Challenging dogmas in pancreatic surgery: biliary drainage, outcome and beyond

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SUMMARY

The core of this thesis is dedicated to evaluation of the value of preoperative biliary drainage (PBD) in patients with pancreatic or periampullary cancer. Other areas in hepatopancreatobiliary surgery that could be studied comprise the rational continuum of establishing diagnosis and indication for surgical treatment, and evaluation of short- and long-term outcomes. Where appropriate we attempted to consider results in light of the IDEAL framework of surgical innovation and evaluation from the Balliol Colloquium, an international consensus document on the arrangement of surgical research. This thesis is in part based on basic experimental studies, in part on critical analyses of literature, and in part on evaluation of retrospective and prospective (multicenter controlled trial) data.

The general outline of the thesis consists of five parts. What is the value of PBD for pancreatic cancer? (Part 1). How do we define and register complications and what is the critical influence of complications on survival? (Part 2) How can chronic pancreatitis be treated surgically, what is the result and what determines outcome? (Part 3) What is the optimal diagnostic algorithm of hepatopancreatobiliary malignancies and which variables determine prognosis? (Part 4) What are the patient reported outcomes and perspectives of treatment of pancreatic tumors and what is the association of these outcomes with survival? (Part 5). Diverse in subjects the different parts of this thesis exemplify the multimodal aspects of hepatopancreatobiliary surgery.

The department of surgery at the Academic Medical Center (AMC) in Amsterdam has a long tradition and experience to treat hepatopancreatobiliary disorders and serves as one of the largest tertiary referral centers in the Netherlands. The large patient series, continuously maintained at prospective databases, offer the unique opportunity to analyze and test hypotheses of a relatively rare disease entity. The research was conducted in the period 2006-2010 in close collaboration with the departments of radiology, gastroenterology, internal medicine, pathology, medical psychology, and clinical epidemiology and biostatistics of the AMC. The multicenter studies were performed in close collaboration with the departments gastroenterology and surgery of the different participating centers.

Perhaps somewhat provocative the title of the thesis [Challenging Dogmas in Pancreatic Surgery] refers to critical appraisal of established assertions in the practice of pancreatic surgery with sound data. Much of the procedures in surgical practice and conventions of how to treat our patients have been the result of traditions, rather than investigational-proven evidence. This claim is not restricted to pancreatic surgery, the view can be extrapolated to other fields of surgery, as has been the working experience of the author. Although the concept of evidence-based medicine has been introduced 15-20 years ago, close acquaintance of this principle in surgery seems to be of more recent date, if not still heavily under construction; so-called eminence-based surgery is not uncommon. It very well reflects the need the initiators of the Balliol Colloquium felt to standardize the evaluation of our proceedings in surgery in order to provide the best care for our patients.
In the following discussion, a summary of our main findings per chapter is provided for all five topics. Thereafter, relevant aspects for clinical practice are discussed and directives for future research are suggested.

**Part I: The Role of PBD for Pancreatic Cancer**

To improve the outcomes of the major surgery implicating resection of a tumor in the pancreatic head area, PBD was introduced for the presumed association between obstructive jaundice and complications. The summary in CHAPTER 2 shows that in experimental models, PBD is almost exclusively associated with beneficial results: improved liver function and nutritional status; reduction of systemic endotoxemia; cytokine release; and, subsequently an improved immune response. Mortality was significantly reduced in these animal models. However, the clinical evidence of use of PBD in the treatment of pancreatic cancer with obstructive jaundice has witnessed a remarkable reversal in the past 10-15 years. Initially considered beneficial, the “best-evidence” currently available clearly shows that routine PBD does not yield the appreciated improvement in outcome. However, for the large part available data are outdated or suffer from methodological deficits, thereby limiting the strength of evidence and thus recommendations for clinical practice.

Bile salts are potent detergents and therefore subject to rigorous regulation. Bile duct obstruction due to tumor growth in the pancreatic head area leads to accumulation of biliary constituents (salts) in the liver, which triggers an adaptive response that aims to minimize hepatocellular damage by reducing de novo bile salt synthesis and promoting nonbiliary secretion routes. CHAPTER 3 describes a strong expression of hepatic FGF19, normally absent in the liver, and elevated plasma FGF19 in patients with extrahepatic cholestasis. Since FGF19 downregulates target genes for control bile salt synthesis these adaptations could be involved in some way of auto-protection to hepatic damage in case of obstructive jaundice.

In CHAPTER 4 we found that cholestatic patients showed lower concentrations of plasma vitamin K-dependent factors II and VII, whereas prothrombin time (PT), activated partial thromboplastin time (aPTT), and factor V were unaltered. Despite the decreased vitamin K-dependent coagulation factor synthesis, thrombin generation was increased, likely because of systemic inflammatory response in patients with obstructive cholestasis. The haemostatic alterations because of cholestasis were almost completely reversed after PBD.

CHAPTER 5 describes the results of the DROP study (preoperative Drainage versus direct Operation strategy). In this multicenter, randomized trial we randomly assigned 202 patients with obstructive jaundice and a bilirubin level between 40 and 250 µmol to PBD for 4 to 6 weeks followed by surgery (n=106), or surgery without PBD within one week of the diagnosis (n=96). The primary outcome was the rate of severe complications related to PBD or surgery within 120 days after randomization. There were significantly fewer patients with complications in the early surgery group: 37 (39%) versus 75 (74%) in the PBD group (relative risk [RR] 0.54; 95% confidence-interval [CI]: 0.40-0.71; P<0.001). PBD was successful in 96 patients in
the PBD group (94%) after one or more attempts, with complications in 47 patients (46%). Surgery-related complications occurred in 35 early surgery patients (37%) versus 48 (47%) in the PBD group (RR 0.79; 95% CI: 0.57-1.11). Mortality and hospital stay were not significantly different between groups.

As found in CHAPTER 5 PBD should not be performed to improve outcome in terms of a complication reduction, however, PBD for secondary arguments (e.g., logistics, waiting lists or scheduled neo-adjuvant treatment) could be an option for selected cases. The consequently scheduled delay in surgery, required for an effective period of PBD, could lead to more advanced cancer stages at exploration. In theory this could negatively affect the resection rate and eventually lead to reduced survival. In CHAPTER 6 we analyzed the two treatment strategies as described in the preceding chapter and found that allocation to PBD indeed correlated significantly with a longer interval to surgery (correlation-coefficient: 0.861, P<0.001). However, the resection rate did not differ significantly between groups; in the early surgery group 60 of 89 patients (67%) versus 53 of 91 patients in the PBD group (58%) underwent resection (P=0.20). Significant prognostic factors for overall survival for the entire group were time to surgery (hazard ratio [HR] 0.90, 95% CI: 0.83-0.97), resection (HR 0.26, 95% CI: 0.18-0.37), high bilirubin levels (>200; HR 1.72, 95% CI: 1.06-2.78), and complications of treatment (HR 1.44, 95% CI: 1.00-2.08).

Part II: Complications Associated with Pancreatic Surgery

CHAPTER 7 describes an incidence of 9% of chylous ascites following pancreatic surgery, according to a novel definition, with clinically significant chylous ascites occurring in 4% (grade B, C) based on a proposed grading system. The diagnosis was generally established on postoperative day 6 (median; interquartile range [IQR] 5-8) following introduction of a normal diet. Female gender (OR 1.79; 95% CI: 1.05-3.03) and chronic pancreatitis at pathology (odds ratio [OR] 2.52; 95% CI: 1.19-5.32) were independently associated with development of isolated chylous ascites. All cases could be treated by dietary measures. Isolated chylous ascites was significantly associated with a prolonged hospital stay (P=0.002).

CHAPTER 8 demonstrates that the application of consensus definitions for complications, compared to our former registration system, overall results in higher incidences: PPH occurred in 19 patients (3%) according to former vs. 31 (8%) according to ISGPS definitions; POPF in 81 (13%) vs. 116 (18%); DGE in 162 (26%) vs. 430 (69%). The grading system generally provided a useful insight in the clinical implication of the complications, but for POPF and PPH no major difference in clinical outcome and management was observed between patients without complication and grade A. For all three complications higher ISGPS grades (B, C) corresponded with prolonged hospital stay: for PPH 14 days for patients without complication/grade A vs. 17 days for grade B and 32 days for grade C (P<0.001). For POPF: 33 vs. 22 and 36 days respectively (P<0.001), and DGE 10 vs. 20 and 33 days respectively (P<0.001). Each grade C complication was associated with highest mortality.
The prognostic outcome study in CHAPTER 9 demonstrates that major complications after pancreatic resection for cancer are independently related to an impaired survival for pancreatic cancer. Median survival for pancreatic adenocarcinoma was 22 (IQR 18-25) months following an uncomplicated postoperative course versus 16 (IQR 13-19) months for patients with major surgical complications (P=0.021). Multivariable Cox regression analysis demonstrated that microscopically residual disease (R1), complications, and adjuvant therapy were independent factors for recurrence. Within the R1 group, survival for patients with complications was even more limited, 10 (IQR 8-11) versus 19 (IQR 15-23) for those without (P<0.001). For patients with R1 resection complications were the only independent predictor for a shorter time interval to death (HR 1.96; 95% CI: 1.16-3.30). Complications did not influence survival of patients with periampullary adenocarcinoma.

Part III: Chronic Pancreatitis and its Surgical Treatment

Continuous improvements in imaging techniques, as well as a better understanding of the pathophysiology of CP and the mechanisms causing pain, have led to a more conscious selection of patients who might benefit from surgery for painful chronic pancreatitis. The review article in CHAPTER 10 underlines that type of surgery for chronic pancreatitis depends on whether the pancreatic duct is dilated, the level of obstruction, the presence or absence of an inflammatory mass and the occurrence of complications (e.g. pseudocyst formation, gastric outlet obstruction). Based on the reviewed literature the role of endoscopic therapy, thus far popularized a first-line treatment for chronic pancreatitis, seems to be limited and less effective than surgery. Furthermore, it has been suggested that early surgical intervention might delay and perhaps even halt the disease from progressing.

The observational cohort study in CHAPTER 11 describes the multimodal outcomes of the AMC experience in 223 patients who underwent surgery for chronic pancreatitis, tailored to the anatomical abnormalities as mentioned in the preceding chapter. Median 63 months (range 14-268) after surgery 68% of patients report to be free of pain, 15% suffer from intermediate and 12% from severe pain. Preoperative daily opioid use (OR: 3.04; 95% CI: 1.09-8.49) and high numbers of preceding endoscopic procedures (OR: 3.85; 95% CI: 1.01-14.9) were associated with persistent severe pain. Compared to the general population physical more than mental QoL remained impaired (P<0.05). At follow-up endocrine insufficiency was present in 57% of patients and exocrine insufficiency in 77%. After 20 months (IQR 10-51) following surgery 26 (12%) of 223 patients underwent one or more elective reoperations.

In CHAPTER 12 we describe a systematic literature review of 827 articles to assess the occurrence of pancreatic insufficiency in patients undergoing surgery for painful chronic pancreatitis. The preoperative endocrine insufficiency rate, presumably due to the disease itself, varied from 22.2 per cent (distal resection), 23.0 per cent (pancreaticojejunostomy), to 36.7 per cent (head resection). Postoperative rates increased to 55.6 per cent, 41.9 per cent, and 51.9 per cent respectively. New-onset diabetes following surgery was mainly described in studies with follow-up lengths
Chapter 19 Summary and General Discussion

of more than 2 years. Head resection was characterized by highest presence of pre-operative insufficiency (56.8 per cent). We conclude that pancreatic insufficiency comprises significant and progressive comorbidity in patients with surgically treated painful chronic pancreatitis. However, large variation of follow-up lengths preclude firm conclusions over attributed risk for insufficiency due to surgery per se, or being the consequence of progressive disease over time.

Part IV Diagnosis and Prognosis of Hepatopancreatobiliary Diseases

The value of endoscopic ultrasonography (EUS) in the diagnosis and loco-regional staging of suspected pancreatic head tumors has been widely evaluated, but not in the role as add-on test after a negative CT. In CHAPTER 13 we evaluated the diagnostic accuracy of EUS in detecting solid lesions of the pancreas after inconclusive CT and after inconclusive or negative CT. We compared results with a single imaging strategy (CT only). CT detected a solid lesion in 198 (59%) of 335 included patients, of whom 189 (95%) had a (pre)malignant lesion. CT was inconclusive or negative in 137 (41%) patients. In 106 (77%) of them EUS was performed, which was positive in 63 (59%), of whom 53 (84%) had a (pre)malignant lesion. In the 43 cases where EUS did not demonstrate a lesion 10 (23%) had a (pre)malignant lesion. Sensitivity of a strategy with EUS after inconclusive CT was 90%. A strategy with EUS after inconclusive or negative CT resulted in the largest increase of sensitivity compared to CT only (96 vs. 75%, P<0.001).

In CHAPTER 14 we summarize the results of reexamination of 75 of 160 pathological specimens (46.9%) of patients with adenocarcinoma of the ampulla of Vater who had positive lymph nodes (N1). The relation of extracapsular lymph node involvement with tumor stage and its prognostic significance was evaluated. Extracapsular lymph node involvement was identified in 44 (59%) of 75 patients. Median overall survival in patients with intracapsular lymph node involvement was 30 months and 18 months for patients with extracapsular lymph node involvement (P=0.015). Five-year overall survival was 20 per cent for intracapsular and 9 per cent for extracapsular lymph node involvement, compared to 55% for patients without lymph node involvement (N0). Extracapsular lymph node involvement and tumor differentiation were independent prognostic factors for survival. In N1 patients extracapsular lymph node involvement was the only significant prognostic factor for recurrent disease after radical resection (R0). The presence of extracapsular lymph node involvement identifies a subgroup with a significantly worse survival.

To evaluate the prognostic value of tumor location of extrahepatic cholangiocarcinoma on survival, 175 patients who had undergone a potentially curative resection were analyzed. The outcome study in CHAPTER 15 describes for the entire cohort a cancer-specific survival rate of 81%, 58%, and 26% at 1, 2 and 5 years, respectively. Cancer-specific survival according to location was 42% for proximal, 23% for mid and 19% for distal cholangiocarcinoma after 5 years, but location was not an independent significant predictor (P=0.06). A newly constructed prognostic model using all potential prognostic variables, as well as a reduced model, containing only lymph...
node status, microscopically residual tumor status and tumor differentiation grade, predicted survival slightly better compared to the conventional Tumor Node Metastasis (TNM) staging (concordance index 0.65, 0.66 and 0.63 respectively). Based on this information we developed a nomogram to predict survival.

**Part V: Patient Reported Outcomes Following Pancreatic Surgery**

In CHAPTER 16 we summarized a study in which we assessed health-related quality of life (HRQOL) and treatment preference in patients from the DROP study. Of 73 included patients 38 (52%) underwent early surgery and 35 (48%) PBD. Improvement in mean reported global health status after treatment compared to baseline was significant within groups ($P=0.004$), but there was no between-group difference ($P=0.16$). For another 13 HRQOL domains patients from both groups improved equally. Only for the hepatic symptom domain (jaundice, pruritus) PBD patients improved better ($P=0.02$), while early surgery patients reported a slightly higher treatment satisfaction ($P=0.09$). Most patients expressed before initiation (80%) and after ending treatment (76%) early surgery to be the preferred strategy if they had the possibility to choose between strategies. From the perspective of HRQOL an early surgery and PBD strategy can be considered equivalent. However, the large majority of patients consistently choose early surgery as preferred treatment strategy, an argument in favor for this strategy to prevail as routine strategy.

In CHAPTER 17 we evaluated the prognostic significance on survival of preoperative and early postoperative HRQOL following pancreatic surgery. In the multivariable preoperative model the HRQOL symptom scale pancreatic pain ($P=0.009$) was independently predictive for disease specific survival, weight loss ($P=0.009$) was predictive for overall survival. In the multivariable postoperative model the HRQOL scale fatigue ($P=0.013$), surgical complications ($P=0.008$), and microscopic residual tumor ($P<0.001$) predicted disease specific and overall survival in patients undergoing resection of the tumor. For patients that underwent palliative surgery due to irresectable disease the symptom domain altered bowel habit ($P=0.05$) was the only HRQOL prognosticator approaching significance for survival. We concluded that selected HRQOL symptom scales were independent prognostic predictors for survival, besides established clinical-pathological parameters. These novel findings should be taken into account when surgery for pancreatic cancer is considered, and can be used to more accurately predict survival after treatment.

CHAPTER 18 presents the long-term outcomes of 108 patients who underwent resection of a histology-proven primary cystic lesion of the pancreas. 77 (73%) patients appeared to have undergone resection of a benign lesion. Survival and operative morbidity are important parameters, but for this category long-term HRQOL is another vital outcome. At a median follow-up of almost 5 years generic physical and mental HRQOL scores were equal or better compared to healthy references. Independent predictors for good global health status at follow-up were young age ($P<0.05$), and resected malignancy ($P<0.05$), while for good gastrointestinal QoL male gender ($P<0.01$), limited resection ($P<0.05$), endocrine insufficiency ($P<0.05$), and employ-
ment (P<0.05) were significant predictors. We conclude that, considering the excellent HRQOL outcome, proceeding with surgery is justified once a medical indication for resection of a pancreatic cyst has been established.

**CONCLUSIONS AND FUTURE PERSPECTIVES**

Our main findings (Table 1) and believed implications for practice will be discussed in the following concordant paragraphs. Suggestions for future research based on our results are provided.

**Part I: The Role of PBD for Pancreatic Cancer**

We showed that PBD as a routine procedure should not be performed and is potentially harmful to patients. Decisive evidence has finally settled the longstanding controversy over the presumed benefit of PBD. This finding perfectly signifies the critical appraisal of a procedure of which the decades-old proof of concept (IDEAL stage 1), though well conceivable on pathophysiological grounds, has been falsified in the assessment phase (IDEAL stage 3), based upon up-to-date randomized controlled trial data.

Interestingly, alternative arguments other than the medical evidence for the procedure have already emerged to justify the use of PBD. Logistics and waiting lists, sometimes inevitable, could be factors that influence the decision to opt for PBD, as well as an extended diagnostic workup with laparoscopy (on indication) or scheduled preoperative chemotherapy. Nevertheless, we feel that the organization of healthcare should be organized to optimize outcome (early surgery is the logical option) rather than rigidly dictate the outcome (PBD as necessity for early surgery is not feasible).

With falsification of the hypothesis of PBD being beneficial, surveillance is the logical next step (IDEAL stage 4). We have demonstrated in this thesis that from the perspective of survival both strategies are safe. Further descriptive outcome research, auditing and assessment of regional variation should be directed at the feasibility of implementing an early surgery strategy and the long-term outcome of this strategy outside the trial framework.

From the societal perspective reducing costs of healthcare without compromising quality is very relevant nowadays. To be addressed in a future study the beneficial effect on cost-effectiveness of the proposed early surgery strategy compared to PBD, seems obvious; not performing PBD saves an additional, invasive intervention with a complication risk of 46%, in that case requiring necessary repeated interventions, hospital admissions etc.

Whenever PBD cannot be avoided, scheduled preoperative chemo- and radiation therapy being one of the fairest arguments, we have suggested that self-expandable metal stents (SEMS) can be used as bridge to surgery. In the palliative setting SEMS have proven to be more enduring (i.e. less complications as clotting, cholangitis etc) than plastic stents. Although our study has been criticized over the use of plastic
stents as possible causal factor for the high PBD-related complication rate, application of SEMS for PBD for pancreatic cancer has never been prospectively evaluated and is barely used to date for this indication. The currently ongoing STENT study (Dutch Trial Registry Number: NTR3142) is designed to evaluate and validate the use of SEMS for this indication.

We have demonstrated that PBD reverses coagulation parameters to normal values. Although originally presumed to be hazardous, the alterations in hemostasis observed in our study cohort did not lead to more complications. However, we did not include patients with advanced disease and bilirubin levels over 250 μmol/L. Future studies might be initiated to evaluate the role of PBD in patients with very high bilirubin levels and cholestatic patients requiring extensive liver resection, such as in the case of hilar cholangiocarcinoma. For the latter category no well-designed randomized controlled trials that compare a strategy with and without PBD exist.

The finding of the adaptive response in cholestasis for regulation of bile salt homeostasis and the role of FGF19 is a major novelty. It will be interesting to learn whether and how FGF19 affects expression of other genes, and whether FGF19 is involved in the adaptive response in chronic cholestatic liver diseases such as primary biliary cirrhosis and primary sclerosing cholangitis.

Part II: Complications Associated with Pancreatic Surgery

Chylous ascites following pancreatic surgery is principally a mild complication that might result in a prolonged hospital stay and that is best treated with dietary measures. A definition and grading system for chylous ascites following pancreatic surgery, proposed in this thesis, provide in a deficiency in literature.

Application of ISGPS consensus definitions for three major and prevalent complications following pancreateoduodenectomy result in an increased registration of complications compared to former systems used. The adherent grading system provides a transparent understanding of the severity and clinical consequences of the registered complication, which was not available previously. Several inconsistencies and the fact that grade A complications frequently do not differ from uncomplicated hospital course are issues to be addressed in future research.

Of special notice, adoption without compromise of consensus definitions and grading has been widely propagated for proper comparison between institutions. It is remarkable that the identical claim, at least for its grading system, has been brought forward by another expert group (Clavien-Dindo classification). Both the ISGPS and Clavien-Dindo classification have already been applied extensively in publications on pancreatic surgery, in essence recreating the same problem of transparent comparison of outcome between institutions. Future studies could be directed at direct head-to-head comparison of the classifications, but ideally efforts are directed to find consensus and develop a single system of registration. To be successful achieving the latter goal shall probably involve a great deal of politics, rather than having merely a scientific basis.
Complications after resection are independently related to an impaired survival following pancreatoduodenectomy for pancreatic, but not periampullary cancer. The effect is even more profound in patients who had a microscopically incomplete resection. The finding underlines that attempts to minimize complications for this major surgery, e.g. further centralization, careful patient selection, should be an ongoing effort to offer the best chances for disease-free survival. Whether immunologic host factors enhance microscopic residual disease, and as such provide a possibility for targeted intervention, should be subject of further research in this specific patient population.

**Part III: Chronic Pancreatitis and its Surgical Treatment**

For patients with chronic pancreatitis proper and early diagnosis is crucial for future perspectives, while it has become clear that early surgery might delay and even halt the disease from progression. Furthermore, highest level of evidence, added with long-term outcome results (IDEAL stage 4), demonstrates superiority of surgery over endoscopic therapy for painful chronic pancreatitis in patients without an inflammatory mass.\textsuperscript{10,11} Prospective, standardized registration of every newly diagnosed patient with chronic pancreatitis, preferably on a national level as suggested by our group, is an important aid in the care of these patients.\textsuperscript{12} The suggestion has led to institution of a national Chronic pAncreatitis REGistry (CARE) in the Netherlands. In line with the IDEAL framework (stage 3) the concept of benefit from early intervention as derived from descriptive series, is the primary subject of the ongoing ESCAPE trial: Early Surgery versus optimal Current step-up prActice for chronic PancrEatitis, a multi-centre randomized controlled trial (Dutch Trial Registry Number: NTR2794).\textsuperscript{13}

To perform a tailored surgical approach for chronic pancreatitis, i.e. no head resection when the diameter is $<4\text{cm}$, is supported by excellent to fair patient reported outcomes, and the observation that surgical drainage in the absence of an enlarged head is more likely to preserve pancreatic function. Prospective evaluation and registration, including baseline measurements of pain and HRQOL with validated questionnaires, should further strengthen this hypothesis. The observed operative failure rate may improve once we achieve a better understanding of the pathogenesis of pancreatic neuropathic pain.

Pancreatic insufficiency comprises significant and progressive comorbidity in patients with surgically treated painful chronic pancreatitis. Heterogeneous follow-up lengths of available studies preclude firm conclusions over attributed risk for insufficiency due to surgery or as a consequence of progressive disease over time. The CARE registry and the ESCAPE trial might provide an answer to this question.

**Part IV: Diagnosis and Prognosis of Hepatopancreatobiliary Diseases**

We demonstrated that a diagnostic strategy for detecting solid pancreatic lesions with application of EUS as add-on test after inconclusive or negative CT results in a significant gain of accuracy. Future studies should externally validate our defined diagnostic algorithm, and should also address cost-effectiveness of this strategy.
Management when both tests are negative, i.e., follow-up, timing of repeat investigations, timing of surgery, is unclear and should be defined considering the risk for malignancy of around 23%.

For more sophisticated and individualized prognostication after resection of cancer, extending the value of pathological features other than TNM staging can be advocated. In patients with an adenocarcinoma of the ampulla of Vater, extracapsular lymph node involvement identifies a subgroup of patients with a significantly worse long-term survival. We feel that assessment of this feature should be included in the protocol of pathological examination of the surgical specimen. Further research is warranted on the correlation of extracapsular lymph node involvement with different histological types and to investigate the influence in other periampullary tumors. Comparable to staging systems for esophageal cancer the presence of extracapsular lymph node involvement should be considered for pancreatic and periampullary tumors.

In patients who underwent resection of extrahepatic cholangiocarcinoma we found a trend for distal lesions to be associated with a less favorable cancer-specific survival after resection compared to mid or proximal lesions. However, location was not an independent prognostic factor. A microscopically margin negative resection was the only prognostic factor determined by the surgical procedure. Specifically for mid lesions this implicates that, in order to improve survival, the surgical procedure should be extended either with partial liver resection or with pancreatoduodenectomy, depending on the location of the lesion closer to liver or pancreas. A prognostic model using lymph node status, microscopically residual tumor status, and tumor differentiation grade was better compared to TNM staging. The nomogram of the prognostic model should be externally validated in another large series.

Part V: Patient Reported Outcomes Following Pancreatic Surgery

Performing PBD for the presumed benefit on symptomatology of obstructive jaundice, i.e., anorexia, pruritus, abdominal pain, did not translate in significant better health-related quality of life HRQOL. From the perspective of HRQOL an early surgery and a PBD treatment strategy for patients with pancreatic cancer can be considered equivalent. Furthermore, we observed that the large majority of patients indicated to prefer early surgery, both before initiation and after completing treatment.

Application of HRQOL scales in clinical practice can aid in estimating more accurately prognosis when surgery for pancreatic cancer is considered; e.g., low preoperative pancreatic pain scores might more firmly establish the decision to operate. Early postoperative use of HRQOL scales helps reassess individual prospects in addition to pathological staging. Future studies with larger sample sizes are strongly required to externally validate these novel findings and to establish more robust models with larger numbers of HRQOL variables.

For patients who have undergone a pancreatic resection under the assumption of having a primary malignant cyst the long-term HRQOL is excellent. Although a treatment strategy with low threshold to surgery for this particular pathology results...
in an anticipated high rate of resected benign lesions, potential concerns about a major negative impact on long-term outcome is not justified. The decision to proceed with treatment, once an indication for surgical resection of a pancreatic cyst has been established, is valid.

The purpose of measuring HRQOL in randomized trials is to guide future decision making. However, it has been suggested that, despite the interest in the area of HRQOL, there seems to be a gap between measuring HRQOL outcomes and using the information to change surgical practice. The next challenge is to translate the HRQOL and patient reported outcomes of this thesis into daily surgical practice. Especially in the area of oncological pancreatic surgery patient-reported outcomes may prevail over clinical outcomes. Shared decision-making could be the tool to achieve highest patient satisfaction.

In this light memorable opinions of two patients, whom we encountered during the recruitment phase of the DROP-trial, deserve to be mentioned. After successful placement of a stent for PBD one patient refused further surgical treatment. In light of the poor prognosis of pancreatic cancer, even after resection, she had taken the decision not to be operated upon in perfect understanding of the consequences. A few months later she died of the consequences of disseminated disease. Another patient was referred to us for establishing the diagnosis of his obstructive jaundice and possible trial inclusion. Eligible for participation he had been randomized to the PBD strategy, but before stent placement could take place he withdrew from all further treatment. Common in his family was dying of ‘jaundice’ at or before the age of 65. Considering the fact that already he had reached the age of 71 years old he was perfectly satisfied to choose for no more life-prolonging interventions. He died a few weeks later from the sequelae of hepatic failure.
**EPICRISIS**

In this thesis we have presented the results of 5 years of basic and clinical research on pancreatic surgery. Traditions have been evaluated, controversies have been settled, physician-centered and patient-centered outcomes were evaluated, and many suggestions for clinical practice and future research were provided.

Pancreatic and periampullary cancer are relatively rare disease entities with dismal prognoses. Eligibility to treat the disease surgically is limited to a minority of patients, and even then cure is exceptional. In the near future much is expected from novel molecular markers and whole genome sequencing, which might elucidate the oncogenic context and expose potential therapeutic vulnerabilities. Considering the rarity of pancreatic disorders these initiatives are preferably executed in close collaborative networks, such as the recently founded Dutch Pancreatic Cancer Group (DPCG) and the Dutch Pancreatitis Study Group. Biobanking (e.g. AMC’s BIOPAN, Parelsoen) within these networks can provide the biological substrates that allow for this novel, multidisciplinary research to be carried out.

Finally, the process of surgical innovation is as old as the surgical practice itself, but evaluation within a standardized framework has only just begun. Conscientious and critical application of the IDEAL framework is the key to improve surgical care such that interventions will become safer and better.
Table 1  Answers to the 17 study questions raised in this thesis.

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<tr>
<th>Chapter</th>
<th>Study Questions and Answers</th>
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<tr>
<td>2</td>
<td><strong>What is the history and current status of PBD?</strong>&lt;br&gt;Evidence does not support the use of PBD for the primary indication, to improve postoperative outcome, but is nevertheless assimilated widely for secondary arguments (logistics, waiting lists etc).</td>
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<td>3</td>
<td><strong>How are plasma levels of FGF19 affected in extrahepatic cholestasis and what are the adaptive changes in the liver?</strong>&lt;br&gt;The liver expresses FGF19 under conditions of extrahepatic cholestasis, which is accompanied by a number of adaptations aimed at protecting the liver against bile salt toxicity. FGF19 signaling may be involved in some of these adaptations.</td>
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<td>4</td>
<td><strong>What is the effect of PBD on coagulation and fibrinolysis in severe obstructive cholestasis?</strong>&lt;br&gt;Obstructive cholestasis is associated with a procoagulant state, despite an impaired vitamin K-dependent coagulation factor synthesis, but virtually all alterations in coagulation and fibrinolysis can be reversed by PBD.</td>
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<td>5</td>
<td><strong>What are the benefits of PBD in patients with obstructive jaundice caused by a tumor of the pancreatic head?</strong>&lt;br&gt;Routine PBD in patients undergoing surgery for cancer of the pancreatic head increases the rate of complications.</td>
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<td>6</td>
<td><strong>Does the therapeutic delay associated with PBD influence survival?</strong>&lt;br&gt;In patients with pancreatic head cancer, the delay in surgery associated with PBD does not impair or benefit survival rate.</td>
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<td>7</td>
<td><strong>What is the incidence, management and outcome of chylous ascites following pancreatoduodenectomy?</strong>&lt;br&gt;According to our novel definition the incidence following pancreatoduodenectomy is 9% for significant chylous ascites. Timely recognition allows early introduction of proper dietary measures, which may limit the associated prolonged hospital stay.</td>
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<td>8</td>
<td><strong>What is the influence of ISGPS consensus definitions of complications and grading systems in pancreatic surgery?</strong>&lt;br&gt;The ISGPS definitions lead to an increase in complication registration, but the grading system provides a hitherto lacking transparent insight in clinical relevance.</td>
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<td>9</td>
<td><strong>How do complications influence cancer recurrence and survival after pancreatic surgery for cancer?</strong>&lt;br&gt;Major surgical complications are independently related to an impaired survival following pancreatoduodenectomy for pancreatic, but not periampullary cancer. The effect is even more profound in patients with an R1 resection.</td>
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<tr>
<td>10</td>
<td><strong>What are decisive considerations for surgical management of chronic pancreatitis and how does it compare to endoscopic therapy?</strong>&lt;br&gt;Type of anatomical abnormalities determines type of surgical procedure. More enduring pain relief and possible delaying of pancreatic insufficiency are major arguments to opt for surgery rather than endoscopy.</td>
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Chapter Study Questions and Answers

11. What are the long-term outcomes of tailored surgery for chronic pancreatitis?
Tailored surgery results in excellent to fair long-term pain relief. High preoperative pain levels, suggested through daily opioid use and high numbers of endoscopic procedures, are associated with less favorable outcome.

12. How is pancreatic function affected by surgery for chronic pancreatitis?
Pancreatic insufficiency comprises significant and progressive comorbidity. Heterogeneous literature precludes firm conclusions over attributed risk for insufficiency due to surgery, or as a consequence of progressive disease.

13. What is the value of endoscopic ultrasound in detecting pancreatic cancer?
Endoscopic ultrasound as add-on test after inconclusive or negative CT results in a significant gain of accuracy.

14. What is the prognostic significance of extracapsular lymph node involvement in patients with adenocarcinoma of the ampulla of Vater?
The presence of extracapsular LNI identifies a subgroup with a significantly worse survival for which adjuvant therapy after resection is advised.

15. Is location of resected extrahepatic cholangiocarcinoma associated with survival?
Tumor location does not independently predict cancer-specific survival after resection. An alternative prognostic model predicted survival better than TNM staging.

16. How is health-related quality of life (HRQOL) affected by PBD for pancreatic cancer?
HRQOL in a PBD strategy can be considered equivalent to early surgery, but the large majority of patients choose early surgery as preferred treatment strategy.

17. What is the association of HRQOL with survival in patients undergoing surgery for pancreatic cancer?
Preoperative, and early postoperative HRQOL symptom scales were independent prognostic predictors for survival, besides established clinical-pathological parameters, which can be used to more accurately predict survival after treatment.

18. What are long-term reported QOL and medical outcomes following pancreatic cyst resection?
Long-term QOL is equal to healthy references, pancreatic insufficiency is prevalent, but does not impair QOL. The excellent outcome justifies proceeding with surgery once a medical indication for resection has been established.
Chapter 19 Summary and General Discussion


