Shifting emphasis in pancreatic surgery: Pre-, intra-, and postoperative determinants of outcome
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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
GENERAL INTRODUCTION

THE PANCREAS

Due to its inaccessible retroperitoneal location, kept out of sight by duodenum, stomach, liver, spleen, and transverse mesocolon, and its indistinct appearance and function, the pancreas has been a longstanding abdominal enigma. Its denomination is based on the ancient Greek *pan kreas*, meaning ‘all flesh’, a Hippocratic concept describing the composition of glandular structures. However, in the era in which the pancreas’ nomenclature emerged, its function as a gland was not yet to be recognized for ages; Aristotle (384-322 BC) considered the pancreas merely a structure protecting the large vessels in its immediate vicinity. The influential Roman physician Claudius Galenus (129-216 BC), a pioneer in anatomy and surgery, upheld the viewpoint of the pancreas as a protective organ, describing it as a cushion for the stomach. His theories would remain leading for centuries, aided by the hampering influence on science of the church during the Dark Ages.

After the church loosened its grip, at the beginning of the Renaissance, observation became the cornerstone of science again. In Padua, the Flemish anatomist Andreas Vesalius (1514-1564) published his *De Humani Corporis Fabrica*, in which the first anatomic depiction of the pancreas appeared. The stomach cushion theory was questioned by Italian anatomist Gabriele Falloppio (1523-1562), who argued that the pancreas would then be useless in animals, with the pancreas situated above instead of below the stomach. It would take another century, though, before a role of the pancreas in digestion was suggested. An important event that preceded this further elucidation of pancreatic function, was the discovery in 1642 by Johann Georg Wirsung (1589-1643) of the main pancreatic duct, which to date wears his name. Sadly, he would never learn the role of the pancreatic duct and its juicy content, since he was murdered shortly after his discovery, presumably a jealousy-driven crime. In Leiden, Regnier de Graaf (1641-1673) of Delft was the first to perform investigations on pancreatic juice, obtained from self-created pancreatic fistulas in dogs. In his *De succo pancreatico*, he asserted that one of its roles was to initiate ‘segregation of the useful food elements’. Further progress was later deterred by the conclusion of Johann Conrad Brunner (1653-1727) that the pancreas was not essential to life, after observing that pancreatectomized dogs survived for almost a year. It was the French Claude Bernard (1813-1878) who redirected attention to the pancreas again; his experiments on the absorption of fats after ligation of the pancreatic ducts led to his
1849 paper *du suc pancréatique et de son rôle dans les phénomènes de la digestion*. Finally, the great importance of the pancreas as an organ involved in digestion and metabolism was widely recognized.

The pancreas is situated in the retroperitoneal region of the upper abdomen. It consists of a head (caput), body (corpus) and tail. The head makes up most of its mass and lies in intimate contact with the inner curve of the duodenum. The common bile duct passes behind the pancreatic head, partly or completely surrounded by pancreatic tissue, and drains into the duodenum at the ampulla of Vater, together with the pancreatic main duct. An extension of the head, the uncinate process, curves down- and leftwards around the superior mesenteric vessels, in front of the aorta and vena cava. The corpus is situated behind the stomach, separated from it by the double peritoneal covering of the omental bursa. The tail stretches out leftwards and ‘tickles’ the spleen.

Pancreatic blood supply comes from branches of the celiac trunk and superior mesenteric artery. The celiac trunk gives rise to the gastroduodenal artery and then the anterior and posterior superior pancreaticoduodenal arteries, which form arcades with their inferior counterparts from the superior mesenteric artery, supplying the pancreatic head and duodenum. The splenic artery, also from the celiac trunk, gives rise to the dorsal pancreatic artery, which supplies the body and tail. Venous drainage of the pancreas occurs via the portal, superior mesenteric and splenic veins.

Pancreatic tissue consists of acinar and islet cells. Acinar cells are exocrine cells, clustered in acinar units; they produce digestive enzymes such as amylase, lipase, trypsin, chymotrypsin, and carboxypeptidase, that are secreted into the intestinal system through a system of ducts. The islet cells lie clustered in the islets of Langerhans and take charge of the pancreas’ endocrine function, by producing insulin and glucagon.

**PANCREATIC CANCER**

Pancreatic cancer is lethal. With a 5-year survival rate of around 5%, its mortality rates reach up to its incidence. It is the fourth most frequent cause of cancer-related mortality in Europe and the United States of America. Risk factors are smoking, type 2 diabetes mellitus, obesity, heavy alcohol consumption, male gender, increasing age, and chronic pancreatitis. Apart from environmental risk factors, inherited genetic predispositions can contribute to the development of pancreatic cancer.
Pancreatic ductal adenocarcinoma is the most common solid tumor in the pancreas, consisting of pancreatic duct cells forming glands and infiltrating into neighboring tissues. It usually arises in the pancreatic head, where it grows without localizing symptoms until the common bile duct becomes obstructed. Patients then present with jaundice, weight loss, and anorexia, and sometimes abdominal and/or back pain. Along with the yellow discoloration of the skin and sclerae, stool becomes decolored and urine gets dark. At presentation, the majority of patients have locally advanced or metastatic disease, rendering them unfit for surgery, which offers the best chance for longterm survival.

**PANCREATODUODENECTOMY**

The surgical procedure of choice for pancreatic head tumors, including distal common bile duct and ampullary tumors, is a pancreateoduodenectomy, which involves resection of the duodenum and the pancreatic head. The first surgeon to perform an actual pancreateoduodenectomy was the Italian surgeon Codivilla (1861-1912), although he did not resect the complete duodenum, and did not anastomose or close the pancreatic stump. His patient died within a month. The German surgeon Walter Kausch (1867-1928) described the first pancreateoduodenectomy with a successful pancreaticoenterostomy in 1912; his operation did not involve a resection of the complete duodenum. It was the American surgeon Allen Oldfather Whipple (1881-1963) who laid the foundations of modern pancreatic surgery, with his 1935 publication *Treatment of carcinoma of the ampulla of Vater*. He was the first to describe complete removal of the duodenum and a large portion of the pancreatic head, initially as a two-stage procedure, in which jaundice first was relieved by cholecystogastrostomy. He later on developed a one-stage procedure, aided by the discovery of Vitamin K supplementation to confront the coagulation disorders in jaundiced patients, with complete removal of the duodenum and pancreatic head, pancreaticoenterostomy on a jejunal limb, and choledochoenterostomy; much like the operation of today. Whipple’s publications demonstrated the feasibility of pancreatic resection and heralded an era of pancreatic surgery being performed on a larger scale.

The operation that is performed mostly nowadays is the pylorus-preserving pancreateoduodenectomy. The pancreas is divided at the level of the portal vein, the duodenum just distal to the pylorus and around the duodenojejunal flexure, and the common bile duct above the cystic duct. The extracted specimen thus contains the gallbladder, common bile duct, pancreatic head and duodenum.
Reconstruction is performed by pancreaticojejunostomy, hepaticojejunostomy, and duodenojejunostomy. In case of unresectability, a palliative bypass procedure may be performed, consisting of a hepaticojejunostomy, with or without a gastrojejunostomy.

**OUTCOME OF PANCREATODUODENECTOMY**

In recent decades, mortality of the procedure has dropped dramatically, to 1-2% in high-volume centers. Morbidity however remains high; complications occur in up to 50% percent of patients. Three of the most important complications after pancreatectoduodenectomy, postoperative pancreatic fistula (POPF), postpancreatectomy haemorrhage (PPH) and delayed gastric emptying (DGE), have recently been defined in consensus statements from an international group of leading pancreatic surgeons.

The most feared complication, POPF, results from failure of the pancreaticoenteric anastomosis. It occurs in approximately 10-15% of patients. Pancreatic tissue is soft, and especially when there is no dilation of the pancreatic duct, the pancreaticoenteric anastomosis is at risk for leakage. Pancreatic fistula can lead to haemorrhagic and septic complications, and contribute significantly to mortality of pancreatectoduodenectomy.

PPH is another major contributor of mortality after pancreatectoduodenectomy, occurring in approximately 3% of patients. Late onset bleeding can result from local infectious complications, and can result in delayed massive hemorrhage and death. Both POPF and PPH, as well as another anastomotic complication, biliary leakage, have been extensively explored in studies and theses from the Academic Medical Center (AMC) in the past years. In the current thesis, we shift our emphasis to the most prevalent complication after pancreatectoduodenectomy: DGE.

**DELAYED GASTRIC EMPTYING**

DGE after pancreatectoduodenectomy was first described by Warshaw and Torchiana in the 1980s. It can be described as a state of gastroparesis, requiring prolonged nasogastric drainage and delaying return to solid food intake. Many centers used to have their own criteria for the diagnosis of DGE. The consensus definition by the International Study Group of Pancreatic Surgery from 2007 aimed at applying uniformity in reporting DGE, in order to enable comparison between centers. This definition is based on the duration of nasogastric drainage and return to solid food intake, and it provides a grading system, reflecting the clinical impact of the
complication. In this definition, grade A DGE is present when nasogastric drainage was required beyond the third postoperative day, or when no solid food was tolerated by postoperative day 7. Grade B or C DGE is present after one, respectively two weeks of nasogastric drainage, or when solid food is not tolerated for two or three weeks, respectively. Grade B and C are considered to be clinically relevant, while grade A has minimal impact on the postoperative course. Although there is a clear relationship with intra-abdominal complications, the etiology of DGE has never been fully elucidated.
OUTLINE OF THE THESIS

The outcome of pancreatic surgery depends on various pre-, intra-, and postoperative determinants. Preoperatively, careful staging must be performed to identify patients with potentially resectable tumors. One must decide which tests should be included in the diagnostic work-up, and whether or not to perform preoperative biliary drainage in case of obstructive jaundice. Intraoperatively, many decisions have to be made: whether resection is feasible, how far the resection should extend, how to restore continuity after resection. Postoperatively, several complications may occur that interfere with outcome, and one should decide how to treat these conditions. The aim of the present thesis is to investigate pre-, intra-, and postoperative determinants of outcome of pancreatic surgery. The core of the thesis focuses on the etiology and prevention of pancreateoduodenectomy’s most frequent complication: DGE.

The first part of the thesis addresses preoperative determinants of outcome. Chapter 2 attends to the work-up of patients with pancreatic head tumors. Although staging laparoscopy used to be a mainstay in the diagnostic work-up of patients with pancreatic head tumors, its routine use is not advocated nowadays. We aimed to identify patients with high risk of distant metastasis, in whom staging laparoscopy could preclude a nontherapeutic laparotomy. The subject of chapter 3 is preoperative biliary drainage. For years, the issue of preoperative biliary drainage has been a matter of debate. Even Whipple’s initial two-stage procedure was based on relieving jaundice first. A recent multi-center randomized trial initiated at the AMC showed that the overall complication rate was significantly higher in patients allocated to preoperative biliary drainage, than in patients who proceeded directly to surgery; it was advocated that operable patients with jaundice due to a pancreatic head tumor should undergo ‘early surgery’. In this chapter we evaluate the relation between the therapeutic delay associated with preoperative biliary drainage and survival, in participants of the trial with a malignancy. In chapter 4 we looked into one of the most prevalent complications after pancreateoduodenectomy, DGE. Patients who develop this complication may require endoscopic placement of a nasojejunal feeding tube, which is not routinely inserted intraoperatively. In this study we correlated preoperative symptoms of gastric outlet obstruction to delayed gastric emptying after pancreateoduodenectomy, in order to identify high-risk patients who could profit from intraoperative placement of a feeding tube.
The second part evaluates intraoperative determinants of surgical outcome. Chapter 5 returns to delayed gastric emptying. Some studies suggest that the route of the gastroenteric anastomosis in pancreatoduodenectomy may be of importance for the incidence of this bothersome complication. This anastomosis can be positioned retrocolic (behind the transverse colon) or antecolic (in front of the transverse colon). It was claimed that an antecolic route led to a lower incidence of DGE.24,25 This led to a gradual shift in the AMC from predominantly retrocolic to predominantly antecolic gastroenteric anastomoses. In this chapter we evaluated whether the antecolic anastomosis led to a lower incidence of DGE in the AMC population. In chapter 6 the same question was investigated, but now in the setting of a multi-center, randomized controlled trial. In ten participating centers, patients undergoing pancreatoduodenectomy were randomly allocated to a retrocolic or antecolic gastroenteric reconstruction. Main outcome parameter was delayed gastric emptying. In chapter 7 some important secondary outcomes of this randomized controlled trial are presented: gastric emptying speed at scintigraphy, and quality of life. Apart from comparing patients with a retrocolic and antecolic gastroenteric reconstruction, we aimed to objectivate the burden on quality of life of DGE. In chapter 9, we describe the incidence and consequences of an aberrant right hepatic artery. Arterial variations are common in hepatobiliary anatomy, and an aberrant right hepatic artery is encountered frequently during pancreatoduodenectomy.26,27 We specifically paid attention to the intraoperative handling of this anomaly, and its influence on short- and long-term outcomes.

The third part of the thesis takes a deeper look in the consequences of some postoperative events after pancreatoduodenectomy. Chapter 9 describes the clinical presentation, treatment and outcome of leakage of the gastroenteric anastomosis, a rare but life-threatening complication after pancreatoduodenectomy.28 In chapter 10 we investigated the correlation between hyperglycemia in the intraoperative and early postoperative period and the occurrence of complications after pancreatoduodenectomy; this correlation had been demonstrated in various types of surgery, but had never been investigated for this particular operation.29,31
REFERENCES


