2013, Topal et al. (115) conducted a large multicenter randomized controlled clinical trial involving 8 Belgian centers with adequate experience in pancreatic surgery but not including Ghent University Hospital. They found a CR-POPF rate of 19.8% following PD with pancreaticojejunostomy (PJ) and a CR-POPF rate of 8% following PD with pancreaticogastrostomy (PG), therefore concluding the superiority of the latter technique. However, even in the group where PG was performed, their CR-POPF rate is still twice as high as in our series, although PJ was used as the standard anastomotic technique for all patients in Ghent University Hospital. This could possibly be explained by a difference in experience between surgeons. Although all surgeons contributing to the Belgian multicenter analysis were reported to have several years of experience with PD, one of the inclusion criteria was that they had performed a minimum of 5 PG and 5 PJ anastomoses. In Ghent University Hospital PJ is used as the standard anastomotic technique, implying that the surgeons had significantly higher experience with this technique compared to the minimum of 5 procedures described above. It is plausible that the surgeon’s experience with one technique over the other is more important in influencing CR-POPF rate than the suggested superiority of PG over PJ.

Twenty-nine out of 57 patients (50,9%) developed a fistula following pancreatic corpus and/or tail resection. This fistula rate is fairly high compared to other reports such as the one by Goh et al. (116) reporting a POPF rate of 31% and the multicenter analysis by McMillan et al. (110) reporting a POPF rate of 34.5% after DP. Fistula rates following DP differ significantly between institutions despite the fact that all of these publications used the ISGPF classification to define POPF. Despite the high overall pancreatic fistula rate, only 10 patients (17.5%) within our cohort developed a clinically significant (grade B or C) POPF whereas studies by Goh et al. (116) and McMillan et al. (110) report 14% and 15% rates for clinically relevant POPF respectively. A recent multi-institution analysis of more than 2000 DP’s by the Distal Pancreatectomy Study Group reported a CR-POPF rate of 15,1% (117). These reported rates are not so different from our own results, especially when taking into account a correction for using lipase versus amylase based incident rates. A large monocentric series of 302 consecutive DP’s published by Kleeff et al. (118) reported an even lower incidence of 11.6% clinically relevant POPF. In conclusion, the incidence of any grade of POPF after DP in our institution is quite high, but the majority of these concerned grade A POPF (biochemical leaks). The incidence of clinically relevant grade B and C POPF on the other hand is relatively comparable to the rates published by other institutions. In analogy with the relatively low CR-POPF rates after PD, it could have been expected that CR-POPF rates after DP would be lower than average as well given the extensive experience of the surgeons. However, as distal pancreatectomy is technically less demanding and does not involve constructing a pancreatic anastomosis, we believe that this type of surgery is less prone to influences from surgeon experience. Closure of the pancreatic remnant was performed using a linear stapler with progressive closure and additional sutures were used if thought necessary by the surgeon. This technique is in accordance with current literature data showing that stapler closure or the combined use of stapler and sutures is associated with significantly lower POPF rates than hand-sewn closure. Various other strategies such as transection of the pancreas with bipolar scissors, harmonic scalpels or radiofrequency ablation devices are being tested but at the present time data are too limited to draw any conclusions (119).

### Risk factors for POPF

Since POPF is frequently associated with other major complications making it the leading risk factor for postoperative death, it is of paramount importance to be able to predict which patients are at risk of developing POPF (13, 15, 31, 34). Based upon literature research and the data that were available in our retrospective study, ten potential risk factors for POPF were identified and analyzed within this patient cohort.

In most studies, the 2005 ISGPF definition for POPF together with its grading system proposing a distinction between grade A, B and C POPF, is applied. However, this grading system also became subject of criticism with some authors questioning the practical relevance of grade A POPF (30). An article by Hackert et al. (120) in 2016 further accentuated the need for an update of the ISGPS definition and grading system for POPF which was published soon after (121). As multiple validation studies showed that there was no difference between grade A POPF and the absence of fistula, it was decided to redefine the former grade A POPF as biochemical leaks (122, 123). The definition of POPF became more strict as this implied that the condition of increased amylase activity found in the drain fluid had to impact clinical outcome in order to be defined as a fistula (121).

As these changes in the 2016 update of the POPF definition were indeed found to be relevant towards clinical practice, it was decided to also analyze the selected ten risk factors using this revised grading system. Former grade A fistula (now biochemical leaks) were therefore analyzed together with ‘no fistula’ so that this group could be compared to those patients suffering from clinically relevant grade B or C fistula (CR-POPF). It is primarily these clinically relevant POPF that are potentially life-threatening complications, therefore making the analysis of CR-POPF related risk factors more relevant for clinical practice as compared to the identification of risk factors for all grades of POPF (including the former grade A).

Using univariate analysis, all ten variables were compared between the group of patients without any fistula and the group with grade A, B or C POPF. The same method was then used to compare the variables between the group without CR-POPF (no fistula or biochemical leak) and CR-POPF grade B or C. In first instance, the analysis was performed on the total patient cohort, which allowed us to confirm the type of surgery (meaning PD versus DP) as a risk factor. Distal pancreatectomy showed to be a significant risk factor for POPF compared to pancreaticoduodenectomy (P<0.001). The same was true for clinically relevant pancreatic fistula (P = 0.002). As mentioned before, this could be attributed to the differences in surgical technique with the remaining of a pancreatic stump after DP versus an anastomosis of the pancreatic duct to bowel or stomach after PD. This finding is confirmed in the study by McMillan et al. (110) who found a significantly higher POPF rate after DP compared to PD. Soft pancreatic texture and high BMI (>25kg/m2) both showed to be significant risk factors for POPF (P = 0.009 and P = 0.041 respectively) irrespective of the type of surgery performed, but this result is not clinically relevant as the same observations did not apply to CR-POPF. Also, these findings are less meaningful as this analysis included all patients. For reasons previously explained, further analysis of risk factors for POPF was performed for PD and DP separately.

Further univariate analysis was performed for (pylorus-preserving) PD and for DP separately using the variables male gender, BMI, diabetes, age, neoadjuvant therapy, drain perdu, soft pancreatic texture, DGE and PPH as potential risk factors. Soft pancreatic texture was the only significant risk factor for all grades of POPF after PD (P<0.001). This finding has also been described in numerous other studies, making it a widely accepted major risk factor for POPF which is explained by the increased technical difficulty of performing an anastomosis on a soft pancreatic gland (53, 124, 125). Pancreatic texture has also been implemented in POPF risk scores such as the one proposed by Callery et al. (126). Despite its general acceptance as a risk factor, soft pancreatic parenchyma was not found to be associated with clinically relevant POPF after PD in our patient cohort (P = 0.114). However, care should be taken making conclusions based upon this finding as there were only 8 patients suffering from CR-POPF after PD, thereby reducing the power of the statistical analysis. It is more plausible that statistical significance for this well-known risk factor could be proven in a larger patient group, as was also found by Pratt et al. (127).

The same argumentation can be used to explain the fact that soft pancreatic texture was also found to be no significant risk factor for POPF as well as CR-POPF following distal pancreatectomy. More specifically, there was only a very small sample size with 10 patients in the group with fistula and 6 patients in the group without fistula after DP (we did not have data on pancreatic texture for the remaining 41 patients in this cohort) which did not allow for statistical significance to be proven. As for CR-POPF, data on pancreatic texture were only available for 4 out of 10 patients suffering from grade B or C fistula. It is however important to note that no anastomosis has to be made during DP, thus implying that soft pancreatic parenchyma does not necessarily influence the technical difficulty of the procedure in the same way as it does for PD. On the other hand, one can assume that the closure of the distal remnant of the pancreas will likely be more fragile and prone to leakage if the pancreatic gland is soft because it is less efficient in holding onto the sutures or staples. In general, the evidence for soft pancreatic texture as a risk factor for POPF following DP is less established compared to PD, but a recent meta-analysis by Peng and colleagues (128) did show a significantly higher incidence of POPF.

One of the problems with evaluating pancreatic texture as a risk factor for POPF or using soft pancreatic texture in risk scores, is the fact that this parameter is subjectively judged by the surgeon through direct intraoperative palpation of the gland. However, in recent years there has been research in using imaging techniques to evaluate pancreatic texture preoperatively in a non-invasive and quantitative (objective) way. According to Harada et al. (129) an ultrasound elastographic technique called acoustic radiation force impulse imaging (ARFI) can be used to evaluate tissue hardness by measuring the shear wave velocity (SWV). The SWV was shown to correlate significantly with pancreatic fibrosis (and thus with harder pancreatic texture). There was a significant positive association between soft pancreatic texture, defined as SWV< 1.54 m/s, and the incidence of POPF. The advantage of using this technique is that it is fast and non-invasive and it is readily available as it is used in clinical practice to determine hepatic fibrosis. More recently, Kuwahara et al. (130) suggested the use of endoscopic ultrasonography-guided elastography (EUS-EG) to evaluate pancreatic texture by measuring the Mean Elasticity (ME). A ME >70 was shown to be an independent predictor for POPF after PD. Moreover, this cut-off value showed to be superior in predicting POPF compared to the pancreatic texture as defined by the surgeon’s intraoperative palpation of the gland. As was also argued by the authors of this article, one of the disadvantages of ARFI imaging is the inability to visualize the pancreas and measure the SWV in obese patients. This problem is overcome by using EUS-EG, giving it an advantage over transabdominal ultrasonographic elastograpic techniques despite its more invasive nature. Finally, there have also been some studies concerning the use of MRI in evaluating the pancreatic texture. A recent publication by Hong et al. (131) showed that the apparent diffusion coefficient (ADC) in diffusion-weighted imaging (DWI) negatively correlated with fibrosis (and thus harder texture) of the pancreatic gland. Other, more advanced MRI techniques have also been investigated to evaluate pancreatic fibrosis (and therefore gland texture). Shi and Colleagues (132) found that 3D-Magnetic resonance elastography could possibly be used to measure the stiffness of the pancreatic gland. Yoon and colleagues (133) showed that intravoxel incoherent motion (IVIM) diffusion-weighted (DW) imaging could provide information on the amount of fibrosis in the pancreatic gland, and that the IVIM DW imaging parameter ‘perfusion fraction’ was significantly correlated with POPF. However, these studies are all very recent and only limited data are available. To the best of our knowledge, there are currently no studies that compare these different imaging techniques and their ability to assess the pancreatic gland texture or predict the risk for POPF. In conclusion, it seems attractive to implement transabdominal ultrasonography with ARFI in Ghent University Hospital to determine pancreatic texture as this non-invasive technique is readily available and can be performed within a few minutes during the presurgical evaluation. The major advantage of this is the fact that it makes the parameter ‘pancreatic texture’ available prior to surgery and thus would allow to adapt the surgical strategy based on the preoperative POPF risk estimate. Due to its more invasive nature, performing an EUS-EG of the pancreas may rather be positioned as a technique to be used for patients who have to undergo EUS anyhow, than as a standard routine. MRI techniques for determining pancreatic fibrosis and gland texture can be useful but their additional value may not be enough to outbalance their inherently higher costs and waiting times, making it harder to implement them in clinical practice.

Male gender was not significantly associated with POPF or CR-POPF, although multiple other studies show significant correlation with an increased fistula rate (14, 53, 109). The same can be said for age, DGE and PPH, which showed no significant association to fistula rate but have each been proposed as possible risk factors in one or more studies (14, 53, 134). However, DGE did show a trend towards significance for developing clinically relevant POPF after DP (P = 0.062). Forty percent of the patients with CR-POPF also suffered from delayed gastric emptying. This association between DGE and CR-POPF has been reported repeatedly (63, 135). In a recent study by Liu et al. (136) CR-POPF and intra-abdominal collection were found to be significantly correlated to DGE in univariate analysis. Moreover, they were identified as independent risk factors using a multivariate logistic regression model. This association can be explained by the fact that DGE after pancreatic surgery is most commonly caused by intra-abdominal complications and specifically by POPF, which is referred to as secondary DGE (60).

High BMI (>25kg/m2) was not significantly associated with fistula rate after PD. On the other hand it was a significant risk factor for POPF (but not for CR-POPF) after distal pancreatic resections (P = 0.034). A similar association between BMI and POPF after DP was found by Seeliger and colleagues (137) who showed a 6-fold increased risk for POPF with a BMI >25. This also supports the reported association between high BMI (>25kg/m2) and intra-abdominal morbidity rate following DP by Sledzianowsky et al. (138) since POPF is one of the major factors contributing to intra-abdominal complications in this setting. However, these results are not sufficient to draw any conclusions because there is a possibility of confounding influences. For example, high BMI might influence the extent of fibrosis present in the pancreatic gland as was proposed by Kawaida and colleagues (139). Another possibility is the increased technical difficulty of any procedure in obese patients. Seemingly contradictive, there have been some studies indicating low serum albumin levels as an independent risk factor for POPF after DP, although they did not use the ISGPS definition for POPF (140, 141). As BMI and serum albumin are both markers for nutritional status, one could assume that both malnutrition and obesity are possible risk factors for POPF. As no serum albumin levels were measured in our patient cohort, it was not possible to evaluate these factors. Eventually, we were also unable to show significant association between high BMI and clinically relevant POPF after DP although this might be attributed to a lack in statistical power which is why further analysis with augmented patient cohorts is needed to draw clear conclusions on this matter. A recent meta-analysis by Peng and colleagues (128) did identify high BMI as a significant risk factor for POPF following DP, but this analysis had some serious limitations considering the heterogeneity of the included data because the cut-off value for ‘high BMI’ differed between included studies.

Unlike the previously mentioned variables, neoadjuvant chemotherapy was analyzed as a potential protective factor in our patient cohort. However no significant correlation with POPF or CR-POPF could be found. This is in contrast with findings of Cheng et al. (142) who retrospectively compared a group receiving neoadjuvant chemoradiotherapy followed by PD to a group undergoing classical PD. They found a significantly lower fistula rate in those patients that received neoadjuvant chemoradiotherapy. However, when comparing these results it should be noted that patients in our study only received neoadjuvant chemotherapy (Folfirinox and Avastin) without neoadjuvant radiotherapy. This explanation is supported by the findings of Ishikawa et al. (143) in 1991 who found neoadjuvant radiotherapy to be a protective factor for POPF because it supposedly decreased exocrine pancreatic function. Also, the number of patients receiving neoadjuvant treatment in our cohort (n=12) was probably too small to detect any association with POPF.

Another potentially protective factor is diabetes. This indeed proves to be a significant protective factor for POPF after DP (p = 0.044). However, diabetes was not significantly associated with a lower occurrence of clinically relevant fistula after DP. Also no significant association was observed between diabetes and both the occurrence of POPF and CR-POPF after (pylorus-preserving) pancreaticoduodenectomy. Despite the lack of statistical significance, it was observed that the percentage of diabetic patients in the group without POPF was always higher than in the group of patients who did develop this complication. This could possibly indicate that insufficient power for the statistical analysis did not allow for statistical significance to be proven and by consequence the possibility of diabetes being a protective factor for POPF development cannot be ruled out based on these data. Our finding that diabetes is a significant protective factor POPF after DP is contradicted by the before mentioned meta-analysis by Peng and colleagues (128). However, there are a lot of conflicting findings in published literature and the association between diabetes and POPF after both PD and DP is still a matter of debate. Several studies even indicate that a history of diabetes increased the likelihood of developing postoperative fistulas, rather than being protective (144, 145). On the contrary, there are also several studies, including a meta-analysis by Xia and colleagues (146) that show a clear association between the absence of diabetes and an increased incidence of POPF although this was not proven to be significant in multivariate regression models (53, 109, 147). Our findings suggest that the protective effect of diabetes could indeed be true and an explanation for this is provided by Mathur et al. (147). They found that diabetes was associated with significantly less fat and more fibrosis in the pancreas. The presence of POPF on the other hand, was found to be associated with significantly more fat and less fibrosis in the pancreatic gland thereby explaining the possible protective effect of diabetes. Furthermore, they also remarked the fact that intuitively one could assume that higher fat content of the pancreas implies a softer pancreatic parenchyma, which in itself is an established risk factor for POPF. Finally, another group showed that increased fibrosis in the pancreatic gland, is associated with decreased exocrine activity which would be an additional argument to suggest a protective effect of diabetes (148). Taken together, there are some arguments that support the possible protective effect of diabetes and our results do not refute this hypothesis, but more large series are needed to make definite conclusions.

## Other postoperative complications (DGE & PPH)

Morbidity after pancreatic resections is still as high as 30-50% and this is also caused by complications such as DGE and PPH, which by consequence also require attention. As mentioned in the introduction, DGE is the second most important postoperative complication as it is highly troublesome and results in longer hospital stay, compromising quality of life (9, 60-62). As the importance of DGE is clear, it was one of the aims of this study to assess the occurrence of DGE in Ghent University Hospital and compare these results to literature data.

The total complication rate (including POPF, DGE and PPH) was 29.8% after (pylorus-preserving) PD and 24.4% after DP. There was no significant difference between these two groups of pancreatic resections. Delayed gastric emptying was observed in 37 patients (18.8%) following PD and 10 patients (17.5%) following DP. Reported incidences of DGE differ significantly but this DGE rate after PD is comparable to those reported by other single-center studies such as those by El Nakeeb et al. (63) and Liu et al. (136) which report a DGE rate of 17.9% and 36.2% respectively. The occurrence of DGE after DP is usually lower compared to PD, which could possibly be explained by the fact that no alteration of the normal bowel anatomy is made in DP. Reported incidences of DGE after DP vary from 9% by Yamamato et al. (149) to 24% by Glowka et al. (135). The large variation in these reported incidences is probably explained by the influence of many confounding factors such as the administration of prokinetic drugs and postoperative care which are not uniform across institutions (62). Another factor that influences reported DGE rates is the used definition, as not all publications use the ISGPS definition (135).

A third very important complication after pancreatic surgery is postoperative hemorrhage. In 2007, the ISGPS suggested a definition for postpancreatectomy hemorrhage (PPH) with the intention of creating an internationally accepted definition for this severe complication (28). Although the incidence of PPH is lower than other complications its significance becomes clear when reflecting the fact that it is responsible for up to 40% of overall mortality in pancreatic surgery, which illustrates why it was one of the aims of this study to assess the incidence of PPH in Ghent University Hospital (9, 28). PPH rate after PD was 5.6% compared to 1.8% after DP, which implied no significant difference in PPH rate by type of surgery. This is in accordance with a large series published by Correa-Gallego et al. (78) who also did not find any significant difference in PPH between PD and DP. Postpancreatectomy hemorrhage rate in this study was found to be in the same range as other recent reports. Wellner and colleagues (81) found a PPH rate of 7.2% in a large series of more than 1000 pancreatic resections and Chen et al. (77) and Manas-Gomez et al. (79) found a PPH rate of 8.8% and 16.8% respectively. It can be concluded that the PPH rate in Ghent University Hospital is relatively low since all of these studies used the same ISGPS definition of PPH. Future research should focus on further identifying risk factors for PPH and defining optimal treatment modalities.

# Conclusion

In conclusion, the initial research question of the dissertation can now be answered. The first goal was to investigate the incidence of POPF in Ghent University Hospital and compare this to other literature data. The observed (CR)-POPF rate after Whipple surgery is fairly low compared to other series which can probably be attributed to high surgeon experience and the consistent use of the same anastomosis technique. CR-POPF rate after distal pancreatectomy is comparable to other series and this type of surgery is probably less prone to influences from surgeon experience. Progressive closure of the pancreatic remnant with a linear stapler was used and this is the best technique according to current literature data but more research on alternative techniques is needed.

The second aim of this research was to investigate potential risk factors for POPF. First of all, distal pancreatectomy is accompanied by a significantly higher incidence of POPF than Whipple surgery and could therefore be seen as a ‘risk factor’ itself. Secondly, soft pancreatic texture is a significant risk factor for POPF after PD, which supports its use in POPF risk scores. A larger patient cohort would probably also show a significant correlation with CR-POPF after PD and with POPF after DP. In the same context, it could be beneficial to implement transabdominal ultrasonography with ARFI in Ghent University Hospital to determine pancreatic texture objectively, making this parameter available prior to surgery and thus allowing the adaptation of surgical strategy based on preoperative POPF risk estimates. Thirdly, DGE showed a trend towards significance for developing CR-POPF after DP, indicating that it is probably worth investigating this association in a larger sample size. Furthermore, High BMI showed to be a significant risk factor for POPF after DP but the risk for confounding influences is high. Serum albumin levels should also be measured in future studies to evaluate the effects of nutritional status in more detail. Finally, diabetes proved to be a significant protective factor for POPF after DP and the percentage of diabetic patients in the group without POPF was always higher than in the group who did develop this complication. Multiple explanations supporting these findings have already been proposed in other studies and these results warrant further research to make more solid conclusions concerning the conflicting data found in current literature.

The third aim of this retrospective study was to investigate the incidence of DGE and PPH after pancreatic surgery in Ghent University Hospital and compare this to other literature data. The incidence of DGE is comparable to other reported series but further research concerning the underlying mechanisms of this complication is desirable. The PPH rate on the other hand, is relatively low compared to other data, indicating that no significant flaws in surgical technique or postoperative care are present. Future research should focus on identifying risk factors for PPH and defining optimal treatment modalities.

This study is of value as the presented series of pancreatic surgeries adds to the available data on POPF and its risk factors, thereby expanding the evidence to draw definite conclusions on the association between certain patient, disease or operative risk factors and the occurrence of complications. Future research should focus on analyzing which treatment options are optimal for different grades of POPF, using end points such as fistula closure time, duration of hospitalization and in hospital mortality. Another benefit of this study is that the three most important complications (POPF, PPH and DGE) were analyzed within the same patient cohort, allowing the investigation of associations between these complications. However, it would have been of added value if we had analyzed potential risk factors for DGE and PPH as well. In general, the biggest limitation of this study is its retrospective design. Inherent to this study design was the problem of frequent missing data for some variables, which substantially limited the statistical power of certain analyses. Also, the variables that were available for analysis were determined when this database was created, implying the absence of some relevant data such as serum albumin levels. The use of lipase instead of amylase to identify POPF might also be a point of criticism, as it is not in accordance with the ISGPS definition. However, it should be taken into account that quite possibly the use of lipase implies that our CR-POPF rates are overestimated compared to other studies using the ISGPS definition.

# References

1. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016;388(10039):73-85.

2. Barone E, Corrado A, Gemignani F, Landi S. Environmental risk factors for pancreatic cancer: an update. Arch Toxicol. 2016;90(11):2617-42.

3. Amundadottir LT. Pancreatic Cancer Genetics. Int J Biol Sci. 2016;12(3):314-25.

4. Manohar M, Verma AK, Venkateshaiah SU, Sanders NL, Mishra A. Pathogenic mechanisms of pancreatitis. World J Gastrointest Pharmacol Ther. 2017;8(1):10-25.

5. Forsmark CE, Vege SS, Wilcox CM. Acute Pancreatitis. N Engl J Med. 2016;375(20):1972-81.

6. Duggan SN, Ni Chonchubhair HM, Lawal O, O'Connor DB, Conlon KC. Chronic pancreatitis: A diagnostic dilemma. World J Gastroenterol. 2016;22(7):2304-13.

7. Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016;387(10031):1957-66.

8. Tillou JD, Tatum JA, Jolissaint JS, Strand DS, Wang AY, Zaydfudim V, et al. Operative management of chronic pancreatitis: A review. Am J Surg. 2017.

9. Clancy TE. Surgery for Pancreatic Cancer. Hematol Oncol Clin North Am. 2015;29(4):701-16.

10. Eskander MF, Bliss LA, Tseng JF. Pancreatic adenocarcinoma. Curr Probl Surg. 2016;53(3):107-54.

11. Hartwig W, Werner J, Jager D, Debus J, Buchler MW. Improvement of surgical results for pancreatic cancer. Lancet Oncol. 2013;14(11):e476-85.

12. Shrikhande SV, D'Souza MA. Pancreatic fistula after pancreatectomy: evolving definitions, preventive strategies and modern management. World J Gastroenterol. 2008;14(38):5789-96.

13. Ridolfi C, Angiolini MR, Gavazzi F, Spaggiari P, Tinti MC, Uccelli F, et al. Morphohistological features of pancreatic stump are the main determinant of pancreatic fistula after pancreatoduodenectomy. Biomed Res Int. 2014;2014:641239.

14. Callery MP, Pratt WB, Vollmer CM, Jr. Prevention and management of pancreatic fistula. J Gastrointest Surg. 2009;13(1):163-73.

15. Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, Falconi M, et al. Pancreatic fistula rate after pancreatic resection. The importance of definitions. Dig Surg. 2004;21(1):54-9.

16. Griffin JF, Poruk KE, Wolfgang CL. Pancreatic cancer surgery: past, present, and future. Chin J Cancer Res. 2015;27(4):332-48.

17. Yabar CS, Winter JM. Pancreatic Cancer: A Review. Gastroenterol Clin North Am. 2016;45(3):429-45.

18. Gordon TA, Bowman HM, Tielsch JM, Bass EB, Burleyson GP, Cameron JL. Statewide regionalization of pancreaticoduodenectomy and its effect on in-hospital mortality. Ann Surg. 1998;228(1):71-8.

19. Kagedan DJ, Goyert N, Li Q, Paszat L, Kiss A, Earle CC, et al. The Impact of Increasing Hospital Volume on 90-Day Postoperative Outcomes Following Pancreaticoduodenectomy. J Gastrointest Surg. 2017;21(3):506-15.

20. van der Geest LG, van Rijssen LB, Molenaar IQ, de Hingh IH, Groot Koerkamp B, Busch OR, et al. Volume-outcome relationships in pancreatoduodenectomy for cancer. HPB (Oxford). 2016;18(4):317-24.

21. Gooiker GA, van Gijn W, Wouters MW, Post PN, van de Velde CJ, Tollenaar RA. Systematic review and meta-analysis of the volume-outcome relationship in pancreatic surgery. Br J Surg. 2011;98(4):485-94.

22. Winter JM, Brennan MF, Tang LH, D'Angelica MI, Dematteo RP, Fong Y, et al. Survival after resection of pancreatic adenocarcinoma: results from a single institution over three decades. Ann Surg Oncol. 2012;19(1):169-75.

23. Schnelldorfer T, Ware AL, Sarr MG, Smyrk TC, Zhang L, Qin R, et al. Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? Ann Surg. 2008;247(3):456-62.

24. Hines OJ, Reber HA. Pancreatic surgery. Curr Opin Gastroenterol. 2009;25(5):460-5.

25. Jilesen AP, van Eijck CH, in't Hof KH, van Dieren S, Gouma DJ, van Dijkum EJ. Postoperative Complications, In-Hospital Mortality and 5-Year Survival After Surgical Resection for Patients with a Pancreatic Neuroendocrine Tumor: A Systematic Review. World J Surg. 2016;40(3):729-48.

26. Soreide K, Labori KJ. Risk factors and preventive strategies for post-operative pancreatic fistula after pancreatic surgery: a comprehensive review. Scand J Gastroenterol. 2016;51(10):1147-54.

27. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138(1):8-13.

28. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142(1):20-5.

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

30. Matthews JB. Prevention, evaluation, and treatment of leaks after pancreatic surgery. J Gastrointest Surg. 2011;15(8):1327-8.

31. Lai EC, Lau SH, Lau WY. Measures to prevent pancreatic fistula after pancreatoduodenectomy: a comprehensive review. Arch Surg. 2009;144(11):1074-80.

32. Malleo G, Pulvirenti A, Marchegiani G, Butturini G, Salvia R, Bassi C. Diagnosis and management of postoperative pancreatic fistula. Langenbecks Arch Surg. 2014;399(7):801-10.

33. Shinchi H, Wada K, Traverso LW. The usefulness of drain data to identify a clinically relevant pancreatic anastomotic leak after pancreaticoduodenectomy? J Gastrointest Surg. 2006;10(4):490-8.

34. Bruno O, Brancatelli G, Sauvanet A, Vullierme MP, Barrau V, Vilgrain V. Utility of CT in the diagnosis of pancreatic fistula after pancreaticoduodenectomy in patients with soft pancreas. AJR Am J Roentgenol. 2009;193(3):W175-80.

35. Bassi C, Malleo G. Pancreas: Postoperative pancreatic fistula: use of enteral nutrition. Nat Rev Gastroenterol Hepatol. 2011;8(8):427-8.

36. Fong YM, Marano MA, Barber A, He W, Moldawer LL, Bushman ED, et al. Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. Ann Surg. 1989;210(4):449-56; discussion 56-7.

37. O'Keefe SJ. Physiological response of the human pancreas to enteral and parenteral feeding. Curr Opin Clin Nutr Metab Care. 2006;9(5):622-8.

38. Spiller RC, Trotman IF, Higgins BE, Ghatei MA, Grimble GK, Lee YC, et al. The ileal brake--inhibition of jejunal motility after ileal fat perfusion in man. Gut. 1984;25(4):365-74.

39. Klek S, Sierzega M, Turczynowski L, Szybinski P, Szczepanek K, Kulig J. Enteral and parenteral nutrition in the conservative treatment of pancreatic fistula: a randomized clinical trial. Gastroenterology. 2011;141(1):157-63, 63 e1.

40. Gans SL, van Westreenen HL, Kiewiet JJ, Rauws EA, Gouma DJ, Boermeester MA. Systematic review and meta-analysis of somatostatin analogues for the treatment of pancreatic fistula. Br J Surg. 2012;99(6):754-60.

41. Bartoli E, Rebibo L, Robert B, Fumery M, Delcenserie R, Regimbeau JM. Efficacy of the double-pigtail stent as a conservative treatment for grade B pancreatic fistula after pancreatoduodenectomy with pancreatogastric anastomosis. Surg Endosc. 2014;28(5):1528-34.

42. Reddymasu SC, Pakseresht K, Moloney B, Alsop B, Oropezia-Vail M, Olyaee M. Incidence of pancreatic fistula after distal pancreatectomy and efficacy of endoscopic therapy for its management: results from a tertiary care center. Case Rep Gastroenterol. 2013;7(2):332-9.

43. Sohn TA, Yeo CJ, Cameron JL, Geschwind JF, Mitchell SE, Venbrux AC, et al. Pancreaticoduodenectomy: role of interventional radiologists in managing patients and complications. J Gastrointest Surg. 2003;7(2):209-19.

44. Munoz-Bongrand N, Sauvanet A, Denys A, Sibert A, Vilgrain V, Belghiti J. Conservative management of pancreatic fistula after pancreaticoduodenectomy with pancreaticogastrostomy. J Am Coll Surg. 2004;199(2):198-203.

45. Sanjay P, Kellner M, Tait IS. The role of interventional radiology in the management of surgical complications after pancreatoduodenectomy. HPB (Oxford). 2012;14(12):812-7.

46. Kwon YM, Gerdes H, Schattner MA, Brown KT, Covey AM, Getrajdman GI, et al. Management of peripancreatic fluid collections following partial pancreatectomy: a comparison of percutaneous versus EUS-guided drainage. Surg Endosc. 2013;27(7):2422-7.

47. Azeem N, Baron TH, Topazian MD, Zhong N, Fleming CJ, Kendrick ML. Outcomes of endoscopic and percutaneous drainage of pancreatic fluid collections arising after pancreatic tail resection. J Am Coll Surg. 2012;215(2):177-85.

48. Onodera M, Kawakami H, Kuwatani M, Kudo T, Haba S, Abe Y, et al. Endoscopic ultrasound-guided transmural drainage for pancreatic fistula or pancreatic duct dilation after pancreatic surgery. Surg Endosc. 2012;26(6):1710-7.

49. Tilara A, Gerdes H, Allen P, Jarnagin W, Kingham P, Fong Y, et al. Endoscopic ultrasound-guided transmural drainage of postoperative pancreatic collections. J Am Coll Surg. 2014;218(1):33-40.

50. Balzano G, Pecorelli N, Piemonti L, Ariotti R, Carvello M, Nano R, et al. Relaparotomy for a pancreatic fistula after a pancreaticoduodenectomy: a comparison of different surgical strategies. HPB (Oxford). 2014;16(1):40-5.

51. Denbo JW, Orr WS, Zarzaur BL, Behrman SW. Toward defining grade C pancreatic fistula following pancreaticoduodenectomy: incidence, risk factors, management and outcome. HPB (Oxford). 2012;14(9):589-93.

52. Gangl O, Froschl U, Hofer W, Huber J, Sautner T, Fugger R. Unplanned reoperation and reintervention after pancreatic resections: an analysis of risk factors. World J Surg. 2011;35(10):2306-14.

53. Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. J Gastrointest Surg. 2004;8(8):951-9.

54. Shrikhande SV, Sivasanker M, Vollmer CM, Friess H, Besselink MG, Fingerhut A, et al. Pancreatic anastomosis after pancreatoduodenectomy: A position statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2017;161(5):1221-34.

55. Connor S, Alexakis N, Garden OJ, Leandros E, Bramis J, Wigmore SJ. Meta-analysis of the value of somatostatin and its analogues in reducing complications associated with pancreatic surgery. Br J Surg. 2005;92(9):1059-67.

56. Gurusamy KS, Koti R, Fusai G, Davidson BR. Somatostatin analogues for pancreatic surgery. Cochrane Database Syst Rev. 2013(4):CD008370.

57. Dong Z, Xu J, Wang Z, Petrov MS. Stents for the prevention of pancreatic fistula following pancreaticoduodenectomy. Cochrane Database Syst Rev. 2016(5):CD008914.

58. Adham M, Chopin-Laly X, Lepilliez V, Gincul R, Valette PJ, Ponchon T. Pancreatic resection: drain or no drain? Surgery. 2013;154(5):1069-77.

59. Van Buren G, 2nd, Bloomston M, Hughes SJ, Winter J, Behrman SW, Zyromski NJ, et al. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. Ann Surg. 2014;259(4):605-12.

60. Noorani A, Rangelova E, Del Chiaro M, Lundell LR, Ansorge C. Delayed Gastric Emptying after Pancreatic Surgery: Analysis of Factors Determinant for the Short-term Outcome. Front Surg. 2016;3:25.

61. Qu H, Sun GR, Zhou SQ, He QS. Clinical risk factors of delayed gastric emptying in patients after pancreaticoduodenectomy: a systematic review and meta-analysis. Eur J Surg Oncol. 2013;39(3):213-23.

62. Wu W, Hong X, Fu L, Liu S, You L, Zhou L, et al. The effect of pylorus removal on delayed gastric emptying after pancreaticoduodenectomy: a meta-analysis of 2,599 patients. PLoS One. 2014;9(10):e108380.

63. El Nakeeb A, Askr W, Mahdy Y, Elgawalby A, El Sorogy M, Abu Zeied M, et al. Delayed gastric emptying after pancreaticoduodenectomy. Risk factors, predictors of severity and outcome. A single center experience of 588 cases. J Gastrointest Surg. 2015;19(6):1093-100.

64. Healy JM, Kunstman JW, Salem RR. Proposal and critical appraisal of exclusion criteria to the international study group for pancreatic surgery definition of delayed gastric emptying. J Am Coll Surg. 2015;220(6):1036-43 e1.

65. Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A, Uchiyama K, et al. Pylorus ring resection reduces delayed gastric emptying in patients undergoing pancreatoduodenectomy: a prospective, randomized, controlled trial of pylorus-resecting versus pylorus-preserving pancreatoduodenectomy. Ann Surg. 2011;253(3):495-501.

66. Ohwada S, Satoh Y, Kawate S, Yamada T, Kawamura O, Koyama T, et al. Low-dose erythromycin reduces delayed gastric emptying and improves gastric motility after Billroth I pylorus-preserving pancreaticoduodenectomy. Ann Surg. 2001;234(5):668-74.

67. Balzano G, Zerbi A, Braga M, Rocchetti S, Beneduce AA, Di Carlo V. Fast-track recovery programme after pancreatico- duodenectomy reduces delayed gastric emptying. Br J Surg. 2008;95(11):1387-93.

68. Nikfarjam M, Kimchi ET, Gusani NJ, Shah SM, Sehmbey M, Shereef S, et al. A reduction in delayed gastric emptying by classic pancreaticoduodenectomy with an antecolic gastrojejunal anastomosis and a retrogastric omental patch. J Gastrointest Surg. 2009;13(9):1674-82.

69. Tani M, Terasawa H, Kawai M, Ina S, Hirono S, Uchiyama K, et al. Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. Ann Surg. 2006;243(3):316-20.

70. Murakami Y, Uemura K, Sudo T, Hayashidani Y, Hashimoto Y, Nakagawa N, et al. An antecolic Roux-en Y type reconstruction decreased delayed gastric emptying after pylorus-preserving pancreatoduodenectomy. J Gastrointest Surg. 2008;12(6):1081-6.

71. Patel AG, Toyama MT, Kusske AM, Alexander P, Ashley SW, Reber HA. Pylorus-preserving Whipple resection for pancreatic cancer. Is it any better? Arch Surg. 1995;130(8):838-42; discussion 42-3.

72. Horstmann O, Markus PM, Ghadimi MB, Becker H. Pylorus preservation has no impact on delayed gastric emptying after pancreatic head resection. Pancreas. 2004;28(1):69-74.

73. Bassi C, Falconi M, Molinari E, Salvia R, Butturini G, Sartori N, et al. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. Ann Surg. 2005;242(6):767-71, discussion 71-3.

74. Lermite E, Pessaux P, Brehant O, Teyssedou C, Pelletier I, Etienne S, et al. Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. J Am Coll Surg. 2007;204(4):588-96.

75. Park YC, Kim SW, Jang JY, Ahn YJ, Park YH. Factors influencing delayed gastric emptying after pylorus-preserving pancreatoduodenectomy. J Am Coll Surg. 2003;196(6):859-65.

76. Park JS, Hwang HK, Kim JK, Cho SI, Yoon DS, Lee WJ, et al. Clinical validation and risk factors for delayed gastric emptying based on the International Study Group of Pancreatic Surgery (ISGPS) Classification. Surgery. 2009;146(5):882-7.

77. Chen JF, Xu SF, Zhao W, Tian YH, Gong L, Yuan WS, et al. Diagnostic and therapeutic strategies to manage post-pancreaticoduodenectomy hemorrhage. World J Surg. 2015;39(2):509-15.

78. Correa-Gallego C, Brennan MF, D'Angelica MI, DeMatteo RP, Fong Y, Kingham TP, et al. Contemporary experience with postpancreatectomy hemorrhage: results of 1,122 patients resected between 2006 and 2011. J Am Coll Surg. 2012;215(5):616-21.

79. Manas-Gomez MJ, Rodriguez-Revuelto R, Balsells-Valls J, Olsina-Kissler JJ, Caralt-Barba M, Perez-Lafuente M, et al. Post-pancreaticoduodenectomy hemorrhage. Incidence, diagnosis, and treatment. World J Surg. 2011;35(11):2543-8.

80. Rajarathinam G, Kannan DG, Vimalraj V, Amudhan A, Rajendran S, Jyotibasu D, et al. Post pancreaticoduodenectomy haemorrhage: outcome prediction based on new ISGPS Clinical severity grading. HPB (Oxford). 2008;10(5):363-70.

81. Wellner UF, Kulemann B, Lapshyn H, Hoeppner J, Sick O, Makowiec F, et al. Postpancreatectomy hemorrhage--incidence, treatment, and risk factors in over 1,000 pancreatic resections. J Gastrointest Surg. 2014;18(3):464-75.

82. Gao F, Li J, Quan S, Li F, Ma D, Yao L, et al. Risk Factors and Treatment for Hemorrhage after Pancreaticoduodenectomy: A Case Series of 423 Patients. Biomed Res Int. 2016;2016:2815693.

83. Dai R, Turley RS, Blazer DG. Contemporary review of minimally invasive pancreaticoduodenectomy. World J Gastrointest Surg. 2016;8(12):784-91.

84. Zhang YH, Zhang CW, Hu ZM, Hong DF. Pancreatic cancer: Open or minimally invasive surgery? World J Gastroenterol. 2016;22(32):7301-10.

85. Conwell DL, Banks PA. Chronic pancreatitis. Curr Opin Gastroenterol. 2008;24(5):586-90.

86. Mitchell RM, Byrne MF, Baillie J. Pancreatitis. Lancet. 2003;361(9367):1447-55.

87. Nassour I, Choti MA. Pancreatic Operations. JAMA. 2016;316(18):1932.

88. Wayne MG, Jorge IA, Cooperman AM. Alternative reconstruction after pancreaticoduodenectomy. World J Surg Oncol. 2008;6:9.

89. Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol. 2016;22(44):9694-705.

90. Malvezzi M, Bertuccio P, Rosso T, Rota M, Levi F, La Vecchia C, et al. European cancer mortality predictions for the year 2015: does lung cancer have the highest death rate in EU women? Ann Oncol. 2015;26(4):779-86.

91. Mayor S. Deaths from pancreatic cancer in Europe continue to increase while rates for other cancers fall. BMJ. 2014;348:g2914.

92. Hidalgo M. Pancreatic cancer. N Engl J Med. 2010;362(17):1605-17.

93. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer. 2008;44(10):1345-89.

94. Goral V. Pancreatic Cancer: Pathogenesis and Diagnosis. Asian Pac J Cancer Prev. 2015;16(14):5619-24.

95. Keane MG, Horsfall L, Rait G, Pereira SP. A case-control study comparing the incidence of early symptoms in pancreatic and biliary tract cancer. BMJ Open. 2014;4(11):e005720.

96. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Eur J Surg Oncol. 2007;33(3):266-70.

97. McIntyre CA, Winter JM. Diagnostic evaluation and staging of pancreatic ductal adenocarcinoma. Semin Oncol. 2015;42(1):19-27.

98. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(8):1028-61.

99. Mayo SC, Austin DF, Sheppard BC, Mori M, Shipley DK, Billingsley KG. Evolving preoperative evaluation of patients with pancreatic cancer: does laparoscopy have a role in the current era? J Am Coll Surg. 2009;208(1):87-95.

100. Tapper E, Kalb B, Martin DR, Kooby D, Adsay NV, Sarmiento JM. Staging laparoscopy for proximal pancreatic cancer in a magnetic resonance imaging-driven practice: what's it worth? HPB (Oxford). 2011;13(10):732-7.

101. Huttner FJ, Fitzmaurice C, Schwarzer G, Seiler CM, Antes G, Buchler MW, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. Cochrane Database Syst Rev. 2016;2:CD006053.

102. Pitt HA, Grace PA. Cancer of the pancreas. Pylorus-preserving resection of the pancreas. Baillieres Clin Gastroenterol. 1990;4(4):917-30.

103. Machado NO. Pancreatic fistula after pancreatectomy: definitions, risk factors, preventive measures, and management-review. Int J Surg Oncol. 2012;2012:602478.

104. Bruns H, Kortendieck V, Raab HR, Antolovic D. Intraoperative Fluid Excess Is a Risk Factor for Pancreatic Fistula after Partial Pancreaticoduodenectomy. HPB Surg. 2016;2016:1601340.

105. Gagniere J, Abjean A, Franz M, Aumont O, Pereira B, Dupre A, et al. A Normal Preoperative Lipase Serum Level Is an Easy and Objective Risk Factor of Pancreatic Fistula After Pancreaticoduodenectomy. Pancreas. 2017;46(9):1133-40.

106. Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol. 2005;11(16):2456-61.

107. Facy O, Chalumeau C, Poussier M, Binquet C, Rat P, Ortega-Deballon P. Diagnosis of postoperative pancreatic fistula. Br J Surg. 2012;99(8):1072-5.

108. Guilbaud T, Birnbaum DJ, Loubiere S, Bonnet J, Chopinet S, Gregoire E, et al. Comparison of different feeding regimes after pancreatoduodenectomy - a retrospective cohort analysis. Nutr J. 2017;16(1):42.

109. Hu BY, Wan T, Zhang WZ, Dong JH. Risk factors for postoperative pancreatic fistula: Analysis of 539 successive cases of pancreaticoduodenectomy. World J Gastroenterol. 2016;22(34):7797-805.

110. McMillan MT, Christein JD, Callery MP, Behrman SW, Drebin JA, Hollis RH, et al. Comparing the burden of pancreatic fistulas after pancreatoduodenectomy and distal pancreatectomy. Surgery. 2016;159(4):1013-22.

111. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg. 2015;220(4):530-6.

112. Aranha GV, Aaron JM, Shoup M, Pickleman J. Current management of pancreatic fistula after pancreaticoduodenectomy. Surgery. 2006;140(4):561-8; discussion 8-9.

113. Kawai M, Kondo S, Yamaue H, Wada K, Sano K, Motoi F, et al. Predictive risk factors for clinically relevant pancreatic fistula analyzed in 1,239 patients with pancreaticoduodenectomy: multicenter data collection as a project study of pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci. 2011;18(4):601-8.

114. McMillan MT, Soi S, Asbun HJ, Ball CG, Bassi C, Beane JD, et al. Risk-adjusted Outcomes of Clinically Relevant Pancreatic Fistula Following Pancreatoduodenectomy: A Model for Performance Evaluation. Ann Surg. 2016;264(2):344-52.

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

116. Goh BK, Tan YM, Chung YF, Cheow PC, Ong HS, Chan WH, et al. Critical appraisal of 232 consecutive distal pancreatectomies with emphasis on risk factors, outcome, and management of the postoperative pancreatic fistula: a 21-year experience at a single institution. Arch Surg. 2008;143(10):956-65.

117. Ecker BL, McMillan MT, Allegrini V, Bassi C, Beane JD, Beckman RM, et al. Risk Factors and Mitigation Strategies for Pancreatic Fistula After Distal Pancreatectomy: Analysis of 2026 Resections From the International, Multi-institutional Distal Pancreatectomy Study Group. Ann Surg. 2017.

118. Kleeff J, Diener MK, Z'Graggen K, Hinz U, Wagner M, Bachmann J, et al. Distal pancreatectomy: risk factors for surgical failure in 302 consecutive cases. Ann Surg. 2007;245(4):573-82.

119. Zhang H, Zhu F, Shen M, Tian R, Shi CJ, Wang X, et al. Systematic review and meta-analysis comparing three techniques for pancreatic remnant closure following distal pancreatectomy. Br J Surg. 2015;102(1):4-15.

120. Hackert T, Hinz U, Pausch T, Fesenbeck I, Strobel O, Schneider L, et al. Postoperative pancreatic fistula: We need to redefine grades B and C. Surgery. 2016;159(3):872-7.

121. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161(3):584-91.

122. Kim WS, Choi DW, Choi SH, Heo JS, Kim MJ, Song SC, et al. Clinical validation of the ISGPF classification and the risk factors of pancreatic fistula formation following duct-to-mucosa pancreaticojejunostomy by one surgeon at a single center. J Gastrointest Surg. 2011;15(12):2187-92.

123. Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, Vollmer CM, Jr. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg. 2007;245(3):443-51.

124. Murakami Y, Uemura K, Hayasidani Y, Sudo T, Hashimoto Y, Nakagawa N, et al. A soft pancreatic remnant is associated with increased drain fluid pancreatic amylase and serum CRP levels following pancreatoduodenectomy. J Gastrointest Surg. 2008;12(1):51-6.

125. Wellner UF, Kayser G, Lapshyn H, Sick O, Makowiec F, Hoppner J, et al. A simple scoring system based on clinical factors related to pancreatic texture predicts postoperative pancreatic fistula preoperatively. HPB (Oxford). 2010;12(10):696-702.

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

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

128. Peng YP, Zhu XL, Yin LD, Zhu Y, Wei JS, Wu JL, et al. Risk factors of postoperative pancreatic fistula in patients after distal pancreatectomy: a systematic review and meta-analysis. Sci Rep. 2017;7(1):185.

129. Harada N, Ishizawa T, Inoue Y, Aoki T, Sakamoto Y, Hasegawa K, et al. Acoustic radiation force impulse imaging of the pancreas for estimation of pathologic fibrosis and risk of postoperative pancreatic fistula. J Am Coll Surg. 2014;219(5):887-94 e5.

130. Kuwahara T, Hirooka Y, Kawashima H, Ohno E, Yokoyama Y, Fujii T, et al. Usefulness of endoscopic ultrasonography-elastography as a predictive tool for the occurrence of pancreatic fistula after pancreatoduodenectomy. J Hepatobiliary Pancreat Sci. 2017.

131. Hong TH, Choi JI, Park MY, Rha SE, Lee YJ, You YK, et al. Pancreatic hardness: Correlation of surgeon's palpation, durometer measurement and preoperative magnetic resonance imaging features. World J Gastroenterol. 2017;23(11):2044-51.

132. Shi Y, Glaser KJ, Venkatesh SK, Ben-Abraham EI, Ehman RL. Feasibility of using 3D MR elastography to determine pancreatic stiffness in healthy volunteers. J Magn Reson Imaging. 2015;41(2):369-75.

133. Yoon JH, Lee JM, Lee KB, Kim SW, Kang MJ, Jang JY, et al. Pancreatic Steatosis and Fibrosis: Quantitative Assessment with Preoperative Multiparametric MR Imaging. Radiology. 2016;279(1):140-50.

134. Matsusue S, Takeda H, Nakamura Y, Nishimura S, Koizumi S. A prospective analysis of the factors influencing pancreaticojejunostomy performed using a single method, in 100 consecutive pancreaticoduodenectomies. Surg Today. 1998;28(7):719-26.

135. Glowka TR, von Websky M, Pantelis D, Manekeller S, Standop J, Kalff JC, et al. Risk factors for delayed gastric emptying following distal pancreatectomy. Langenbecks Arch Surg. 2016;401(2):161-7.

136. Liu QY, Li L, Xia HT, Zhang WZ, Cai SW, Lu SC. Risk factors of delayed gastric emptying following pancreaticoduodenectomy. ANZ J Surg. 2016;86(1-2):69-73.

137. Seeliger H, Christians S, Angele MK, Kleespies A, Eichhorn ME, Ischenko I, et al. Risk factors for surgical complications in distal pancreatectomy. Am J Surg. 2010;200(3):311-7.

138. Sledzianowski JF, Duffas JP, Muscari F, Suc B, Fourtanier F. Risk factors for mortality and intra-abdominal morbidity after distal pancreatectomy. Surgery. 2005;137(2):180-5.

139. Kawaida H, Kono H, Watanabe M, Hosomura N, Amemiya H, Fujii H. Risk factors of postoperative pancreatic fistula after distal pancreatectomy using a triple-row stapler. Surg Today. 2017.

140. Schnelldorfer T, Mauldin PD, Lewin DN, Adams DB. Distal pancreatectomy for chronic pancreatitis: risk factors for postoperative pancreatic fistula. J Gastrointest Surg. 2007;11(8):991-7.

141. Sierzega M, Niekowal B, Kulig J, Popiela T. Nutritional status affects the rate of pancreatic fistula after distal pancreatectomy: a multivariate analysis of 132 patients. J Am Coll Surg. 2007;205(1):52-9.

142. Cheng TY, Sheth K, White RR, Ueno T, Hung CF, Clary BM, et al. Effect of neoadjuvant chemoradiation on operative mortality and morbidity for pancreaticoduodenectomy. Ann Surg Oncol. 2006;13(1):66-74.

143. Ishikawa O, Ohigashi H, Imaoka S, Teshima T, Inoue T, Sasaki Y, et al. Concomitant benefit of preoperative irradiation in preventing pancreas fistula formation after pancreatoduodenectomy. Arch Surg. 1991;126(7):885-9.

144. Srivastava S, Sikora SS, Pandey CM, Kumar A, Saxena R, Kapoor VK. Determinants of pancreaticoenteric anastomotic leak following pancreaticoduodenectomy. ANZ J Surg. 2001;71(9):511-5.

145. Chu CK, Mazo AE, Sarmiento JM, Staley CA, Adsay NV, Umpierrez GE, et al. Impact of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. J Am Coll Surg. 2010;210(4):463-73.

146. Xia X, Huang C, Cen G, Qiu ZJ. Preoperative diabetes as a protective factor for pancreatic fistula after pancreaticoduodenectomy: a meta-analysis. Hepatobiliary Pancreat Dis Int. 2015;14(2):132-8.

147. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ, et al. Fatty pancreas: a factor in postoperative pancreatic fistula. Ann Surg. 2007;246(6):1058-64.

148. Friess H, Malfertheiner P, Isenmann R, Kuhne H, Beger HG, Buchler MW. The risk of pancreaticointestinal anastomosis can be predicted preoperatively. Pancreas. 1996;13(2):202-8.

149. Yamamoto Y, Sakamoto Y, Ban D, Shimada K, Esaki M, Nara S, et al. Is celiac axis resection justified for T4 pancreatic body cancer? Surgery. 2012;151(1):61-9.

# Appendix 1: List of abbreviations

**Abbreviation explanation**

ADC apparent diffusion coefficient

AJCC American Joint Cancer Committee

ARFI acoustic radiation force impulse imaging

BMI body mass index

CR-POPF clinically relevant postoperative pancreatic fistula

CT computed tomography

DGE delayed gastric emptying

DP distal pancreatectomy

DWI diffusion-weighted imaging

EN enteral nutrition

EUS endoscopic ultrasonography

EUS-EG endoscopic ultrasonography-guided elastography

ISGPF International Study Group for Pancreatic Fistula

ISGPS International Study Group of Pancreatic Surgery

IVIM DW intravoxel incoherent motion diffusion-weighted imaging

ME mean elasticity

MRI magnetic resonance imaging

NCCN National Comprehensive Cancer Network

NGT nasogastric tube

PC pancreatic cancer

PD pancreaticoduodenectomy

PDA pancreatic ductal adenocarcinoma

PG pancreaticogastrostomy

PJ pancreaticojejunostomy

POD postoperative day

POPF postoperative pancreatic fistula

PPH postpancreatectomy hemorrhage

RCT randomized controlled trial

SWV shear wave velocity

TPN total parenteral nutrition

US ultrasonography