Resection and palliation of pancreatic and periampullary carcinoma
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SUMMARY AND CONCLUSIONS
Chapter 13

Summary
In this thesis different aspects of intentional curative treatment of patients with pancreatic or periampullary carcinoma are described, such as the influence of hospital volume, surgeon volume, a multidisciplinary setting, and portal or mesenteric vein resection on morbidity and mortality after pancreaticoduodenectomy. Secondly, long-term outcome after pancreaticoduodenectomy in terms of survival and other aspects such as gastrointestinal pH and hormone secretion, and re-admissions are discussed. Finally, issues in palliation such as pain management, and treatment of cancer cachexia are discussed.

In chapter 2, factors influencing mortality after pancreaticoduodenectomy are analysed in a series of 300 consecutive patients from a single institution. The mortality rate was approximately 1% and complications occurred in 41% of the patients. The percentage of complications decreased during the study period while the number of resections increased from 17 to more than 50 per year. Significant independent factors predicting complications were serum creatinine level, blood transfusion, and the time period (year) of resection. In the second part, the influence of hospital volume on hospital mortality after pancreatic resection in the Netherlands is analysed using data from a national healthcare database. The mortality rate was around 10% and did not change during the study period (1994-1998). The mortality rate in a high volume centre (≥25 resections/year) is significantly lower than in low volume centres (<5 resections/year), 14.6 versus 0% respectively in 1998. From this study it can be concluded that the overall death rate after pancreaticoduodenectomy did not decrease significantly during the period, and it was greater in low-volume hospitals and older patients. The lower death and complication rates in high-volume hospitals, including the single-centre outcomes, were similar to those reported in other countries and may be due to better prevention and management of complications. Pancreaticoduodenectomy should be performed in centres with sufficient experience and resources for support.

In chapter 3 the importance of a multidisciplinary approach in the management of complications after pancreatic resection is illustrated in a case report. An overview of the available literature on hospital volume and hospital mortality is presented. Some studies show an advantage of high volume hospitals over low volume hospitals, whereas others do not. Furthermore different definitions of high volume centres complicate this overview.

Therefore a meta-analysis on the relation between hospital volume and hospital mortality after pancreatic resection was performed as presented in chapter 4. Different volume categories with cut-off values of approximately 2, 5, 10, and 20 resections per year were used for analysis. In all volume categories the mortality in high volume centres was significantly less than in low volume centres (p<0.001). However, most studies used national or regional health care databases that carry limited data. Therefore case mix can not always be identified. This study indicates that centralisation of pancreatic resection can avoid unnecessary deaths and that the definition of high volume criteria can be a practical one, dictated by infrastructure and capacity.
Chapter 5 describes the results after portal or superior mesenteric vein (PV/SMV) resection during pancreaticoduodenectomy for suspected tumour involvement in 34 patients out of a consecutive series of 215 patients that underwent pancreaticoduodenectomy. Tumour free resection margins could be obtained in 41% of the patients and the portal or superior mesenteric vein margin was the only positive margin in only 15%. Morbidity and mortality after this procedure were 41% and 0% respectively and the median survival was 14 months. Although this resection is technically possible without increased morbidity or mortality it does not increase the percentage of resections with tumour free margins or survival.

The functional outcome after pylorus preserving pancreaticoduodenectomy with respect to gastrointestinal pH profiles is analysed in detail in chapter 6. Since a low gastrointestinal pH can negatively influence enzyme function and food digestion this may contribute to malabsorption after pylorus preserving pancreaticoduodenectomy. We assumed that gastrointestinal pH would be negatively affected after this resection because of loss of feedback inhibition on acid secretion. The median 24 hour and intragastric pH after pylorus preserving pancreaticoduodenectomy were not different from healthy controls, with values of 1.7 versus 1.7, respectively. The postprandial intragastric pH was not significantly different either. The median 24 hour intrajejunal pH after pylorus preserving pancreaticoduodenectomy was not lower but even higher than the intraduodenal pH in healthy controls, 6.3 versus 6.0 respectively, mainly as a result of the increased intestinal pH in the nocturnal period. Therefore, changes in gastrointestinal pH after resection do not negatively influence food digestion.

In chapter 7, the effect of pancreaticoduodenectomy and duodenum preserving resection of the head of the pancreas on gastrointestinal pH was compared with non-operated chronic pancreatitis patients. There were no significant differences in median 24 hour or postprandial gastrointestinal pH or circadian rhythms between these patients. In the circadian period from 10.00-18.00 hours, intragastric pH in the PPPD group was significantly higher than in the chronic pancreatitis patients, 1.8 versus 1.6, respectively (p=0.05). In the nocturnal period intestinal pH in the pylorus preserving pancreaticoduodenectomy group was significantly higher than in the group that underwent a duodenum preserving resection of the head of the pancreas, 6.2 versus 5.8 (p=0.05). Resection does not further change gastrointestinal pH patterns that are already disturbed due to chronic pancreatitis.

Proximal and distal postprandial gut hormones secretion after pylorus preserving pancreaticoduodenectomy, duodenum preserving resection of the head of the pancreas, was compared with non-operated patients with chronic pancreatitis, and healthy controls in chapter 8. The peak increment of plasma cholecystokinin secretion and the integrated plasma cholecystokinin secretion in patients after pylorus preserving pancreaticoduodenectomy (0.6 ± 0.1 pmol/l and 25 ± 6 pmol/l ·120 min, resp.) were significantly lower than in patients after duodenum preserving resection of the head of the pancreas (1.7 ± 0.3 pmol/l; p<0.01 and 86 ± 32 pmol/l ·120 min; p<0.05, resp.), and non-operated chronic pancreatitis patients (1.5 ± 0.2
pmol/l; p<0.01 and $84 \pm 17$ pmol/l \cdot 120 min; p<0.01). The peak increment and integrated plasma peptide YY secretion in patients after pylorus preserving pancreaticoduodenectomy was not significantly different from the peak increment of peptide YY secretion in patients after duodenum preserving resection of the head of the pancreas or non-operated chronic pancreatitis patients. Basal peptide YY levels were however significantly higher in pylorus preserving pancreaticoduodenectomy patients. In non-operated chronic pancreatitis patients proximal hormone secretion is decreased and distal hormone secretion is increased compared to healthy controls. After duodenum preserving resection of the head of the pancreas there are no significant changes in proximal or distal hormone secretion compared to CP patients, whereas after pylorus preserving pancreaticoduodenectomy proximal hormone secretion is decreased and distal hormone production is increased. Because the degree of exocrine insufficiency was comparable between the different groups, it is suggested that resection of the duodenum is a major factor contributing to changes in hormone secretion.

Long-term outcome after pancreaticoduodenectomy in terms of re-admissions after pancreaticoduodenectomy are analysed in chapter 9. Out of 283 patients, 106 patients (38%) were re-admitted. 64 Patients (60%) were re-admitted with tumour recurrence for indications such as gastrointestinal obstruction, biliary obstruction and pain, of which half were in a pre-terminal condition. Median survival after surgical treatment was 58 days, and ascites was significantly associated with poor survival. Forty-seven (44%) of the patients were re-admitted for surgical complications such as abscess, fistula, gastrointestinal obstruction. Median hospital free survival after re-admission for surgical complications was 1035 days. Re-admission after pancreaticoduodenectomy is frequent. Survival after surgical bypass procedure for tumour recurrence was limited, in particular when ascites was present. Patients re-admitted for complications of surgery have a good prognosis.

In chapter 10 the most important determinant of long-term outcome namely survival was analysed in a consecutive series of 204 patients. The median survival after pancreaticoduodenectomy for pancreatic carcinoma (n=108), distal bile duct carcinoma (n=32) and ampullary carcinoma (n=64) is 16, 25, and 24 months, respectively. Tumour location, type of resection (standard or portal or superior mesenteric vein resection), blood transfusion, resection margins, lymph node status, and tumour differentiation influenced survival. In a multivariate analysis, tumour positive resection margins (HR 1.6), tumour positive lymph nodes (HR 2.1) and low tumour differentiation (Low-high: HR 3.8; intermediate versus high: HR 2.1) were independent predictors of poor survival. Despite improved perioperative management, survival after resection for pancreatic and periampullary carcinoma is still limited and resection margins, lymph node status, and tumour differentiation are the most important determinants for survival.

In chapter 11 pain treatment by means of pain medication, coeliac plexus blockade and radiotherapy were analysed in patients that underwent bypass surgery for pancreatic cancer. The postoperative consumption of pain medication in the three group increased during follow-up from 15, 17 and 13% before surgery to 52, 57 and 46% respectively at three-quarter of the
survival time (NS). In the radiotherapy group the median pain medication free survival was significantly longer than in the other groups (9.3 vs 3.1 and 3.3 months, \( p=0.02 \)). Radiotherapy resulted in an increased pain medication free survival (9.3 vs 3.3 months, \( p=0.02 \)), hospital free survival (10.3 vs 6.8 months, \( p=0.01 \)) and overall survival (10.8 vs 7.1 months, \( p=0.01 \)) compared to the celiac plexus blockade. A positive effect of a celiac plexus blockade on pain could not be confirmed in the present study. These effects are probably partly related to patient selection because there significantly more patients with preoperative pain in the coeliac plexus blockade group compared to controls and in the radiotherapy group no patients with metastases were included because this was an contraindication for this treatment.

In chapter 12 the effect of N-3 fatty acids, especially eicosapentaenoic acid, enriched oral supplement on cachexia in patients with pancreatic cancer is described. The AMC participated in an international multicentre study co-ordinated by professor K. Fearon. Two hundred patients were randomised for an oral supplement with or without N-3 fatty acids. The intention to treat analysis showed no significant differences. In the experimental group significant correlations between their total intake of protein and both weight gain \( (r=0.52, \ p<0.001) \) and increase in LBM \( (r=0.46, \ p=0.004) \) were found. Such correlations were not observed in control patients. Increased plasma eicosapentaenoic acid levels in the experimental group were associated with weight and LBM gain \( (r=0.50, \ p<0.001; \ r=0.51, \ p=0.001) \), maximal effect was at 1.5-2 cans/day. Weight gain was associated with improved quality of life. The use of a protein and energy dense oral supplement can attenuate weight loss in cancer cachexia. When enriched with n-3 fatty acids and antioxidants and taken in sufficient quantity, net gain of weight and lean tissue can be achieved.

Conclusions
Hospital mortality correlates with hospital volume (number of resections per year) after pancreatic resection, therefore this type of surgery should be performed in centres with experience and in a multidisciplinary setting. Portal or mesenteric vein resection during pancreaticoduodenectomy does not improve survival. Pancreaticoduodenectomy does not effect gastrointestinal pH profiles in a way that it could interfere with food digestion. After pylorus preserving pancreaticoduodenectomy proximal hormone secretion is decreased and distal hormone production is increased. Re-admission rate after pancreaticoduodenectomy is relatively high (39%). Most patients are re-admitted for sequelae of recurrent disease (60%) and often in a preterminal stage. Seventeen percent of the patients is re-admitted for complications of the initial surgical procedure. Survival after pancreaticoduodenectomy for pancreatic and periampullary carcinoma did not improve during the past years and is still limited. The positive effect of coeliac plexus blockade on pain as previously described was not confirmed. Radiotherapy increased pain medication free survival although patient selection might be partly responsible. The use of a protein and energy dense oral supplement can attenuate weight loss in cancer cachexia. When enriched with n-3 fatty acids and antioxidants and taken in sufficient quantity, net gain of weight and lean tissue can be achieved.