Improving outcomes of pancreatic surgery

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CHAPTER 15

GENERAL SUMMARY, DISCUSSION, FUTURE PERSPECTIVES AND CONCLUSIONS

In this thesis, several aspects of multidisciplinary management of pancreatic surgery were investigated. This final part summarizes the results and implications of the studies and discusses future perspectives.

General summary and discussion

Part I International evaluation of clinical practice in pancreatic surgery

In **Part I** an overview was provided of clinical practice regarding the use of tumor resection and (neo)adjuvant therapy and outcomes in patients with pancreatic cancer in Europe in a real-world scenario. Also in this part, a survey study among surgeons was performed to obtain a global assessment of perioperative Enhanced Recovery After Surgery (ERAS) practices regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing pancreatoduodenectomy.

Chapter 2 describes the use of (neo)adjuvant therapies and outcomes of patients who underwent tumor resection for resectable (stage I and II) pancreatic adenocarcinoma in national, regional and a single center cancer registries in the European Registration of Cancer Care (EURECCA) Pancreas Consortium. This study included 3901 patients diagnosed in 2012-2013 of which the majority had stage II disease. The use of neoadjuvant therapy was limited in most registries (3-16%). Large variations in the use of adjuvant therapy (41-70%), 90-day mortality (1-14%) and overall survival exist. Some variation may be explained by the inherent differences between national, regional, and single-center registries. Though, the variations illustrate the difficulty of the implementation of universally accepted guidelines and that results from clinical trials are not easily extrapolated to the general population.

Chapter 3 provides real-world evidence on treatment and survival of elderly patients (≥70 years) with resectable pancreatic cancer stage I-II. The study included 3624 patients diagnosed in 2012-2016 of which the majority had stage II disease. Variations were observed in tumor resection rate (36-50%), rate of (neo)adjuvant chemotherapy (14-56%) and palliative chemotherapy (6-40%). Also differences in outcome were observed regarding 90-day mortality (5-12%), overall survival in patients who underwent tumor resection (median 16-25 months) and overall survival in patients who did not undergo tumor resection (median 4-7 months). The absence of a clear pattern between (neo)adjuvant and palliative chemotherapy and overall survival suggests that further research is needed on selection criteria for (non)-surgical treatment, so that clinicians can tailor treatment and improve overall survival. Although the quantity and quality of randomized clinical trials in pancreatic cancer is increasing, it is still expected that elderly patients will often be excluded from these trials.[1] Therefore, the utilization of cancer registry data offers a solution in research of elderly patients. Another advantage over randomized clinical trial data, is that cancer registry data

is readily available and population-based, thereby minimizing selection bias. EURECCA aims to create awareness of the large variation in treatment strategies between cancer registries, generate new hypotheses for future research and also underlines the need for uniform registration as international comparisons will become increasingly important pillars of international guidelines.[2,3]

Chapter 4 gives insight into the current global perioperative ERAS practices regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing pancreatoduodenectomy. The results of this international survey among 236 surgeons showed that only 61% of pancreatic surgeons practice ERAS protocols and large variations in practices were observed. The preferred method for analgesia was epidural analgesia (50%, EA), followed by intravenous morphine (25%). Restrictive fluid therapy is practiced by 58% of surgeons. Mechanical and chemical thromboprophylaxis are frequently used after pancreatoduodenectomy (90% and 88%), however the duration of chemical prophylaxis varied considerably. In case of minimally invasive surgery, most surgeons only changed the analgesia technique (51%), but did not amend fluid therapy (30%) or thromboprophylaxis (7%). The results of this study will help to create more uniformity of ERAS protocols over the globe and to further optimize the perioperative care after pancreatoduodenectomy by the design of new studies. Also, the observed variations have to be considered during interpretation and extrapolation of study results from another hospital or region.

Part II Surgical and oncological aspects of venous resections in pancreatic surgery

Part II focused on the surgical and oncological aspects of venous involvement in pancreatic surgery. Guidelines are lacking for surgical decision making, postoperative management and pathological grossing techniques of pancreatoduodenectomy with venous involvement (more specific: the portal-superior mesenteric vein [PV-SMV]).

In **Chapter 5**, a systematic literature search was performed to identify international expert surgeons and pathologists who published relevant studies in the last decade. These experts (N=190) and Dutch pancreatic surgeons and pathologists (N=37) were approached to complete an online survey. Several important findings were noted. Correspondence between preoperative imaging, intraoperative findings and pathology regarding venous involvement was considered to be suboptimal. Type 3 reconstruction (segmental resection with primary anastomosis) was most popular (61%). Half of the surgeons expected a higher risk of complications after venous resection, especially PV-SMV thrombosis. Heparinization during venous resection, standard postoperative imaging protocols and thromboprophylaxis regimens differed substantially. Analyzing international expert surgeons compared to Dutch surgeons, the estimated percentage of venous resection was higher, Type 3 venous resection was relatively more often

preferred over Type 1, an increase of the risk of complications after venous resection was less often expected (namely less PV-SMV thrombosis within 90 days after surgery) and they performed the venous resection more often themselves. Most pathologists assess tumor infiltration in the wall of the resected vein. However, only half of the pathologists assess the resection margins of the resected vein itself. Assessment of depth of tumor infiltration differed between pathologists. This study highlights the lack of evidence and emphasizes the need for research on imaging modalities, surgical techniques, postoperative management and standardization of the pathological assessment.

The effect of the type of venous resection (wedge or segmental) on morbidity and survival is poorly understood in current literature.[4-6] Nationwide studies with recent data that represent current clinical practice are lacking. In the international survey most pancreatic surgeons preferred a venous segment resection over a partial venous wedge resection, because of a lower estimated risk of complications. In **Chapter 6** the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity, mortality and overall survival was evaluated. A nationwide retrospective analysis of 1311 patients who underwent pancreatoduodenectomy was performed within the Dutch Pancreatic Cancer Group (DPCG, 2013-2017). A venous resection was performed in 27% patients (65% wedge resection; 35% segmental resection). Patients with segmental resection had more Clavien-Dindo ≥III complications (adjusted odds ratio [OR] 1.90, 95% confidence interval [CI] 1.22-2.98) and worse survival (adjusted hazard ratio 1.40, 95% CI 1.10-1.78) compared to no venous resection. In patients treated with neoadjuvant therapy, survival was comparable between types of venous resection, although patients with segmental resection had more Clavien-Dindo ≥III complications compared to venous wedge and without venous resection (52% versus 19% versus 21%, respectively). The results of this study mainly implicate that an upfront segment resection is associated with poor morbidity and survival. This finding supports recent guidelines in that neoadjuvant chemotherapy should be considered in borderline resectable disease and suspected venous involvement. Improvements in surgical outcome should focus on identifying optimal reconstruction techniques and perioperative protocols in patients who have suspected venous involvement at preoperative imaging. After the results of this study, we started the development of a hands-on workshop on surgical anatomy and operative techniques during venous resection in patients with pancreatic cancer for Dutch pancreatic surgeons.

In **Chapter 7**, we explored the potential causes and the consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands in the same cohort as Chapter 6. The number of venous resection per center during the study period varied from 5-52 patients (10-53%) with an annual median of four venous resections per center. There was no clear relationship between

center pancreatoduodenectomy volume and rate or type of venous resection and between anatomical, biological and conditional patient characteristics, center characteristics and rate or type of venous resections per center. Adjusted for predictive factors (female sex, lower BMI, neoadjuvant therapy, venous involvement and venous stenosis on imaging), three centers performed significantly more and three centers performed significantly less venous resections than expected. Patients with venous resection in centers with an above median annual volume of venous resections had less postoperative PV-SMV thrombosis, mortality, and major morbidity and longer overall survival. Further research is needed to define the volume-outcome relationship in pancreatoduodenectomy with venous resection and determine its possible clinical relevance. We believe pancreatoduodenectomy with venous resection is technically challenging for the surgeon and also more challenging for the multidisciplinary team (e.g. perioperative hemodynamic monitoring by the anesthesiologist and intensive care team, postoperative thromboprophylaxis by the vascular medicine specialist). Therefore, multidisciplinary efforts are needed to identify best practices, minimize unwanted practice variation among institutions and improve outcomes of patients with pancreatic cancer and suspected venous involvement.

As previously mentioned, one of the main challenges for a pancreatic surgeon when confronted with possible tumor invasion in the PV-SMV is distinguishing tumor from peritumoral inflammation and fibrosis. **Chapter 8** studied the association between venous resection, tumor invasion in the resected PV-SMV, recurrence patterns and overall survival. A multicenter retrospective study of 531 patients who underwent pancreatoduodenectomy for pancreatic cancer (2010-2017) was performed (28% with venous resection). Tumor invasion in the resected PV-SMV was observed in 53% of patients. Patients with venous resection had a higher rate of R1 margin as compared to patients without venous resection (69% versus 37%). Most frequent R1 margins were the PV-SMV (24%) and the superior mesenteric artery margin (20%). Moreover, a very small number of patients had a R1 margin solely at the PV-SMV margin (5%). Venous resection and tumor invasion in the resected PV-SMV were not independent predictors for time to recurrence and overall survival. Additionally, a systematic literature search of large studies (≥500 patients) showed that pathological assessment of the resected PV-SMV is not adequately standardized and studies regarding venous resection and recurrence patterns are scarce. The results of this study have a number of implications. There is need for improvement in patient selection for venous resection, as half of patients do not have tumor invasion in the resected PV-SMV. The promising results of intraoperative ultrasound have led to the initiation of the ULTRAPANC study within the DPCG investigating the added value of intraoperative ultrasound in the assessment of vascular involvement in pancreatic cancer. The high percentage of R1 resections also support recent guidelines in that neoadjuvant chemotherapy should be considered in

(borderline) resectable disease. The fact that only few patients had a R1 margin solely at the PV-SMV margin indicates that a more extensive resection at this margin is often not sufficient to improve radicality. In these patients, neoadjuvant therapy in combination with a TRIANGLE operation and in selected cases also arterial divestment could be considered.[7, 8] Furthermore, the pathological assessment of the resected PV-SMV has now been standardized in the Netherlands.

Part III Surgical complications in pancreatic surgery

Part III consisted of studies on the two most notorious complications in pancreatic surgery: postoperative pancreatic fistula and abdominal infectious complications.

In **Chapter 9** we evaluated surgical strategies (i.e. completion pancreatectomy versus pancreas-preserving procedure) in 162 patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy in nine Dutch institutions (2005-2018). Completion pancreatectomy was associated with higher mortality rate (56 versus 32%; adjusted OR 2.44, 95% CI 1.02-5.85). The meta-analysis of 33 observational cohort studies, including 745 patients, confirmed this finding (random-effects model, OR 1.97, 95% CI 1.03-3.80). In the cohort study, there was no difference between the two groups in the proportion of additional reinterventions after relaparotomy (64 versus 67%, P=0.76) or duration of hospital stay. As this evidence is based on observational studies, residual confounding cannot be ruled out. On the other hand, level 1 evidence is hard to get as the included study population is increasingly rare as a minimally invasive step-up approach seems to be the preferred strategy in the management of pancreatic fistula (e.g. primarily percutaneous catheter drainage and, in case of failure of percutaneous catheter drainage, a pancreas-preserving surgical strategy if possible).[9-11]

To further highlight this, we reacted to a recent study in **Chapter 10**. In their study, Garnier et al. concluded that pancreas-preserving surgical interventions are associated with more reoperations and mortality and that simple surgical drainage should not be adopted.[12] In our cohort, patients who underwent simple surgical drainage and other pancreas-preserving surgical interventions did not differ at baseline. Mortality was 29% following simple surgical drainage versus 37% (range 30-44%) for the other subgroups (P=0.79) and additional reinterventions were performed in 65% following simple surgical drainage versus 70% (range 60-83%) for the other subgroups (P=0.60). Therefore, we believe that, after failure of percutaneous drainage, simple surgical drainage is a viable option in the management of pancreatic fistula following pancreatoduodenectomy

No consensus exists on the predictive role of bile cultures in the prevention or treatment of abdominal infectious complications after pancreatoduodenectomy. **Chapter 11** investigated the association between positive bile cultures and abdominal infectious complications after pancreatoduodenectomy in a prospective single center study. We introduced the definition of an isolated organ space infection (OSI): OSI without a simultaneous complication potentially contaminating the intraabdominal space. Intraoperative bile cultures were prospectively and routinely obtained in 114 patients undergoing pancreatoduodenectomy (2016-2019). The positive bile culture rate was 61%, predominantly in patients after preoperative biliary drainage (98% versus 26%). OSIs occurred in 35 patients (31%) and isolated OSIs in nine patients (8%) and were not associated with positive bile cultures (OSIs: OR 0.6, 95% CI 0.25-1.23, isolated OSIs: odds ratio 0.77, 95% CI 0.20-3.04). Complete concordance between microorganisms in the bile and OSI cultures was observed in only one patient. However, our patients received standard antibiotic prophylaxis for five postoperative days, which is different than most other centers where patients for example only receive preoperative antibiotic prophylaxis and postoperative antibiotics only on indication. This may have influenced the results of this single center cohort study. In the meta-analysis, 15 studies reporting on 2047 patients showed no association between positive bile cultures and abdominal infectious complications (pooled OR 1.3, 95% CI 0.98-1.65). Altogether, this study suggests that routinely obtained bile cultures are an inadequate predictor for the development of abdominal infectious complications after pancreatoduodenectomy as well as its causing pathogens and routine performance should be reconsidered. The concept of isolated OSI in pancreatic surgery can be incorporated in future studies.

Part IV Perioperative anesthesiological management in pancreatic surgery

Part IV discussed perioperative anesthesiological management in pancreatic surgery with special regards to analgesic and fluid therapy as patients undergoing pancreatoduodenectomy may experience severe postoperative pain and considerable fluid shift perioperatively.[13-15]

In **Chapter 12** we assessed our own experience with EA and non-EA in 262 patients undergoing open pancreatectomy (2013-2017). EA was used in 73% of patients and there were several important outcomes of the comparison between EA and non-EA patients: (1) initial analgesia was prematurely converted to another form of analgesia in 33% of EA patients versus 11% of non-EA patients; (2) EA patients had lower mean pain scores and fewer reported unacceptable pain on postoperative days 0–1. However, termination of EA led to higher mean pain scores and more patients reported unacceptable pain on postoperative days 3–4, which led to the need for the liberal administration of supplemental opioids; (3) the EA group received more vasoactive medication perioperatively and also cumulative fluid balances were significantly higher on

postoperative days 1–3; (4) postoperative complications and length of hospital stay were similar between both groups. The results of our study implicate that: (1) An adaptation of protocol is required in order to improve pain scores after termination of EA, either by extending the EA phase or by a supplemental preemptive analgesic treatment (opioid or non-opioid), and (2) We need a better alternative for EA and iv morphine, since EA has a high failure rate (33%) and that the most used alternative (iv morphine) provides less pain control.

The systematic review and meta-analysis of available literature **in Chapter 13** aimed to see if EA has superior clinical outcomes compared to non-EA in patients undergoing pancreatoduodenectomy. Three randomized trials and eight cohort studies (25089 patients) were included. EA provided statistically significant though only marginally lower pain scores on postoperative day 0 to 3 compared with iv morphine patients (mean difference -0.50, 95% CI -0.80 - -0.21). Results of separate postoperative days showed lower pain scores in EA patients namely on postoperative days 1 and 2 compared with iv morphine. Treatment failure of EA occurred in 29% of patients, mainly as a results of hemodynamic instability or inadequate pain control. Furthermore, there could be a benefit of EA over iv morphine regarding complications (OR 0.69, 95% CI 0.061-0.79), length of hospital stay (mean difference -2.7 days, 95% CI -2.8 - -2.6) and mortality (OR 0.69, 95% CI 0.51-0.93). Based on these results, we weakly recommend the use of EA over iv morphine as first choice for reducing early postoperative pain in eligible patients undergoing pancreatoduodenectomy. This systematic review showed there are only a few studies available and therefore further research is needed to identify the optimal analgesic technique(s) after pancreatoduodenectomy.

After we reviewed our own experience and evidence available in literature on analgesic management in patients undergoing pancreatic surgery, we designed a randomized trial "*Postoperative Pain relief following Pancreatoduodenectomy (Triple P): sublingual sufentanil versus standard-of-care*". **Chapter 14** described the results of 36 randomized patients (2018-2021) and found that the mean difference in pain score on postoperative day 1 to 3 was -0.10 (95% CI -0.72 – 0.52) and therefore non-inferiority of sublingual sufentanil compared to standard-of-care (EA or iv morphine) was demonstrated. Early treatment failure occurred in 24% of patients in the sublingual sufentanil group and in 16% of patients in the standard-of-care group. Additional outcomes such as pain scores, Overall Benefit of Analgesia Score and patient satisfaction scores did not differ between the two groups. Also, perioperative hemodynamics and postoperative outcomes did not differ between the two groups. It should be noted that this study investigated multimodal treatment strategies, including standard use of paracetamol and if needed metamizole and ketamine besides sublingual sufentanil or standard-of-care, and therefore no conclusions can be drawn on the effectiveness of the individual components of the

treatment strategy. In our institution, sublingual sufentanil is now added to the pallet of postoperative pain treatment strategies following pancreatoduodenectomy. Future research is needed to confirm that these findings are applicable to other settings, preferably by studies with larger sample sizes and multicenter study designs.

Future perspectives

The incidence of pancreatic cancer is rising and the predicted pancreatic cancer mortality exceeded the breast cancer mortality in Europe in 2017.[16] The indications for pancreatic surgery in (pre-)malignant and benign disease are broadening and the care for pancreatic patients is becoming increasingly complex with a wide variety of medical disciplines involved. Therefore, future studies and multidisciplinary efforts are needed to improve outcomes for pancreatic patients.

Part I International evaluation of clinical practice in pancreatic surgery

Our studies within the EURECCA Pancreas consortium showed that more work needs to been done to uniform and tailor treatment across countries. Well-designed randomized trials, preferably by including international academic and non-academic, teaching and non-teaching hospitals, with adequate external validity have the potential to improve clinical practice. Examples of such trials are the ESPAC, PRODIGE 24–ACCORD and CCTG PA groups. For the subgroup of patients that are not suitable for inclusion in clinical trials, cancer registry based cohort studies are a valuable alternative to further investigate best practices. These studies can provide valuable evidence for the development of (inter) national guidelines since these results can be directly translated to daily practice. Adequate patient selection, prehabilitation, enhanced recovery protocols, and centralization of pancreatic surgery for (elderly) patients to improve outcomes are interesting topics for upcoming research.[17-21] Others have advocated a multidisciplinary approach to high-risk elderly patients undergoing major surgery[22], and several studies have illuminated the importance of geriatric assessment to improve the outcomes of cancer treatment.[23] A recent study in our cohort of pancreatic cancer patients >70 years undergoing pancreatectomy showed that the Safety Management System (VMS) frailty score, risk assessment tool evaluating four geriatric domains: risk for delirium, undernutrition, physical impairments and fall risk, is an useful tool associated with overall survival and discharge not-to-home. This information may be used in the shared decision-making process and the design of new studies.

A recent meta-analysis showed that ERAS programs in pancreatic surgery are safe and effective, can decrease postoperative complication rates, and can promote recovery for patients.[24] Unfortunately, only retrospective case control studies were included in this

analysis. Additional prospective and randomized studies are needed to confirm these findings. Our survey study showed that 61% of surgeons practice ERAS guidelines. The next step is to further optimize, standardize, and implement ERAS guidelines after pancreatic surgery into daily practice. The development and use of an internationally accepted ERAS guideline is pivotal for performing multicenter studies (e.g. allow benchmarking), the subsequent external validity of these results and implementation into clinical practice.

Part II Surgical and oncological aspects of venous resections in pancreatic surgery

The studies on venous resection in pancreatic surgery demonstrated that there is much to gain with regards to patient selection, surgical technique, postoperative management, pathological assessment and follow-up. This will become even more relevant with the increasing use of neoadjuvant therapy in pancreatic cancer.[25, 26] A standardized approach for patients with pancreatic cancer and suspected venous involvement is needed to uniform treatment and could improve outcomes. The upcoming results of our ULTRAPANC study within the DPCG will provide useful data on the assessment of vascular involvement with intraoperative ultrasound. These results will lay the basis for the ULTRAPANC-II study which will focus on the use of intraoperative ultrasound for patient selection for venous resection after neoadjuvant therapy. Furthermore, we have set up a hands-on workshop (surgical anatomy and operative techniques during venous resection) for Dutch pancreatic surgeons and the upcoming PREOPANC-4 trial within the DPCG (investigates the implementation of a best-practice algorithm for patients with locally advanced pancreatic cancer) have the potential to further improve surgical technique and management of patients undergoing venous resection in the Netherlands. Recently defined international benchmark outcomes for pancreatoduodenectomy with venous resection are currently used to assess outcomes within the DPCG and identify areas for further improvement on a hospital, regional or national level.[27] Our nationwide study on the impact of type of venous resection during pancreatoduodenectomy showed a significantly higher rate of PV-SMV thrombosis in patients with venous segment resection and vascular complications (PV-SMV thrombosis or hemorrhage) were the indication in 18 out of 23 patients who underwent relaparotomy after segmental resection. However, no data were available on management and outcome of PV-SMV thrombosis and this is therefore investigated in an ongoing study within the DPCG. In future studies on patient selection, surgical technique, postoperative management, pathological assessment and follow-up it is of upmost importance to use internationally accepted definitions and perioperative standards-of-care.

Part III Surgical complications in pancreatic surgery

In our studies on the surgical treatment of postoperative pancreatic fistula, we confirmed that a minimally invasive step-up approach should be the preferred strategy in the management of pancreatic fistula (e.g., primarily percutaneous catheter drainage

and, in case of failure of percutaneous catheter drainage, a pancreas-preserving surgical strategy if possible). The DPCG recently published the results of the nationwide PORSCH trial which showed that the implementation of a standardized best practice algorithm for early recognition and adequate drainage of postoperative pancreatic fistula after pancreatic resection improves clinical outcomes. This included an approximate 50% reduction in mortality at 90 days.[28] A recent paper on postoperative pancreatic fistula from international pancreatic experts highlighted the importance of dedicated (interventional) radiology and endoscopy and critical care support to avoid unnecessary laparotomies.[29] These experts also advocated for more focus on international top-quality surgical education by for instance sharing and reviewing video content, more randomized clinical trials and more research from a basic science and translational point-of-view on prevention and treatment of postoperative pancreatic fistula.

The study on the bile cultures and abdominal infectious complications resulted in a more critical note about the predictive role of routinely obtained bile cultures. Since expanding antibiotic resistance and stewardship is a relevant topic at this moment, our current postoperative prophylactic antibiotic treatment is being evaluated in a dual center retrospective study (standard antibiotic prophylaxis for five postoperative days versus preoperative antibiotic prophylaxis and postoperative antibiotics on indication). The result of this study may lead to evading unnecessary use of antibiotic prophylaxis. The proportion of patients undergoing preoperative biliary drainage (i.e. bile contamination) is expected to rise due to the increasing use of neoadjuvant chemotherapy in pancreatic cancer.[20, 21] These patients may require an different, or tailor-made, approach. Currently there are several trials ongoing which investigate the optimal preoperative antibiotic prophylaxis, whereas other trials investigate the use of standard versus targeted preoperative antibiotic prophylaxis.[30, 31] The external validity of these trials should be thoroughly scrutinized before implementation into clinical practice, since previous studies have suggested that there is significant interinstitutional variability in bile cultures and antibiotic resistance patterns.[32]

Part IV Perioperative anesthesiological management in pancreatic surgery

In the last part of this thesis, we showed that EA is the most used type of analgesia in patients undergoing pancreatoduodenectomy.[33] Although EA has some marginal advantages over the used alternatives, it cannot unambiguously be recommended for all patients as it has a relatively high failure rate (~30%). The same holds true for sublingual sufentanil. Our randomized trial in a small cohort of patients proved that it can be added to the standard pallet of postoperative analgesia as it was non-inferior to our standard-of-care in the treatment of pain on postoperative day 1 to 3. The increase of pain scores on postoperative day 3 in both groups might be explained by ending the primary pain treatment. In our opinion, more multimodal efforts are needed to improve the transition

from primary to secondary pain treatment and prevent an increase in pain scores. The authors of the recent randomized PAKMAN trial found comparable effectiveness and safety of EA and iv morphine after pancreatoduodenectomy.[34] They also stated that the recommendation for EA in the ERAS guidelines needs critical reconsideration. This is in line with a previous systematic review and meta-analysis of analgesia after abdominal surgery in an ERAS setting could not prove that EA is associated with a shorter duration of hospital stay.[35] More research is needed to determine the optimal analgesic techniques for open and separately for minimally invasive pancreatic surgery. Careful patient selection, a multimodal treatment strategy and a dedicated and specialized team, including the Acute Pain Service[36], are pivotal for a successful postoperative pain treatment.

Conclusions

In this thesis, several aspects to improve the multidisciplinary management of pancreatic surgery were identified, implemented and used to design future studies. More than 15 medical disciplines were involved during the studies involved in this thesis. Highly needed further improvement of outcome of pancreatic patients can be made by multidisciplinary collaborations on a hospital, regional, national and international level.

Table 1. Summary of main findings and answers to the research questions

Chapter 1	**General introduction and outline of this thesis**
PART I	**INTERNATIONAL EVALUATION OF CLINICAL PRACTICE IN PANCREATIC SURGERY**
Chapter 2	**Is there variation in the use of (neo)adjuvant therapies and outcomes of patients who underwent tumor resection for resectable (TNM stage I and II) pancreatic adenocarcinoma in the EURECCA Pancreas Consortium?** The use of neoadjuvant therapy was limited in most registries. Large variations in the use of adjuvant therapy, 90-day mortality and overall survival exists. The differences observed give us the chance to further investigate the best practices and improve outcomes.
Chapter 3	**How are treatment strategies and survival outcomes of patients aged ≥70 years with stage I–II pancreatic cancer in a real-world scenario in the Belgian, Dutch, and Norwegian national cancer registries?** Variations were observed for the rate of tumor resection rate, (neo)adjuvant chemotherapy and palliative chemotherapy. Also differences were observed regarding 90-day mortality, overall survival in patients who underwent tumor resection who did not undergo tumor resection. Future studies should focus on selection criteria for (non)surgical treatment in older patients so that clinicians can tailor treatment.
Chapter 4	**Is there international variation regarding pain management, fluid therapy and thromboprophylaxis after pancreatoduodenectomy between pancreatic surgeons?** The results of this international survey showed that only 61% of surgeons practice ERAS protocols. Although the majority of surgeons presume a relationship between pain management, fluid therapy and thromboprophylaxis and clinical outcomes, variations in practices were observed. Additional studies are needed to further optimize, standardize and implement ERAS protocols after pancreatic surgery.
PART II	**SURGICAL AND ONCOLOGICAL ASPECTS OF VENOUS RESECTIONS IN PANCREATIC SURGERY**
Chapter 5	**Is there variation regarding surgical management and pathological assessment of pancreatoduodenectomy with suspected venous involvement between international experts and Dutch surgeons and pathologists?** This international survey showed variation in the surgical management and pathological assessment of pancreatoduodenectomy with venous and highlights the lack of evidence and emphasizes the need for research on imaging modalities for improved patient selection, surgical techniques, postoperative management and standardization of the pathological assessment.
Chapter 6	**What is the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity, mortality and overall survival?** Patients who underwent venous segment resection, and not venous wedge resection, showed more major morbidity and worse overall survival. In the patients who received neoadjuvant therapy, overall survival was markedly higher and showed no difference between the categories of venous resection, whereas major morbidity and postoperative mortality rates remained high after venous segment resection. The results of this study urge the need to improve outcomes in patients who require a venous segment resection.
Chapter 7	**What are the potential causes and the consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands?** Practice variation between institutions in the Netherlands with regards to venous resection and reconstruction during pancreatoduodenectomy for pancreatic cancer were not explained by variations in patient characteristics only. The decision to perform a venous resection is apparently also dependent on variables not available in the registry, and might be associated with characteristics and preferences of the surgical team. The clinical outcomes of venous resection appear to be related to the volume of the procedure.

Chapter 8	**Are venous resection, tumor invasion in the resected vein, recurrence patterns and overall survival associated?** Venous resection and tumor invasion in the resected vein are not associated with recurrence patterns and overall survival. The pathological assessment of the resected portal-superior mesenteric vein has now been standardized in the Netherlands.
PART III	**SURGICAL COMPLICATIONS IN PANCREATIC SURGERY**
Chapter 9	**What should be the preferred surgical strategy when performing a relaparotomy for pancreatic fistula after pancreatoduodenectomy?** Completion pancreatectomy is associated with a doubling of the mortality and a similar rate of additional reinterventions compared to a pancreas-preserving procedure. Based on the current data, a pancreas-preserving procedure seems preferable to completion pancreatectomy in whom relaparotomy is deemed necessary for pancreatic fistula after pancreatoduodenectomy.
Chapter 10	**Correspondence to Garnier et al. and their study on standardized technique for completion pancreatectomy in patients with pancreatic fistula after pancreatoduodenectomy** Simple surgical drainage was not associated with more reinterventions or mortality in our cohort compared to other pancreas-preserving surgical interventions. Therefore, we believe that, after failure of percutaneous drainage, simple surgical drainage is a viable option in the management of pancreatic fistula following pancreatoduodenectomy.
Chapter 11	**Do bile cultures obtained during pancreatoduodenectomy have added value in the prevention or treatment of abdominal infectious complications after pancreatoduodenectomy?** Similar rates of postoperative abdominal infectious complications were observed in patients with positive and negative bile cultures. Regarding the low pathogenicity of the cultured microorganisms and the substantial incidence of confounding non-infectious complications, the predictive value of bile cultures in infectious complications seems limited. Thus, the routine performance of bile cultures should be reconsidered.
PART IV	**PERIOPERATIVE ANESTHESIOLOGICAL MANAGEMENT IN PANCREATIC SURGERY**
Chapter 12	**What are the analgesic and clinical outcomes after epidural and non-epidural analgesia after open pancreatectomy?** In our cohort, patients with epidural analgesia experienced significantly lower pain scores in the first postoperative days compared with non-epidural analgesia, yet higher pain scores after epidural analgesia had been terminated. Although epidural analgesia patients required more vasoactive medication and fluid therapy, the complication rate was similar. We need a better alternative for EA and iv morphine, since EA has a high failure rate and that the most used alternative (iv morphine) provides less pain control.
Chapter 13	**Does epidural analgesia have superior clinical outcomes compared with non-epidural analgesia in patients undergoing pancreatoduodenectomy in current the literature?** Epidural analgesia provides marginally lower pain scores in the first postoperative days than intravenous morphine, and appears to be associated with fewer complications, shorter duration of hospital stay and less mortality. There are only a few studies available and therefore further research is needed to identify the optimal analgesic technique(s) after pancreatoduodenectomy.
Chapter 14	**Is sublingual sufentanil a non-inferior analgesic compared to standard-of-care in the treatment of postoperative pain in patients following pancreatoduodenectomy?** This study demonstrated that the sublingual sufentanil treatment strategy is a non-inferior analgesic compared to our standard-of-care in the treatment of pain following pancreatoduodenectomy. In our institution, sublingual sufentanil can definitely be added to the pallet of postoperative pain treatment strategies following pancreatoduodenectomy. Future research is needed to confirm that these findings are applicable to other settings, preferably by studies with larger sample sizes and multicenter study designs.
Chapter 15	General summary, discussion, future perspectives and conclusions

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Chapter 15 - General summary, discussion, future perspectives and conclusions