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General Introduction and Outline of the Thesis
GENERAL INTRODUCTION

The Pancreas

Ever since its first description by the Greek anatomist and surgeon Herophilus around 300 B.C., the pancreas (πανκρεας, ἄναν ‘all’, κρεας ‘flesh’) has been surrounded with fascination, mystique, and even crime. The German anatomist Johann Georg Wirsung discovered the main pancreatic duct in 1642 in Padua, Italy, where he was a prosector performing autopsies for his mentor Johann Wesling. A year after his discovery, still regarded to date as Wirsung’s duct, Johann Georg Wirsung was assassinated. Reportedly Wesling, but also a co-worker named Giacomo Cambier is mentioned, were accused of the crime, the motive rumored to be jealousy.

Confusion over the gland’s nomenclature can also be regarded as indicative for the huge fascination of the organ. Whereas in the years of Hippocrates the word πανκρεας was used for all glands of the body, later authors, in particular Galen used the word καλικρεας (kalikreas; καλός ‘beautiful’).

Galen (Claudius Galenus; Pergamon 129 – 216 Rome) at the age of 28 was appointed "physician of the gladiators", a position of grand status and eventually the overture to the prestigious position of "Physician in Ordinary" in Rome. Combining keen clinical observation with detailed knowledge of anatomy Galen is regarded as a pioneer in surgery. He conducted numerous experiments on live animals to demonstrate the
functions of various organs and parts of the body: e.g. tying ureters of living animals to show that urine comes from the kidneys and severing spinal cords to demonstrate paralysis. Galen may have compared pancreatic juice to saliva and may have been the first to have had a vague idea of its digestive function. Contrarily a somewhat disparagingly description of the pancreas was also his: “a cushion of the stomach and pad supporting the (mesenteric) vessels”. Because of his undisputable reputation and almost divine medical authority this erring view was held up for more than 1500 years until Wirsung and contemporaries such as Joseph Conrad Brunner (1653–1727) ‘rediscovered’ the organ.

Pancreatic Surgery

A brief overview

The overview presented here only highlights some of the pioneering work as published throughout centuries of innovation on pancreatic surgery. For further details the interested reader is kindly referred to the quoted articles, original publications and books on the topic.

Surgery of the pancreas dates back to approximately the time of Wirsung and contemporaries, the Golden Age of Dutch Medicine. In the intellectual environment of Leyden the Dutch physiological experimentalist Regnier de Graaf (1641–1673) was stimulated to great extent by the physician Franciscus de le Boë, also known as Franciscus Sylvius, to date well-known for his achievements on cerebral anatomy (but also accredited being the inventor of ‘genever’ [gin]). De Graaf resolved to put the
doctrines of his master to the test of experiment. He constructed canine pancreatic fistulae to determine the nature of pancreatic secretion, and was urged by Sylvius to publish his findings in a treatise: *Disputatio Medica de Natura Succi Pancreatici*. A decade later Brunner undertook the first series of partial resections of canine pancreas.

In 1886 Nicholas Senn demonstrated that experimental extirpation of the pancreas in animals was associated with ‘a fatal result in every instance from a few hours to nine days after the operation’. Combined with the unavailability of antibiotics and limited technical expertise this fatal outcome could have initiated a firmly reluctant approach towards pancreatic surgery.

During the 19th century reports of pancreatic resections and the suggestion to intervene in disease processes that afflict the pancreas occasionally occur. However, these approaches provided the foundations of more successful procedures developed in the 20th century. The first surgical procedure for any pancreatic tumor was performed by Albert Lücke in 1867, who removed a cystic tumor of the pancreas, while Friedrich Trendelenburg successfully excised a solid tumor of the tail of the pancreas in 1882. The first cholecystojejunostomies, performed as palliative procedure for pancreatic cancer, were successfully undertaken by Otto Kappeler in 1887 in Switzerland and by Nestor Dmitrievic Monastyrski in Russia. By performing a 1-stage en bloc excision of the major part of the duodenum and the head of the pancreas Alessandro Codivilla in 1898, who later achieved prominence as an orthopedic surgeon, is considered being the first surgeon to perform a so-called pancreateoduodenectomy. Codivilla anastomosed the stomach and gallbladder to the small intestine, but his operation notes do not mention the pancreatic duct, nor is it clear how he managed the pancreatic remnant. The patient died 24 days later. In the same month, William Halsted undertook the first resection of an ampullary tumor in a 60-year-old female with a 6-month history of painless jaundice. The operation included common bile duct exploration, transduodenal papillectomy with reanastomosis of the pancreatic and bile ducts, and tube cholecystostomy. Although the reports have an anecdotic character, slowly the possibility of operating on the pancreas took ground.

**The 20th century**

At the beginning of the 20th century the association between a profound coagulation disorder and obstructive jaundice in patients with biliary obstruction due tumors at the pancreatic head was postulated. Malabsorption of the fat-soluble agent from the gut, vitamin K as would be discovered by Henrick Dam in 1929, ultimately resulted in coagulopathy and rendered major surgery hazardous, and in many instances fatal. An appreciation of the inherent risks associated with the presence of jaundice as well as the recognition of the dismal prognosis of pancreatic cancer led to the development of a two-stage operation. The first step was to relieve the “choleemia”, followed by removal of the tumor at second stage. Application of a bilio-enteric anastomosis at the first stage relieved obstructive jaundice with bile returning to the intestinal tract, which facilitated correction of the coagulation deficiency. In addition malnutrition,
regularly associated with jaundice, was reversed. After restoration of normal coagulation parameters pancreatic resection could be safely undertaken at second stage several weeks later.

Codivilla’s pancreatoduodenectomy probably comprised the first report of application of a bilo-enteric anastomosis specifically after pancreatic resection. However, earlier reports of varying forms of bilo-enteric anastomosis date back to 1880 when Alexander von Winiwarter performed a cholecystocolostomy in a patient with obstruction and an enlarged gallbladder. In following years successful experiments with choledochojejunostomy or duodenostomy for choledocholithiasis were published, but the true success for pancreatic surgery came with the introduction of the Roux-en-Y cholecystojejunostomy by Ambrose Monprof in 1904 and the Roux-en-Y choledochojejunostomy by Robert Dahl in 1908. These advances made the concept of operative excision of the head of the pancreas with its intrapancreatic bile duct a possibility.

In Berlin Walter Kausch performed in 1909 one of the first documented successful pancreatoduodenectomies, according to more ‘modern’ principles, in a patient with a carcinoma of the ampulla of Vater. Because of malnutrition and risk of bleeding due to established jaundice a 2-stage procedure was planned. First, Kausch relieved jaundice by making a cholecystojejunostomy, while 2 months later he resected the second and third part of the duodenum, the distal bile duct, and the pancreatic head during the second stage of the operation. A posterior gastrojejunostomy was performed and the pancreatic remnant was anastomosed to the open end of the distal duodenum. Nine months after the second operation the patient died from sepsis due to acute cholangitis.

The Legacy of Allen Oldfather Whipple

In 1935 Allen Oldfather Whipple published *Treatment of Carcinoma of The Ampulla of Vater*, thereby laying the fundamental groundwork for modern pancreatic surgery. In his paper Whipple advocates the two-stage procedure as operation of choice for periampullary tumors and describes critical factors in the success of this operation: (I) determination of the extent of the procedure; (II) avoidance of pancreatic anastomosis, (III) use of silk sutures. Although strictly not being the first surgeon to perform pancreatoduodenectomy, Whipple was the first to demonstrate the feasibility of pancreatic resection on a larger scale. He confirmed that patients could survive this type of surgery while maintaining acceptable quality of life, in his opinion a very important aspect of surgical care. As frequently occurs with important novelties Whipple’s own technical contributions to pancreatic surgery came unintended. Being observed as lecturer in 1940 to visiting surgeons Whipple operated on a patient thought to have a gastric carcinoma. However, intraoperatively he found that the suspected mass in fact was a tumor of the head of the pancreas. Because the patient was not jaundiced he concluded that ‘the ultimate procedure was not materially endangered’ (resection), and felt that a 1-stage procedure could be carried out. This operation, most likely the first anatomic, 1-stage pancreatoduodenectomy with
Antrectomy and complete removal of the duodenum, marks the beginning of modern pancreatic head resection. Since danger of hemorrhage could be controlled by now available preoperative vitamin K therapy, Whipple from then on plead for the 1-stage procedures to be the procedure of choice for periampullary tumors. This approach should reduce the risk of a second anesthesia and simplified the operation by the absence of operative adhesions. In his experience mortality could be brought down from 38 to 31% compared to the 2-stage procedure.

With further experience, technical refinements to the procedure were made, as well as for pre- and postoperative care. Blood transfusions, gastric decompression, antibiotics, and intra- and postoperative intravenous fluid resuscitation became widely available and routine. With respect to the surgical procedure the 1-stage option became the preferred operation. Nevertheless, in case of long-standing biliary obstruction, profound malnutrition or liver cirrhosis a staged approach remained common use.

Pancreatic surgery for benign disease
Pancreatic surgery in the early days was confined to malignant lesions. For benign pancreatic diseases such as chronic pancreatitis Whipple judged in 1942 that “surgery in these (vague) lesions (...) has not made any definite advances”, and, except for a bilio-enteric anastomosis for biliary complications, was best abandoned. Nevertheless, alongside the evolution of pathophysiologic understanding of pancreatic disease, early attempts were made to decompress and drain the pancreatic duct surgically.

Figure 3  Allen Oldfather Whipple (1881–1963). Courtesy of Archives & Special Collections, Columbia University Health Sciences Library, New York, New York.
for the hypothesis of pancreatic duct hypertension as a factor in the development of chronic pancreatitis.\textsuperscript{16} In 1951, William Longmire performed a caudal pancreatectomy with end-to-end pancreaticojejunostomy, later popularized by Merlin DuVal in 1954.\textsuperscript{17,18} In 1958, Charles Puestow and William Gillesby modified this procedure to a caudal pancreatectomy with splenectomy, an extended longitudinal opening of the pancreatic duct, and a Roux-en-Y, end-to-side or side-to-side pancreaticojejunostomy.\textsuperscript{19} Finally in 1960, Philip Partington and Robert Rochelle simplified the procedure by eliminating the caudal pancreatectomy and splenectomy.\textsuperscript{20}

Whenever patients suffered from an associated inflammatory pancreatic head enlargement pancreatoduodenectomy served as primary surgical procedure for removal of the pancreatic head for many years.\textsuperscript{21,22} However, the mentioned pancreatic duct drainage procedures paved the way to the lateral pancreaticojejunostomy with limited, non-anatomic pancreatic head resection described by Charles Frey in 1987 and the duodenum-preserving partial pancreatic head resection described by Hans Beger in 1980.\textsuperscript{23,24}

\textit{Biliary Drainage in the Context of Pancreatic Surgery}

\textbf{Historical perspective}

The staged approach as developed in the days of Kausch and Whipple can be considered the introduction of the concept of preoperative biliary drainage (PBD) to improve outcomes. However, the burden of surgical diversion of the biliary tree is significant, especially for patients who are already in a poor condition due to malnutrition. Possibly this could explain the generally reluctant approach to surgery for deeply jaundiced patients; to undergo major surgery twice simply was too much. Interest in the staged approach was renewed with the advent of a non-operative first stage (Table 1). External and later internal or combined (rendez-vous) techniques allowed for less-invasive PBD and, in case of internal drainage, restoration of the enterohepatic circulation. It was accomplished by inserting percutaneously a transhepatic stent (external drainage) into the biliary tract, or internally, by endoscopic retrograde cannulation of the bile duct with insertion of a stent (internal drainage).

With evolving technical refinements in the following decades, improved post-operative care and initiation of high-volume centers of excellence, pancreatic surgery arrived at the stage of becoming a feasible, regular treatment option rather than being exceptional and high-risk surgery.\textsuperscript{6,25,26} Parallel, PBD, either through external or internal drainage became the established first-line treatment for jaundiced patients with pancreatic or hepatobiliary malignancies. The firm place PBD has obtained in the treatment algorithm is well explained. In general, the first evaluation of jaundiced patients is done by internists and gastroenterologists. Percutaneous or endoscopic cholangiography was, and to date still is, routinely performed to visualize the biliary tree and hopefully discover the cause of the obstruction causing jaundice. Since most patients with pancreatic or hepatobiliary malignancies suffer from symptomatic jaundice with pruritus, and some degree of abdominal pain, this diagnostic
procedure is immediately followed by therapeutic stent placement. To some extent, it is hoped that this stenting will provide symptomatic improvement. Both of these procedures have been suggested to reflect the conditioned responses of the physician encountering a jaundiced patient, also referred to as the “barber phenomenon” – when you go to the barber, you get a haircut.

Table 1: Selected important developments in biliary drainage for pancreatic cancer.

<table>
<thead>
<tr>
<th>Year</th>
<th>Development</th>
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<tbody>
<tr>
<td>1909</td>
<td>Concept of surgical staged approach by Walther Kausch</td>
</tr>
<tr>
<td>1937</td>
<td>Introduction of technique of percutaneous transhepatic cholangiography (PTC)28</td>
</tr>
<tr>
<td>1964</td>
<td>Non-surgical percutaneous transhepatic drainage (external drainage) through use of PTC29</td>
</tr>
<tr>
<td>1968</td>
<td>Flexible ‘Chiba’ needle development allowing easy and thereby widespread use of PTC for external biliary drainage28</td>
</tr>
<tr>
<td>1978</td>
<td>Introduction of PTC drainage in the Netherlands by Prof. dr. D.J. Gouma</td>
</tr>
<tr>
<td>1970s</td>
<td>Introduction of endoscopic biliary drainage (internal drainage)</td>
</tr>
<tr>
<td>1990s</td>
<td>Self-expandable metal stents for internal drainage</td>
</tr>
</tbody>
</table>

The evidence

In the late 1970s, the first small studies on the effect of PBD indeed reported a reduced postoperative death rate in jaundiced patients who had undergone external drainage.30;31 Since then, numerous studies, randomized as well as retrospective, have compared the outcome of PBD followed by surgery with surgery without PBD. Studies in experimental animals have shown benefit of PBD, especially after internal drainage when the enterohepatic circulation was restored.32;33 However, clinical studies have failed to show this benefit, and although the procedure of PBD can be performed safely, its routine use (the ‘barber phenomenon’) started to be questioned in the late 1990s.34 Supporting this more critical view some later studies even reported deleterious effects of PBD on the postoperative outcome.35 Furthermore, the observation of a significant complication rate related to the procedure of PBD itself, frequently without yielding a beneficial effect on complications after surgery, led to the statement in the 2002 meta-analysis from our center that PBD “with current standards (...) carries no benefit and should not be performed routinely.”35 Criticism to this conclusion related primarily to the heterogeneous pathology and the employed outdated methodology of a large number of studies included in the meta-analysis.36 Also the technique of PBD in most studies was subject of debate: the percutaneous route was believed to be of higher risk and more prone to complications than endoscopic drainage with modern techniques, the current standard of PBD. Endoscopic drainage was used in only a minority of studies.

Appreciated but deemed impossible to achieve for practical (‘barber phenomenon’) and logistical reasons would be a definitive randomized controlled trial that compared PBD via endoscopy followed by surgery versus surgery without PBD.36 Logistic reasons to perform PBD were new but sound arguments: planning major
surgery in a high-volume center requires preparation and time which is provided in by performing PBD as a bridge to surgery. As such the exact clinical benefits of PBD, once introduced to improve the postoperative outcome in patients with obstructive jaundice caused by a tumor of the pancreatic head, remain unclear.

**Surgical Innovation and Outcome Evaluation**

The most common process for innovation in surgery is related to the intrinsically iterative nature of surgical practice itself. Innovation of a procedure in surgery or surgical management often continues as it is adopted into practice. Although for decades implementation of novel procedures occurred automatically, the acknowledged critical importance of assessment of treatment complications and proper outcome registration has challenged several traditions. This ‘evidence-based’ approach requires a framework, such as defined in 2009 by the Balliol Colloquium, which guides staged development and evaluation of surgical interventions. The Colloquium proposes a model (the IDEAL framework) to segment innovation in sequential stages, each requiring critical appraisal: Stage 1 – Innovation; Stage 2a – Development; Stage 2b – Exploration; Stage 3 – Assessment; Stage 4 – Long term evaluation. The primary aim of the framework is to protect patients.

Stage 1 describes the first use of a new procedure in a patient, prompted by the need for a new solution to a clinical problem. The development phase (stage 2a) involves planned use of a procedure in an initial small group of patients to support experience with its first use. The development phase is further explored in stage 2b, where the procedure has been described and main technical aspects worked out. Research information should provide information about the population presenting for the new treatment, which requires a shift from traditional procedure-based to disease-based reporting. Different than the previous stages which focus on development and description of outcomes, stage 3 aims to assess effectiveness against current standards. It is in this stage that randomized controlled trials are the default option. However, trials of surgical practice are sometimes unnecessary (e.g. suturing for repairing large wounds) or not feasible for ethical or pragmatic reasons such as recruitment difficulties (e.g. PBD versus surgery without PBD). In the final stage (stage 4) established procedures are assessed for long-term outcomes, preferably through use of a registry.

Innovation is the start but evaluation should follow to ensure quality of surgical care. In surgical practice traditionally the outcomes have been selected and assessed by surgeons themselves. Also in literature on pancreatic surgery these ‘physician-centered’ outcomes, e.g. procedure-related complications, morbidity, mortality, are extensively present. However, the notion that these outcomes are often not standardized, thus not reproducible and hinder evaluation and external validation is acknowledged. For example to describe leakage of the pancreatic anastomosis following pancreateoduodenectomy 26 definitions existed. Attempts to overcome the absence of standardized surgical terminology for definition of clinical outcomes have led to development of international consensus definitions of complications associ-
ated with pancreatic surgery. In addition to consensus definitions, the use of validated classification systems for complications, which rank adverse events by severity, is an important step forward towards transparency.

Although physician-centered outcomes are important, evaluation of surgery has to be extended to include the patient’s perspective. Patient’s perceptions can differ from the treating physician’s perspective, and an insight in these differences is crucial for patient satisfaction with treatment. Typically, this information is captured in questionnaires assessing health-related quality of life. Furthermore, studies have suggested that patients, who also actively participate in their care are more satisfied with their care and may have better health outcomes. Understanding of patients’ preferences may establish better and more effective decision making. Integrating the preceding paragraph there has been emerging evidence that the use of patient-reported complications might be related to the experienced health gain following surgery. The subject needs further exploration but when proven to be valid it might be a useful tool for outcome registration and measuring performance.

OUTLINE OF THE THESIS

The results presented here are largely based on research carried out on patient cohorts from the Academic Medical Center’s (AMC) Department of Surgery, which serves as a tertiary referral centre for pancreatic and hepatobiliary diseases in the Netherlands. The multidisciplinary and multicenter studies in this thesis were initiated and coordinated from this department.

The thesis summarizes almost 5 years of dedicated research in the field of hepatopancreaticobiliary surgery. The subject of PBD can be considered the stepping stone of this period of research; five chapters address various aspects of PBD for pancreatic surgery, varying from a literature review to basic experimental to clinical studies. The concept of surgical innovation and (multidimensional) evaluation takes another central place in the thesis. A number of presented studies concern outcome studies, in the field of PBD but also on other domains of hepatopancreaticobiliary pathology that could be explored within this timeframe. As such these studies can be seen and discussed in the light of the critical appraisal as outlined in the IDEAL framework.

In short the five main topics regarding diagnosis, treatment and outcome of surgery for pancreatic and hepatobiliary diseases that have been addressed are:

1. The role of PBD for pancreatic cancer
2. Complications associated with pancreatic surgery
3. Chronic pancreatitis and its surgical treatment
4. Diagnosis and prognosis of pancreatic and hepatobiliary diseases
5. Patient reported outcomes following pancreatic surgery

The main study questions are summarized in Table 2. Additional background information is discussed in the following sections.
Table 2  The 17 study questions that are addressed in this thesis.

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Study Question</th>
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<tbody>
<tr>
<td>2</td>
<td>What is the history and current status of PBD?</td>
</tr>
<tr>
<td>3</td>
<td>How are plasma levels of FGF-19 affected in extrahepatic cholestasis and what are the adaptive changes in the liver?</td>
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<tr>
<td>4</td>
<td>What is the effect of PBD on coagulation and fibrinolysis in severe obstructive cholestasis?</td>
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<tr>
<td>5</td>
<td>What are the benefits of PBD in patients with obstructive jaundice caused by a tumor of the pancreatic head?</td>
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<tr>
<td>6</td>
<td>Does the therapeutic delay associated with PBD influence survival?</td>
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<tr>
<td>7</td>
<td>What is the incidence, management and outcome of chylous ascites following pancreatoduodenectomy?</td>
</tr>
<tr>
<td>8</td>
<td>What is the influence of ISGPS consensus definitions of complications and grading systems in pancreatic surgery?</td>
</tr>
<tr>
<td>9</td>
<td>How do complications influence cancer recurrence and survival after pancreatic surgery for cancer?</td>
</tr>
<tr>
<td>10</td>
<td>What are decisive considerations for surgical management of chronic pancreatitis and how does it compare to endoscopic therapy?</td>
</tr>
<tr>
<td>11</td>
<td>What are the long term outcomes of tailored surgery for chronic pancreatitis?</td>
</tr>
<tr>
<td>12</td>
<td>How is pancreatic function affected by surgery for chronic pancreatitis?</td>
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<tr>
<td>13</td>
<td>What is the value of endoscopic ultrasound in detecting pancreatic cancer?</td>
</tr>
<tr>
<td>14</td>
<td>What is the prognostic significance of extracapsular lymph node involvement in patients with adenocarcinoma of the ampulla of Vater?</td>
</tr>
<tr>
<td>15</td>
<td>Is location of resected extrahepatic cholangiocarcinoma associated with survival?</td>
</tr>
<tr>
<td>16</td>
<td>How is health-related quality of life (HRQOL) affected by PBD for pancreatic cancer?</td>
</tr>
<tr>
<td>17</td>
<td>What is the association of HRQOL with survival in patients undergoing surgery for pancreatic cancer?</td>
</tr>
<tr>
<td>18</td>
<td>What are long-term reported QOL and medical outcomes following pancreatic cyst resection?</td>
</tr>
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</table>

PBD – preoperative biliary drainage

Part I: The Role of PBD for Pancreatic Cancer

As described in the general introduction preoperative biliary drainage (PBD) was introduced to improve outcome after surgery in patients suffering from obstructive jaundice due to a potentially resectable proximal or distal bile duct or pancreatic head lesion. While experimental (animal) models showed almost exclusively beneficial results, human studies showed conflicting results. CHAPTER 2 describes this ratio to perform PBD and its historical context. The anticipated clinical benefit, but also potential disadvantages are illustrated by investigating available clinical studies on PBD for distal (pancreatic head area) and proximal bile duct obstruction (so-called Klatskin tumors). In the basic experimental CHAPTER 3 the expression of the bile salt-homeostatic hormone Fibroblast Growth Factor 19 (FGF-19) in the liver of patients with extrahepatic cholestasis is investigated. FGF19 is an endocrine factor produced by the small intestine in response to uptake of luminal bile salts. Whether FGF-19 contributes to regulation of bile salt synthesis under cholestatic conditions is
currently unknown. Further basic research is presented in CHAPTER 4 in which we evaluated the function of coagulation and fibrinolysis in cholestatic patients before and after PBD. Traditionally severe cholestasis has been associated with a derangement of hemostasis, but analysis of global routine coagulation parameters, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), at the time of surgery are typically near or within the normal range. Whether a more detailed analysis of coagulation and fibrinolysis results in out-of-range values, as was shown in a rabbit model of cholestasis, is unknown and was the subject of this study.

Best-evidence has demonstrated that routine PBD does not seem to yield the appreciated improvement in postoperative morbidity and mortality in patients undergoing resection. As mentioned, criticism to this conclusion concerned lack of use of current endoscopic standards in the reviewed studies and old methodology, thereby severely limiting the level of evidence of this conclusion. To provide up-to-date highest class of evidence concerning the benefit of PBD we initiated a multicenter, randomized controlled trial comparing a PBD followed by surgery strategy versus a direct operation strategy. The trial was conceived internationally as the DROP study (preoperative Drainage versus direct Operation strategy). The primary outcome was the rate of severe complications related to PBD or surgery, the results are described in CHAPTER 5. Whether the subsequent delay to surgical treatment caused by the intervention of PBD is safe from an oncological point of view (i.e. survival), is unclear. In CHAPTER 6 we evaluated the potential relation between delayed surgery due to PBD and overall survival in patients with cancer of the pancreatic head, who are scheduled for surgery.

**Part II: Complications Associated with Pancreatic Surgery**

Pancreatic cancer currently is the 4th cancer type for death in western countries with an incidence of 10-15 per 100,000 per year. Radical resection of a tumor in the pancreatic head is the only accepted option that leads to long-term survival. This type of surgery however is still associated with considerable morbidity, up to 40-50%, depending on definitions of complications and the system of registration applied. Part II of the thesis is dedicated to complications.

Leakage of chyle is an uncommon but potentially hazardous complication in thoracic and head-and-neck surgery. Postoperative chylous ascites usually develops as a result of direct operative trauma to the thoracic duct, cisterna chyli or their major tributaries. The accumulation of chyle in the peritoneal cavity, termed chylous ascites, is a rare condition in abdominal surgery, mainly described following aortic surgery and extended retroperitoneal lymphadenectomy for urological malignancies. Except for a few case reports, studies on chylous ascites in patients who underwent pancreatic surgery do not exist. CHAPTER 7 describes a study of assessment of the incidence and management of chylous ascites in patients who underwent pancreatic surgery, an analysis of predisposing factors, and an evaluation of the impact on patient outcome. In line with the Balliol Colloquium recommendations, a grading system is proposed.
The debate over outcome of pancreatic surgery in terms of complications is largely compromised by extensive differences in employed definitions for the various complications in literature. The differences preclude conclusive comparisons between institutions. This lack of objective parameters has been observed by various groups and has led to initiatives for expert meetings to build consensus around definitions. Postoperative pancreatic fistula (POPF), postpancreatectomy hemorrhage (PPH), and delayed gastric emptying (DGE) are three important and prevalent complications following pancreatic surgery. The International Study Group on Pancreatic Surgery (ISGPS) has formulated consensus definitions for these complications and has proposed classification systems to grade severity. In CHAPTER 8 we evaluated the implementation of the new definitions, studied possible changes in registration compared to the former system, and we investigated the additional value of the grading system.

CHAPTER 9 describes a study in which we evaluated the prognostic implications of perioperative complications on survival in patients who underwent potentially curative resection of histological proven pancreatic or periampullary cancer. Studies in esophageal and colorectal cancer confirm that postoperative complications with subsequent perioperative suppression of cell mediated immunity have a negative prognostic impact on recurrence, thus resulting in reduced long-term cancer specific survival. For pancreatic and periampullary cancer the influence of complications on cancer recurrence is unclear.

Part III: Chronic Pancreatitis and its Surgical Treatment

Chronic pancreatitis (CP) is a benign, progressive inflammatory condition causing irreversible histological damage of pancreatic parenchymal tissue. Pancreatic surgery for CP is mainly indicated for intractable abdominal pain, the suspicion of cancer, and complications such as persistent pseudocysts. In the past decades available surgical procedures for CP have witnessed some major advances, and especially pain can be effectively controlled by surgery. CHAPTER 10 describes the review article that summarizes the background of CP and the indications to intervene surgically. Different types of pancreatic surgery for CP are reviewed and discussed against the efficacy of endoscopic therapy, another treatment option.

CHAPTER 11 describes the AMC experience of surgery for CP; Long-term results of various surgical procedures for painful CP in terms of clinical outcomes (e.g. morbidity), patient reported outcomes (e.g. quality of life), and medical outcomes (e.g. endo- and exocrine pancreatic function) are evaluated.

In CHAPTER 12 we summarize a systematic review of available studies evaluating the incidence of endo- and exocrine function in patients who underwent surgery for painful CP. The primary aim was to determine the proportion of patients that were confronted with new-onset insufficiency following surgery.
Part IV: Diagnosis and Prognosis of Hepatopancreaticobiliary Diseases

Pancreatic cancer is associated with a poor prognosis. Metastatic disease or extensive locoregional ingrowth at the time of presentation precludes a curative surgical treatment in most patients. Early and accurate imaging is a prerequisite to identify potentially resectable lesions, but also avoids unnecessary surgery for incurable, or absent disease. The mainstay for the detection and staging of suspected pancreatic and periampullary malignancies (adenocarcinoma of the ampulla of Vater, or of the distal bile duct, or duodenum), is computed tomography (CT), but sensitivity is not 100%. Endoscopic ultrasonography (EUS) is a technique with superior visualization of the pancreas. In CHAPTER 13 we evaluated the value of EUS as add-on test after a negative or inconclusive CT in detection of tumors in the pancreatic head area.

The various types of periampullary malignancies, although locally closely related, vary significantly in prognosis after resection. Patients with an adenocarcinoma of the ampulla of Vater have a more favorable prognosis after radical resection than other periampullary malignancies. However, prognosis depends dramatically on the presence and extent of lymph node dissemination. Extracapsular lymph node involvement has been suggested to act as biological marker for aggressive disease in gastrointestinal malignancies. CHAPTER 14 describes a study of the incidence and extent of extracapsular lymph node involvement in patients with adenocarcinoma of the ampulla of Vater, and an analysis of the prognostic significance with respect to survival.

CHAPTER 15 describes another prognostic outcome study of hepatopancreaticobiliary diseases. Extrahepatic cholangiocarcinoma is the primary cancer of the main bile ducts and best treated with radical resection. A regular differentiation between proximal, mid and distal tumors is based on surgical approach, but also frequently employed to predict survival. However, the role of tumor location for survival after resection has been questioned and was subject of this study. In addition we constructed and analyzed different prognostic models for (more) accurate survival prediction.

Part V: Patient Reported Outcomes Following Pancreatic Surgery

The concept that health-related quality of life (HRQOL) after operation, in particular for pancreatic cancer with its dismal prognosis, should also be considered a crucial outcome measure, besides morbidity and mortality of the operative procedure, is well accepted nowadays. Active participation of patients in their care may result in higher satisfaction, better health outcomes and more effective decision making.

In part I of this thesis we have explored the clinical background and indications to perform PBD for pancreatic cancer, cumulating to the randomized trial we have described in CHAPTER 5. CHAPTER 16 describes patient reported outcomes for this patient cohort with an emphasis on the role of PBD from the HRQOL perspective by comparing the two treatment strategies. Secondly, we investigated which strategy patients would have preferred as assigned treatment strategy.
An increasing number of studies, as well as a systematic review and a meta-analysis of individual patient data suggest that HRQOL scales provide prognostic information in oncological patients in addition to that of socio-demographic and clinical measures. Although for pancreatic cancer series exist that report purely descriptive HRQOL data following surgical treatment, no studies exist that have investigated the potential role of HRQOL as prognostic factor for survival. In CHAPTER 17 we investigated whether pre- and postoperative HRQOL scores, in addition to several established clinical-pathological prognosticators, are associated with survival in patients eligible to undergo surgery for cancer of the pancreatic head. CHAPTER 18 describes long-term outcomes of patients who underwent surgery for pancreatic cystic tumors with a focus on HRQOL. Resection for cystic tumors is selectively indicated due to malignant potential of cystic lesions. However, the difficulty in preoperative differentiation is acknowledged, and thus a surgical strategy will lead to an appreciated significant proportion of patients that appear to have only benign disease at pathological investigation. Especially HRQOL should be considered a vital outcome measure for these patients, but these outcomes have not been reported before.
REFERENCE LIST


