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Improving outcomes of pancreatic surgery

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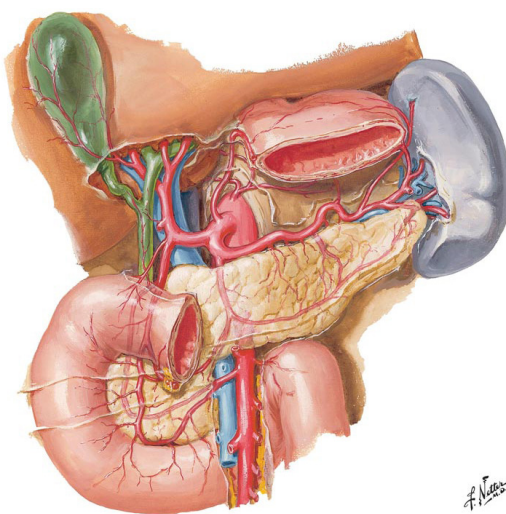
CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

The pancreas

The pancreas is an abdominal organ located in the retroperitoneum, behind the stomach from just right of the aorta to the left where the spleen is located. The pancreas is ± 15 centimeters long with a lobulated structure and a salmon-like color. The pancreas is divided in three parts: head, body, and tail. The pancreas has an endocrine (blood glucose levels) and exocrine function (digestive enzymes). Surgery on the pancreas is mostly performed for (pre)-malignant disease in the peri-ampullary region (pancreas, bile duct, duodenum, ampulla of Vater). The proximity to large vasculature (aorta, celiac trunk, superior mesenteric artery and vein, portal vein, inferior vena cava, renal artery and vein) and other organs (duodenum, stomach, gallbladder and ducts, liver, spleen, colon, kidneys, adrenal glands) makes surgery to the pancreas challenging. For this reason, the area is also called the “surgical soul” of the body. The pancreaticoduodenectomy (Whipple procedure) is the most frequently performed procedure in which the pancreatic head, common bile duct, duodenum and sometimes the distal part of stomach are resected. During the reconstruction phase, the pancreas, duodenum or stomach and the common bile duct are anastomosed to the jejunum separately to restore gastrointestinal continuity.¹

Pancreatic surgery is complex and technically demanding with historical high rates of postoperative morbidity and mortality. Over time, with advancement in surgical technique, perioperative management and dedicated high-volume institutions, the postoperative mortality has decreased from 20-30% in the early 1970s to approximately 2-3% in the last decade.^{2, 3} In the Netherlands, the first initiatives to centralize pancreatic surgery were undertaken in 1997⁴ and nowadays pancreatic surgery is only performed in institutions performing a minimum of 20 pancreaticoduodenectomies annually.⁵



For pancreatic cancer, very little progress has been made in terms of long-term survival over the past decades.⁶ Radical tumor resection combined with neoadjuvant or adjuvant chemo(radio)therapy is the current standard treatment.^{7, 8} Resectability is mainly

determined by contact between the tumor and the venous and arterial vasculature.⁹ Patients with stage I–II pancreatic cancer are generally considered eligible for resection. Unfortunately, about 80% of all patients are not eligible for resection due to advanced or metastatic disease at diagnosis.¹⁰ Still, even after tumor resection of stage I–II pancreatic cancer, prognosis is poor, with a median overall survival of 17–30 months.¹¹

Thesis outline

Pancreatic surgery today involves a wide variety of surgical and non-surgical medical disciplines. Multidisciplinary team meetings have been implemented in practice to increase the number of patients receiving optimal (oncological) diagnosis, treatment and follow-up and to decrease variations in treatment.¹² Enhanced recovery after surgery (ERAS) is a multidisciplinary guideline that has been introduced to decrease surgical stress and postoperative complications and increase recovery after surgery and the rate of patients receiving (oncological) adjuvant therapy. The general objective of this thesis is to improve the multidisciplinary management of pancreatic surgery and is divided in four parts.

Part I International evaluation of clinical practice in pancreatic surgery

Part I provides an overview of clinical practice regarding the variation in tumor resection and (neo)adjuvant therapy in patients with pancreatic cancer and an overview of the use of ERAS guidelines regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing pancreatoduodenectomy.

The European Registration of Cancer Care (EURECCA) Pancreas Consortium uses cancer registry data to compare and improve treatment strategies by identifying best practices in a real-world scenario.¹³ **Chapter 2** is the first study of the EURECCA Pancreas Consortium comparing (neo)adjuvant therapies and outcomes of patients who underwent tumor resection for resectable (stage I and II) pancreatic adenocarcinoma in a national, regional and a single center cancer registry. A recent study with population-based data of multiple pancreatic cancer registries showed that the median age at diagnosis is 70 years.¹⁴ This clearly differs from large randomized trials in pancreatic cancer in which the median age is 61–65 years.^{15, 16} The aim of **Chapter 3** is to compare treatment strategies and survival outcomes of patients aged ≥ 70 years with stage I and II pancreatic cancer in the EURECCA Pancreas consortium.

There is increasing interest in ERAS guidelines as a means of improving clinical outcomes, although to date there is limited data on pancreatoduodenectomy.^{17, 18} Pain management, fluid therapy and thromboprophylaxis are key elements in all ERAS

guidelines. **Chapter 4** aims to obtain an international assessment of current perioperative practices regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing pancreatoduodenectomy among surgeons.

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

Part II focusses on the surgical and oncological aspects of venous involvement (more specific the portal vein-superior mesenteric vein) in pancreatic surgery. Venous involvement will become increasingly important with the growing use of neoadjuvant therapy since it can increase the incidence of suspected venous involvement either by tumor fibrosis and inflammation, which can mimic venous tumor invasion on imaging, or by downstaging the tumor to resectable venous involvement.¹⁹

The aim of **Chapter 5** is to gain insights in the current surgical management and pathological assessment of pancreatoduodenectomy with suspected venous involvement by international and Dutch surgeons and pathologists. Literature regarding risk of complications for the different types of venous resection is contradicting.²⁰⁻²² In **Chapter 6** we evaluate the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity, mortality and overall survival in The Netherlands. To improve outcomes for patients with pancreatic cancer and venous involvement we need to identify best practices and standardize treatment in the Netherlands. **Chapter 7** explores the potential causes and the consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands. One of the main challenges for a pancreatic surgeon when confronted with possible tumor invasion in the vein is distinguishing tumor from peritumoral inflammation and fibrosis. The aim of **Chapter 8** is to study the association between venous resection, tumor invasion in the resected vein, recurrence patterns and overall survival.

Part III Surgical complications in pancreatic surgery

Part III consists of studies on the most notorious complications in pancreatic surgery: postoperative pancreatic fistula and abdominal infectious complications. These complications are associated with a high morbidity and mortality.

Only few studies have been performed on the clinical outcomes of different surgical strategies in patients with pancreatic fistula after pancreatoduodenectomy with a need for a relaparotomy.²³ **Chapter 9** evaluates surgical strategies (i.e. completion pancreatectomy versus pancreas-preserving procedure) in patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy in nine Dutch institutions. Additionally, a systematic review and meta-analysis is performed on this topic to summarize all available evidence. In a recent study, Garnier et al. conclude that their standardized technique for completion pancreatectomy in patients with pancreatic

fistula after pancreatoduodenectomy appears to be relatively safe, reproducible, and could be particularly useful for young surgeons.²⁴ Additionally the authors state that pancreas-preserving surgical interventions are associated with more reoperations and mortality and that simple surgical drainage should not be adopted. **Chapter 10** contains a letter to the editor reacting to this study, we report a subgroup analysis of patients undergoing simple surgical drainage versus other pancreas-preserving surgical interventions.

When not caused by a pancreatic fistula, abdominal infectious complications are often caused by complications of the biliary or enteric anastomosis. No consensus exists about the predictive role of intraoperative bile cultures during pancreatoduodenectomy in abdominal infectious complications. A large multicenter study suggested that institution-specific internal reviews of intraoperative bile cultures should amend current protocols for antibiotic prophylaxis.²⁵ **Chapter 11** investigates the association between positive bile cultures and abdominal infectious complications after pancreatoduodenectomy. Also, the predictive role of intraoperative bile cultures is evaluated by determining microorganism concordance in bile and cultures of abdominal infections. Additionally, a systematic review and meta-analysis summarizes all available evidence on this topic.

Part IV Perioperative anesthesiological management in pancreatic surgery

Part IV discusses the perioperative anesthesiological management in pancreatic surgery with special regards to analgesic and fluid therapy. Epidural analgesia is the perioperative analgesic technique of choice for most open abdominal surgical procedures and has been associated with better pain control.²⁶ On the other hand, it carries the risks of technique-specific complications, technical failure and hemodynamic instability. Therefore, the optimal analgesic technique after pancreatoduodenectomy remains under debate and detailed reports of perioperative analgesic management are lacking.

Chapter 12 describes a patient cohort treated with epidural analgesia versus non-epidural analgesia regarding the analgesic outcomes in the first ten postoperative days and clinical outcomes after open pancreatectomy in our own institution. In **Chapter 13** we assess whether epidural analgesia has superior clinical outcomes compared with non-epidural analgesia in patients undergoing pancreatoduodenectomy by a systematic review and meta-analysis of the literature. Recent studies and experience within our region have shown encouraging results and benefits of sublingual sufentanil (non-invasive, rapid absorption and pain relief, and less side effects) over epidural analgesia and iv morphine.²⁷ Therefore, we designed a randomized trial in patients undergoing pancreatoduodenectomy "Postoperative Pain relief following Pancreatoduodenectomy (Triple P): sublingual sufentanil versus standard-of-care". **Chapter 14** describes the results of this trial

in which sublingual sufentanil is compared to our standard-of-care (epidural analgesia or iv morphine). Finally, **Chapter 15** includes a general summary and discussion of the previous chapters, and discusses the future perspectives of pancreatic surgery and conclusions of this thesis.

Table 1. 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?
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?
Chapter 4	Is there international variation regarding pain management, fluid therapy and thromboprophylaxis after pancreatoduodenectomy between pancreatic surgeons?
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?
Chapter 6	What is the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity, mortality and overall survival?
Chapter 7	What are the potential causes and the consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands?
Chapter 8	Are venous resection, tumor invasion in the resected vein, recurrence patterns and overall survival associated?
PART III	SURGICAL COMPLICATIONS IN PANCREATIC SURGERY IN PANCREATIC SURGERY
Chapter 9	What should be the preferred surgical strategy when performing a relaparotomy 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
Chapter 11	Do bile cultures obtained during pancreatoduodenectomy have added value in the prevention or treatment of abdominal infectious complications after pancreatoduodenectomy?
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?
Chapter 13	Does epidural analgesia have superior clinical outcomes compared with non-epidural analgesia in patients undergoing pancreatoduodenectomy in current the literature?
Chapter 14	Is sublingual sufentanil a non-inferior analgesic compared to standard-of-care in the treatment of postoperative pain in patients following pancreatoduodenectomy?
Chapter 15	General summary, discussion, future perspectives and conclusions

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