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International collaboration to improve surgical treatment of left-sided pancreatic neoplasms

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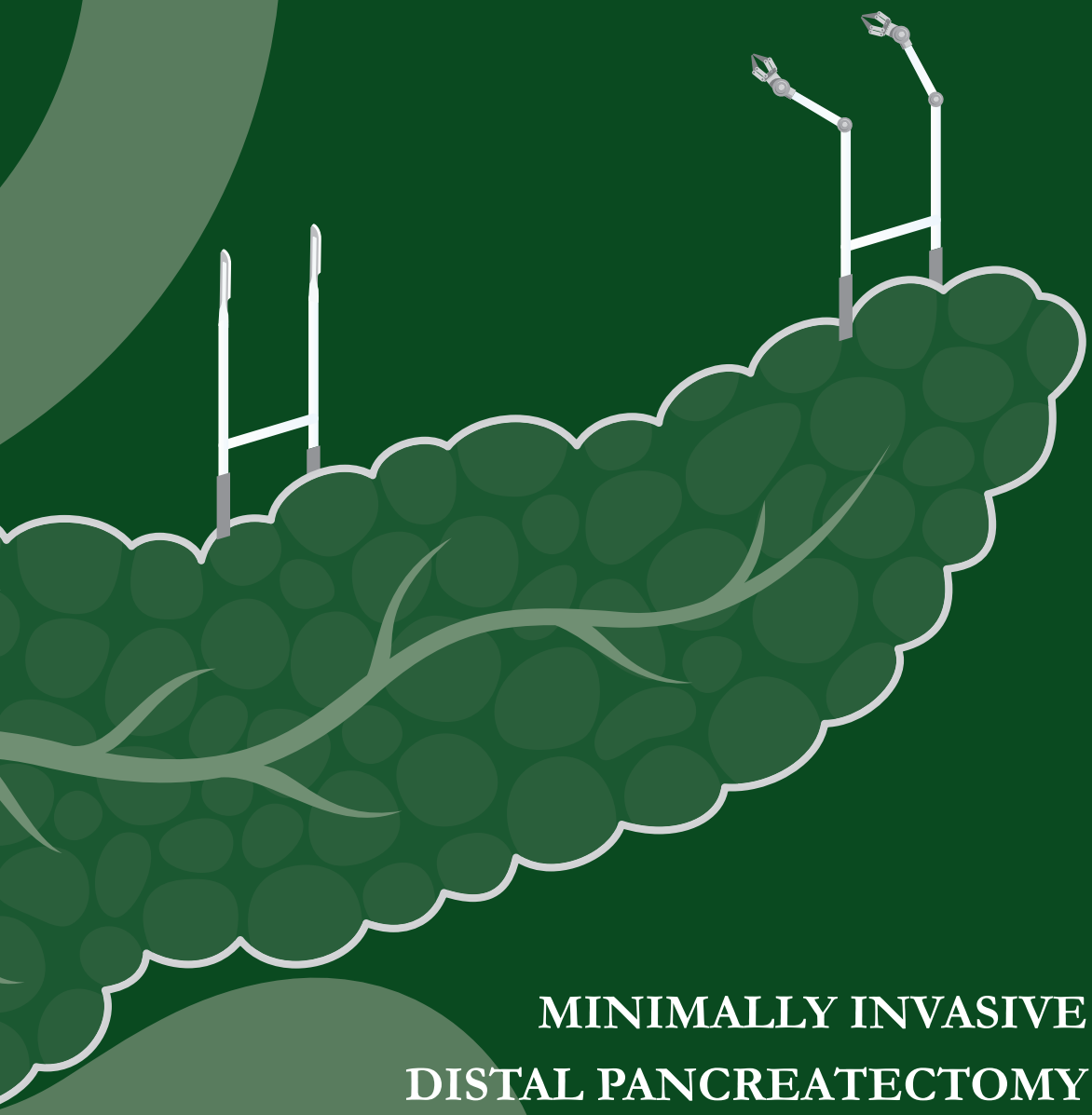

MINIMALLY INVASIVE DISTAL PANCREATECTOMY

International collaboration to improve surgical treatment of left-sided pancreatic neoplasms

Maarten Korrel

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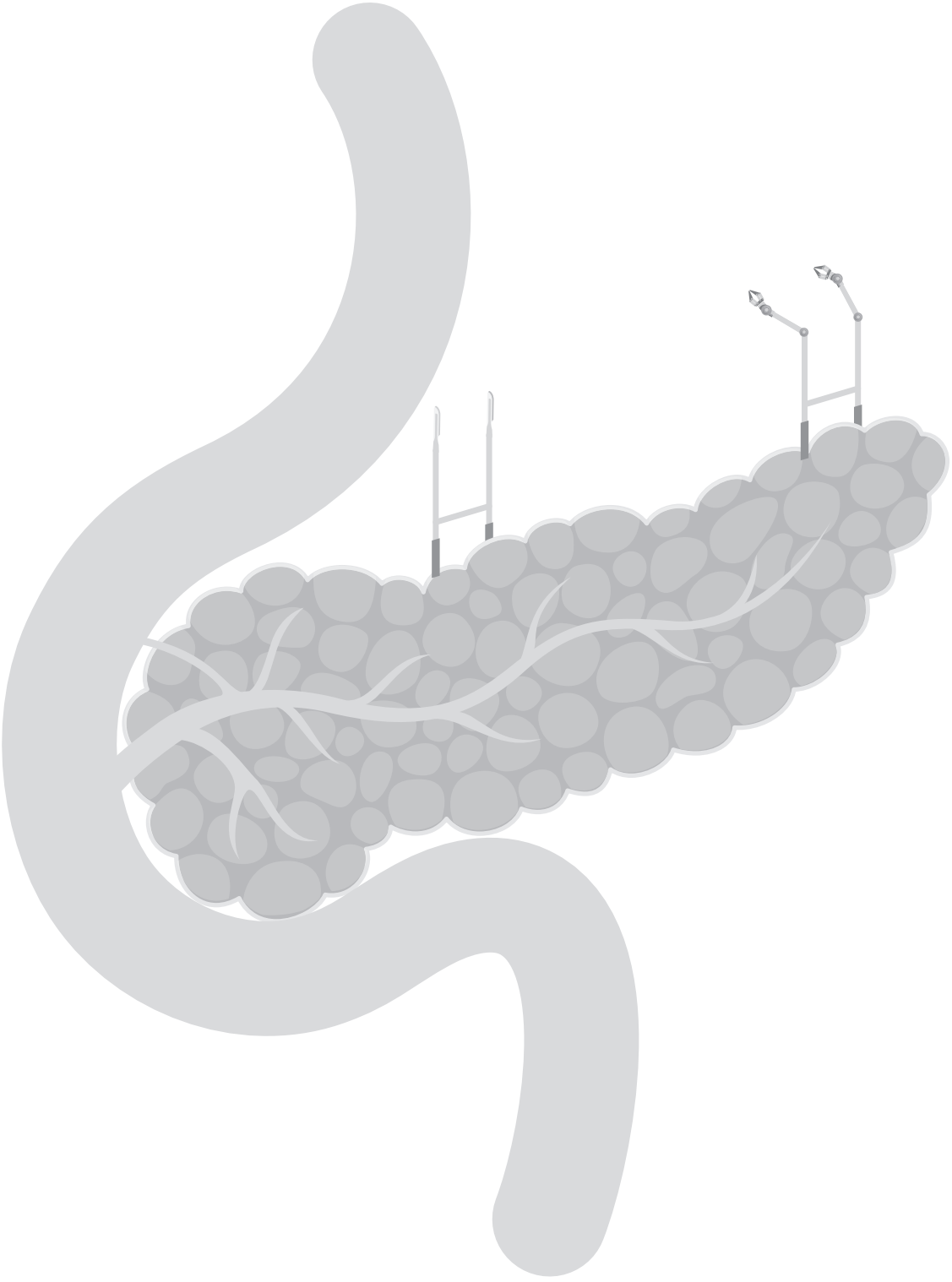

1 INTRODUCTION

GENERAL INTRODUCTION

Pancreatic anatomy and function

The pancreas is part of the gastrointestinal tract and is located in the retroperitoneal region behind the stomach. The pancreas is located between the duodenum and spleen and lies on top of several important blood vessels such as the portal vein, the superior and inferior mesenteric artery and vein, and the celiac trunk. The pancreas itself is divided into the uncinate process and pancreatic head, neck, body, and tail. Especially the superior mesenteric vein plays an important role in the anatomical orientation of the pancreas, as the pancreas is divided into the pancreatic head region ("right pancreas") and pancreatic body/tail region ("left pancreas") at the superior mesenteric vein. The blood supply of the pancreatic body and tail runs mostly via numerous small branches of the splenic artery that originates from the celiac trunk and is located at the dorsal region of the pancreas. Venous blood from the pancreatic body and tail drains mostly into the splenic vein, which meets with the inferior mesenteric vein at the confluence to form the portal vein.

The pancreas plays a crucial role in several parts of metabolism, mainly by the production of several hormones and enzymes. Based on the different types of cells that form the pancreas, its function is divided into two parts: the exocrine and endocrine pancreas. The exocrine pancreas consists of acinar cells, which produce pancreatic fluid that contains amylase. The pancreatic fluid is drained directly into the duodenum, where it is involved in the breakdown of carbohydrates, cholesterol, fat, and several proteins. The endocrine pancreas consists of the Langerhans islets which produce insulin (beta cells), glucagon (alpha cells), and somastatin (delta cells), which are involved in the glucose regulation.[1,2]

Pancreatic diseases and surgical management

Several types of neoplasms may arise from the different cell types of the pancreas, which can be either benign, premalignant, or malignant. The majority of pancreatic lesions is benign or premalignant and consists of intraductal papillary mucinous neoplasms, neuroendocrine tumors, cystadenomas, and several other diagnoses. Approximately one-fourth of pancreatic lesions are malignant, i.e. pancreatic cancer (pancreatic ductal adenocarcinoma), which originate from the ductal epithelial cells and might arise from premalignant precursor lesions (e.g., intraductal papillary mucinous neoplasms, mucinous cystadenomas). Pancreatic cancer is currently the third most lethal cancer in terms of mortality with a five-year survival rate of approximately 5-10%.[3] In fact, its mortality has increased from 8.6/100.000 persons to 9.5/100.000 from 2000 to 2019.[4] Patients with left sided pancreatic cancer represent 20% of all patients with resectable pancreatic cancer. In these patients, when possible, resection followed by adjuvant chemotherapy is the preferred treatment, with a five-year survival rate of 20%.[3,5]

The surgical management of left-sided pancreatic neoplasms consists of distal (also known as 'left') pancreatectomy, in which the pancreas is divided at the pancreatic neck to resect the pancreatic body and/or tail. Distal pancreatectomy is a technically challenging procedure due to the retroperitoneal location of the pancreas and the proximity to major abdominal vascular structures. Although some improvements have been reported, clinically relevant morbidity after distal pancreatectomy remains present in 25-40% of patients.[6,7] This burden is most probably a consequence of the high complex surgery and long learning curves, and consists of pancreatic surgery specific complications such as postoperative pancreatic fistula, postpancreatectomy hemorrhage, and delayed gastric emptying.[8-10]

Traditionally, distal pancreatectomy is combined with concomitant splenectomy. However, when performed for benign and premalignant indications, splenic preservation during distal pancreatectomy is advocated owing to the improved understanding of splenic function and prevention of splenectomy related complications.[11,12] Spleen-preserving distal pancreatectomy can be performed according to two different techniques: (1) the Kimura technique in which both splenic artery and vein are preserved; and (2) the Warshaw technique in which the splenic vessels are transected and splenic perfusion is maintained through the left gastroepiploic artery and the short gastric vessels.[13,14] When performed for pancreatic cancer, distal pancreatectomy requires a more extended resection including resection of Gerota's (i.e. perirenal) fascia, splenectomy, and standardized lymph node harvest for adequate oncological resection.[15,16] Concomitant splenectomy during distal pancreatectomy is performed to optimize radical resection margins and lymph node yield.[15,16] Adequate lymphadenectomy includes the resection of locoregional lymph node stations and should include the yield of at least 19-20 lymph nodes.[17,18]

Minimally invasive distal pancreatectomy

In the modern era, minimally invasive surgery has gained significant interest for several major abdominal surgical procedures. Suggested advantages of minimally invasive surgery include less surgical trauma, less intraoperative blood loss, shorter length of hospital stay, and shorter time to functional recovery.[19] The first minimally invasive distal pancreatectomy (MIDP) was described in 1994 by Cuschieri et al.[20], which was followed by a significant but slow implementation of this technique worldwide.[21] Probable reasons for this rather slow implementation have been the technical complexity owing to the retroperitoneal location of the pancreas and close proximity to major abdominal vascular structures leading to long learning curves, but also the lack of specific training in minimally invasive pancreatic surgery.[22] The subsequent lack of comparative studies might have maintained uncertainty about the clinical benefits compared to open distal pancreatectomy (ODP).[23]

An increasing interest in MIDP has been observed in recent years, demonstrated by a large amount of studies evaluating outcomes as described in the Miami Guidelines on Minimally Invasive Pancreatic Resection.[23] Numerous non-randomized studies have reported short-term benefits of MIDP over ODP, including less postoperative complications, less blood loss, and shorter hospital stay.[24-30] These benefits were confirmed by two recent randomized controlled trials on MIDP versus ODP: the Dutch multicenter LEOPARD trial and the Swedish single-center LAPOP trial[7,31], as both found shorter time to functional recovery, shorter hospital stay, and less blood loss in the MIDP group. Moreover, when evaluating technical outcomes such as splenic preservation rates and postoperative rates of splenic infarction and gastric varices, a minimally invasive approach could improve such outcome as compared to an open approach.[32,33] It is thought that a minimally invasive approach, in particular the robotic approach, could improve the imaging and subsequent handling of vascular structures, which theoretically improves postoperative outcomes but studies are scarce so far.[33] Considering the above, MIDP is now often considered the standard approach to benign and premalignant left-sided pancreatic neoplasms.

On the contrary, concerns remain regarding the oncological safety of MIDP in patients with resectable pancreatic cancer. Those were confirmed by an international survey study wherein one-third of pancreatic surgeons expected inferior oncological outcomes after MIDP, including lymph node yield, radicality of resection, and overall survival as compared to ODP in patients with resectable pancreatic cancer.[34] Additionally, a systematic review and meta-analysis including over 11.000 patients reported comparable radical resection rates and survival, but a decreased lymph node yield during MIDP procedures (mean difference -1.3 lymph nodes).[35] Recently, these concerns were further fueled by a randomized trial that reported worse survival outcomes after minimally invasive hysterectomy in patients with cervical cancer[36], and by two randomized trials that failed to confirm the oncological non-inferiority of a minimally invasive approach in patients with colorectal cancer.[37,38] Results of these studies had significant clinical impact as a decrease in the use of a minimally invasive approach was observed. Randomized studies focusing on oncological outcomes after MIDP and ODP are lacking to date, hence the role of MIDP in treating patients with resectable pancreatic cancer is yet to be established.

Aim of this thesis

The minimally invasive approach to distal pancreatectomy for left-sided neoplasms has become popular over the past decades and is now often preferred over the open approach for benign and premalignant diseases. Although randomized controlled trials have reported benefits of MIDP over ODP, robust evidence on technical short-term outcomes and long-term outcomes such as quality of life is lacking. Moreover, the role of MIDP in the management of malignant left-sided pancreatic neoplasms remains a subject of debate as

randomized controlled trials are lacking. For this thesis, extensive international collaborative research has been conducted in order to provide the highest level of evidence on this topic. Available evidence on oncological outcomes after MIDP is summarized in order to facilitate the initiation and conduct of the first international randomized controlled trial comparing MIDP and ODP in pancreatic cancer. Eventually, this thesis aims to provide suggestions for future research and clinical practice based on the gathered evidence, in order to obtain a safe implementation of MIDP. Altogether, evidence on the potential benefits of minimally invasive distal pancreatectomy was evaluated in an international setting for this thesis, eventually to improve surgical treatment of left-sided pancreatic neoplasms.

THESIS OUTLINE

Part I - Outcomes of minimally invasive distal pancreatectomy

Data from randomized controlled trials provide evidence that MIDP may be preferred over ODP when treating left-sided benign and pre-malignant pancreatic neoplasms.[6,7] This finding is also stated in the Miami guidelines on minimally invasive pancreatic resection.[23] However, since these trials were performed in different clinical settings, the external validity could be questioned. Therefore, an individual patient-data meta-analysis of the two available randomized controlled trials was performed which is described in **Chapter 1**. This study included subgroup analyses in high-risk patients as called for in the Miami guidelines.[23]

Although spleen-preserving procedures, including minimally invasive spleen-preserving procedures, are broadly performed, no studies on outcomes after spleen-preserving MIDP versus spleen-preserving ODP were identified for the Miami guidelines. The European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS) designed a retrospective study evaluating short-term outcomes after spleen-preserving MIDP, which is described in **Chapter 2**. Furthermore, an international multicenter analysis of patients that received either spleen-preserving MIDP or spleen-preserving ODP was performed and compared short- and long-term outcomes, which is described in **Chapter 3**.

Since distal pancreatectomy is mostly performed for diseases with long overall survival, reporting long-term outcomes would be relevant in this group of patients. While health-related quality of life has become an important patient-reported outcome measure after surgery, studies reporting such outcomes after MIDP or ODP are lacking. **Chapter 4** describes a long-term analysis in the LEOPARD trial, which primarily focused on functioning outcomes and generic and disease specific quality of life following MIDP and ODP.

Part II - Minimally invasive distal pancreatectomy for pancreatic cancer

Following the raised concerns regarding the oncological safety of MIDP in pancreatic cancer in an international survey study and systematic review[22], the E-MIPS consortium commenced the DIPLOMA study group to further investigate the oncological feasibility of MIDP. First, the DIPLOMA study group performed a retrospective cohort study[39], followed by a systematic review and meta-analysis summarizing all available evidence regarding this topic, which is described in **Chapter 5**.

A post-hoc analysis of the earlier mentioned DIPLOMA cohort study is described in **Chapter 6**, which assessed long-term outcomes of MIDP and ODP focusing on survival and the prognostic value of MIDP. Surgical parameters with corresponding prognostic value were evaluated in multiple regression analyses. A separate analysis evaluating the effects of neoadjuvant chemotherapy on outcomes of MIDP and survival is described in **Chapter 7**.

Besides oncological concerns, the safety and feasibility of MIDP in patients with pancreatic cancer may be questioned given the high conversion rate reported in current literature (15-25%).[40-43] Conversion, either in elective or emergency setting, may potentially affect patient outcome but studies are lacking. **Chapter 8** describes an analysis focusing on the indications for and effects on oncological outcomes of either elective or emergency conversion in MIDP performed in patients with pancreatic cancer.

Parallel to the conduct of studies reported in Chapters 5-8, the "exploratory phase", the DIPLOMA study group designed the international, multicenter, patient and pathologist blinded, non-inferiority randomized controlled DIPLOMA trial. **Chapter 9** describes this trial, which was performed in high-volume centers participating in E-MIPS, evaluating short- and long-term oncological outcomes of MIDP and ODP.

Part III – Future implementation of minimally invasive distal pancreatectomy

Considering the high complex nature of pancreatic surgery, extensive training is required for a safe worldwide dissemination of minimally invasive pancreatic surgery. Previous studies have reported a significant increase in the use of MIDP following training, but the implementation rate in the Netherlands following the LEOPARD trial is still unknown. **Chapter 10** describes the implementation rate of MIDP in the Netherlands and reports outcomes of these procedures after completion of this trial.

At last, although important efforts have been made with the development of several training curricula, consensus regarding a structured training framework and the inclusion criteria

for surgeons to receive training is lacking. **Chapter 11** describes a Delphi consensus study among international experts in the field of minimally invasive pancreatic surgery, which identified fundamental items in the domains of a framework for training, selection criteria for surgeons to receive training, and selection criteria for surgeons to proctor in training.

SUMMARY OF RESEARCH QUESTIONS ADDRESSED IN THIS THESIS

Chapter	Research question
1	What are outcomes of minimally invasive distal pancreatectomy for all indications when combining individual patient data from the LEOPARD and LAPOP randomized trials?
2	Are the short-term outcomes of the spleen preserving Warshaw and Kimura techniques during minimally invasive distal pancreatectomy comparable?
3	Does a minimally invasive approach to spleen-preserving Warshaw and Kimura distal pancreatectomy improve long-term outcomes as compared to an open approach?
4	How does minimally invasive distal pancreatectomy for all indications affect quality of life outcomes after long-term follow-up as compared to open distal pancreatectomy?
5	Are oncological outcomes of minimally invasive distal pancreatectomy comparable to open distal pancreatectomy in currently available evidence?
6	What are independent predictors for survival after distal pancreatectomy for resectable pancreatic cancer?
7	Does neoadjuvant treatment improve oncological outcomes after minimally invasive distal pancreatectomy for resectable pancreatic cancer?
8	What are predictors for and outcomes of conversion during minimally invasive distal pancreatectomy for pancreatic cancer?
9	Does minimally invasive distal pancreatectomy provide comparable radicality of resection as open distal pancreatectomy in patients with resectable pancreatic cancer?
10	How was MIDP implemented in the Netherlands following the LEOPARD trial and what are outcomes on a nationwide level?
11	What are criteria required for training in minimally invasive pancreatic surgery and what should training include as reported in an international Delphi study?

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