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

This thesis studied factors that determine the outcome of pancreatic surgery, thereby addressing the diagnostic work-up, surgical treatment and postoperative care of patients with pancreatic cancer. The core of the thesis focused on the most prevalent complication after pancreatectoduodenectomy, delayed gastric emptying.

In the first part of the thesis, preoperative determinants of outcome were investigated. In Chapter 2 the place of the staging laparoscopy in the diagnostic work-up of pancreatic cancer patients was evaluated. We aimed to identify potentially resectable patients with a high risk of intraoperatively encountered distant metastasis, in whom staging laparoscopy could preclude a nontherapeutic laparotomy. By performing regression analysis on a consecutive series of patients with and without distant metastasis encountered during explorative laparotomy, we identified the following key predictors for distant metastasis: tumor size on computed tomography (odds ratio [OR] 1.43, 95% confidence interval [CI] 1.16-1.76 per millimetre increase), weight loss (OR 1.28, 95% CI 1.01-1.63 per doubling of the kilograms lost), and history of jaundice (OR 2.36, 95% CI 0.79-7.06). In patients with a tumor larger than three centimeters who had lost more than 10 kilograms, and in patients with a tumor larger than four centimeters who had lost more than 5 kilograms, the proportion of patients with distant metastasis was more than 40%. In these patient groups a staging laparoscopy might be beneficial.

In Chapter 3, we investigated the effect of the therapeutic delay associated with preoperative biliary drainage (PBD) on survival. In this follow-up study of a multi-center trial comparing PBD with early surgery, only patients with malignancies were included. Multivariable Cox regression analyses were performed to evaluate the prognostic role of time to surgery for overall survival. Median times from randomization to surgery were 1.2 (interquartile range [IQR] 0.9-1.5) in the early surgery group and 5.1 (IQR 4.8-5.5) weeks in the PBD group. Median survival from time of randomization was 12.2 (IQR 9.1-15.4) months in the early surgery group versus 12.7 (IQR 8.9-16.6) months in the PBD group (P = 0.91). We found that the delay in surgery associated with PBD does not impair or benefit survival rate. The original trial’s conclusions remain valid, but this study showed that when early surgery is not feasible, a strategy with PBD can be followed without compromising longterm survival.
In *chapter 4* we correlated preoperative symptoms of gastric outlet obstruction to delayed gastric emptying (DGE) after pancreatoduodenectomy, in order to identify high-risk patients who could profit from intraoperative placement of a feeding tube. In a consecutive series of 401 pancreatoduodenectomies, 133 patients (33%) had clinically relevant DGE, and 119 patients (30%) required insertion of a feeding tube postoperatively. Patients with two or more of the following symptoms of gastric outlet obstruction: nausea, vomiting, loss of appetite, postprandial complaints, and dysphagia, developed DGE significantly more often, and had significantly more feeding tubes inserted. In multivariable logistic regression analysis, the presence of two or more of these symptoms was a significant predictor of DGE (OR 3.1, 95% CI 1.7-5.8) and the need for insertion of a feeding tube (OR 3.1, 95% CI 1.7-5.7). In these patients, intraoperative placement of a feeding tube should be considered.

In the second part of the thesis, the influence of several intraoperative findings and decisions on surgical outcome was investigated. In *chapter 5*, the association between route of gastroenteric anastomosis (retrocolic or antecolic) and the incidence of DGE after pancreatoduodenectomy was investigated in a consecutive series from the Academic Medical Center. We included 154 patients, of whom 50% had a retrocolic reconstruction, and 50% an antecolic reconstruction. The antecolic reconstruction was mostly performed in the most recent years of the study period. DGE of any grade occurred in 58% in the retrocolic group, versus 52% in the antecolic group (not statistically significant). ‘Primary’ DGE (without other intra-abdominal complications) occurred in 36% of patients in the retrocolic group, compared to 20% in the antecolic group. However, in multivariable logistic regression analysis, the route of gastroenteric reconstruction was not associated with primary DGE. There were no differences in any of the secondary outcomes, such as other complications and length of hospital stay. We concluded that a well-powered randomized controlled trial was required to truly clarify the question whether an antecolic route leads to a lower DGE incidence.

This multi-center, randomized controlled trial was subsequently carried out, and its results are presented in *chapter 6*. In ten middle- to high-volume centers in the Netherlands, patients undergoing pancreatoduodenectomy were randomized between a retrocolic and antecolic gastroenteric anastomosis. 246 Patients were included, of whom 125 were allocated to the retrocolic group, and 121 to the antecolic group. There was no significant difference in the primary outcome parameter: clinically relevant DGE occurred in 45 patients (36%) in the retrocolic group, versus 41 (34%)
in the antecolic group (absolute risk difference: 2.1%, 95% CI -9.8% to 14%). There were no significant differences in need for postoperative (par)enteral nutritional support, other complications, hospital mortality, and median length of hospital stay. Therefore, we believe that the gastroenteric anastomosis in pancreatoduodenectomy should be routed according to the surgeon’s preference.

In chapter 7, we investigated gastric emptying rate at scintigraphy and quality of life in patients who participated in the trial in the Academic Medical Center. 73 Patients were included, 38 in the retrocolic group, and 35 in the antecolic group. Just like in the original trial, there was no difference in DGE or any other clinical outcome. Gastric emptying speed at scintigraphy was not significantly different between the two groups. The results of the gastric emptying scintigraphy correlated with clinical grade of DGE: of nineteen patients with no delayed emptying at scintigraphy, only three developed clinically relevant DGE. Quality of life did not differ between the retrocolic and antecolic group. There was a general decline in quality of life two weeks postoperatively, which had returned to preoperative levels 12 weeks after surgery. Two weeks postoperatively, patients with DGE had significantly worse quality of life than patients without DGE; this is the first time that the burden on quality of life of DGE has been demonstrated.

In chapter 8, we described the incidence and consequences of a vascular anomaly that is commonly encountered during pancreatoduodenectomy: an aberrant right hepatic artery (aRHA). In a consecutive series of 790 pancreatoduodenectomies, aRHA was encountered in 143 patients (19%). In 130 patients (91%), the aRHA was preserved without damage. In the remaining 13 patients, two had postoperative complications that may have been related to sacrifice of the aRHA, namely hemorrhage and an intra-abdominal abscess in the right upper quadrant. Overall, postoperative morbidity was not higher in patients with an aRHA. Long term survival in aRHA patients with a malignant diagnosis at pathology was not compromised.

The third part of the thesis described the consequences of some postoperative factors after pancreatoduodenectomy. In Chapter 9, we described the clinical presentation, treatment and outcome of leakage of the gastroenteric anastomosis. In a consecutive series of 1036 pancreatoduodenectomies, this complication was encountered in 12 (1.2%) patients. The low number of events precluded a reliable multivariable regression analysis for risk factors, but the complication seemed to be associated with postoperative pancreatic fistula and longer operation time. Median postoperative day of diagnosis was 8 (range 2 – 23). Clinical presentation was mostly
with tender abdomen and high drain output suspicious of gastric content. Seven patients (58%) were treated surgically, four (33%) by percutaneous drainage, and one patient underwent no specific treatment due to his poor clinical condition and died in-hospital, resulting in a hospital mortality of 8%.

In chapter 10, the correlation between perioperative hyperglycemia and glucose variability and complications was investigated in a series of 330 pancreatoduodenectomies. Average glucose values were 7.5 (preoperative), 7.4 (intraoperative), and 7.9 mmol/L (early postoperative). There was no association between pre- and intraoperative glucose levels and complications. Early postoperative hyperglycemia (≥ 7.8 mmol/L), however, was significantly associated with complications (OR 2.9, 95% CI 1.7-4.9). High glucose variability alone was not associated with complications, but in the early postoperative period, a high glucose variability seemed to enhance the risk of hyperglycemia: patients with both high glucose values and high glucose variability in the early postoperative period, had an OR for complications of 3.6 (95% CI 1.9-6.8) compared to patients without hyperglycemia.

FUTURE PERSPECTIVES

The results in this thesis contribute to the everlasting process of improving, refining and renovating surgical care for patients with pancreatic cancer – a process that begun more than a century ago with reports from experts in the field, and is continued until today with large clinical trials. This thesis contains results from randomized controlled trials and from studies performed in the prospectively maintained pancreatic surgery database of the Academic Medical Center, a high-volume, tertiary referral center for patients with hepatopancreatobiliary disorders. The studies in this thesis provide answers on longstanding discussion points, but they also bring along new questions. This section contemplates on the future directions of surgery for pancreatic cancer.

The core of the thesis focused on the most prevalent complication after pancreatoduodenectomy: delayed gastric emptying. The most important matter of debate that has been resolved, is the role of the route of the gastroenteric anastomosis – we have clearly shown that this factor does not influence the incidence of DGE, or any other complication. Further studies on the etiology of DGE are needed. The importance of a better understanding of DGE was recently emphasized by two
randomized controlled trials on the pancreaticoenteric anastomosis, randomizing between pancreaticogastrostomy and pancreaticojejunostomy. In both trials there was a significantly lower rate of pancreatic fistula after pancreaticogastrostomy. Pancreatoduodenectomy may therefore shift towards standard use of pancreaticogastrostomy; however, in one of the trials, this was accompanied by almost a doubling of primary DGE. In the Academic Medical Center, we have set up a cohort study that investigates whether local inflammation in the area of the stomach and gastroenteric anastomosis contributes to DGE, in DGE patients without clinical signs of infection. Positron emission tomography and computed tomography (PET/CT) with $[^{18}\text{F}]$-fluorodeoxyglucose labelled white blood cells is used to detect focal sites of inflammation. Follow-up studies aiming at external validation are needed to evaluate the significance of preoperative symptoms of gastric outlet obstruction. Further studies on surgical techniques to prevent DGE should be performed in the setting of randomized controlled trials. In this field, we await the results of the PROPP-study, randomizing patients between pylorus resection and preservation. The development of the consensus definition of DGE by the International Study Group of Pancreatic Surgery has been a big step forward for uniformity in the reporting of DGE. However, the definition is strict, in the sense that any nasogastric intubation beyond the third postoperative day should be regarded as DGE, and does not take into account underlying complications that may cause DGE. When reporting DGE, we would advocate to include a distinct account of clinically relevant DGE (grade B or C), and ‘primary’ DGE (occurring in the absence of other intra-abdominal complications).

With regard to the preoperative diagnostic work-up, staging laparoscopy may be applied in patients with high risk of distant metastasis to preclude nontherapeutic laparotomies. In the light of the increasing application of neoadjuvant therapies, staging laparoscopy may also be of help in identifying patients who may benefit from neoadjuvant treatment, together with other promising new adjuncts that help outline personalized treatment schemes, such as the assessment of tumor biology by use of biomarkers like CA19-9 (higher levels are associated with worse prognosis), or SMAD4 gene status (loss of SMAD4 expression is associated with worse survival). Selected patients with suspected aggressive resectable tumors may be offered neoadjuvant therapy to control micrometastatic disease. Another question that remains, is what would be the best palliation for patients with metastatic disease encountered during staging laparoscopy. A previous randomized study showed better survival in patients with surgical palliation than in endoscopically palliated patients.
Taking into account the progress in recent years in endoscopy and laparoscopy, a new, well-powered randomized trial randomizing between endoscopic and (laparoscopic) surgical palliation should answer this question.

We have shown that the therapeutic delay associated with preoperative biliary drainage in patients with a pancreatic head tumor does not compromise survival. Others even suggest a survival benefit of relieving jaundice. This means that in patients who are unfit for early surgery, due to cholangitis, logistical reasons, or because neoadjuvant therapy is scheduled, PBD can safely serve as a bridge to surgery without affecting survival. This underscores the necessity of lowering the complication rate of PBD. Retrospective studies have already shown that metal stents yield better results than plastic stents in patients awaiting operation for a pancreatic head tumor. We are now prospectively evaluating the performance of metal stents in patients with pancreatic head tumors who are candidates for surgery in the STENT trial (Netherlands Trial Register registration number NTR3142).

With the evolving of surgical techniques, tumor ingrowth at the confluence of the portal and superior mesenteric veins is no longer considered a contra-indication for resection. If necessary, venous resection in order to obtain negative margins should be undertaken whenever possible. In the intraoperative assessment of resectability, this has led to a shift in emphasis from vein to artery: the ‘artery first’ approach. This implies that after the exclusion of distant metastasis, local exploration is directed towards assessment of superior mesenteric artery involvement. A recent review showed that at least six different approaches to the superior mesenteric artery have been described, each with their own advantages. Given the high prevalence of hepatic arterial variations that we found, and the importance of preoperative planning, we suggest that radiologists should include hepatic arterial anatomy in their standard preoperative imaging reports.

In the final chapter, emphasis shifted to a whole new culprit in the field of postoperative morbidity after pancreateoduodenectomy: hyperglycemia. The underlying mechanisms of the findings in this chapter must be further clarified; practically, the next question that comes to mind, is whether correction of hyperglycemia in the early postoperative period leads to lower morbidity. This should be investigated in a randomized controlled trial on strict versus conventional glucose control. We have made a first step by designing a feasibility study, investigating whether a strategy of strict glucose control is effective in lowering early postoperative glucose levels after pancreateoduodenectomy.
Chapter 11

In conclusion, this thesis offers implications for clinical practice and starting points for further research in the field of pancreatic surgery. New studies on surgical techniques should preferably be performed in the setting of multi-center, randomized controlled trials. Close collaboration between hospitals is an important premise for success; in the Netherlands, we are blessed with a longstanding tradition in multi-center trials, of which chapters 3 and 6 of this thesis are perfect examples. Further organization of the pancreatic field into collaborations like the recently established Dutch Pancreatic Cancer Group, will help creating the right conditions for new high-quality trials.
REFERENCES


