Resection and palliation of pancreatic and periampullary carcinoma
van Geenen, R.C.I.

Citation for published version (APA):
van Geenen, R. C. I. (2001). Resection and palliation of pancreatic and periampullary carcinoma

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CHAPTER 1

Introduction and Outline of the Thesis
Outline of the Thesis
Periampullary carcinoma, including pancreatic, bile duct, and ampullary carcinoma, have a grim prognosis with a 5-year survival between 1 and 25% for pancreatic and 6-50% for ampullary carcinoma. Different treatments are available for patients with these malignancies varying from resection with curative intent such as the pancreaticoduodenectomy (PD) to palliation of symptoms by means of bypass surgery for biliary and gastrointestinal obstruction, endoprostheses for biliary obstruction, pain management, and supportive therapies, as for example nutritional support.

The treatment of first choice is the PD, which offers the only chance for cure. There are three types of resection according to the extent of the resection: the standard, the extended, and the regional resection. In Amsterdam, the standard resection is performed routinely. Traditionally, PD has been associated with a high morbidity (50-70%) and mortality (10-20%). During the last decade morbidity and mortality decreased to acceptable levels.

A parallel development was the mounting evidence that hospital volume inversely related to in-hospital mortality. This resulted in a plea for centralisation. However, the scientific validity of studies on this subject is questioned and further evidence is necessary to convince surgeons of these findings. Still other factors might also influence in-hospital mortality of the PD. For instance, individual perioperative parameters and the experience of the individual surgeon have been described to effect in-hospital mortality. Furthermore the expertise of the different disciplines, such as radiology gastroenterology, intensive care, and surgery, might effect the treatment and outcome of these patients. These aspects need further evaluation.

Different technical modifications of the resection have been described to improve resectability often with increased morbidity and mortality. Resection is often precluded by tumour ingrowth in to surrounding tissue such as the retroperitoneum, or the portal and superior mesenteric vein (PV/SMV). In case of PV/SMV involvement (a part of) the PV/SMV can be resected. There is still discussion about the indication and the technique as well as the effect on outcome of this procedure in terms of morbidity, mortality and survival.

Different aspects influence the final outcome of treatment. Apart from the perioperative results, long-term results such as functional outcome, long-term morbidity, extent of the resection, and survival also determine the final outcome of treatment. PD may affect the complex mechanisms that regulate nutrient digestion such as gastrointestinal motility, release of pancreatic enzymes and gastrointestinal hormones, and intraluminal pH. This may negatively affect nutrient digestion and absorption and thereby long-term outcome. There are limited data available on the gastrointestinal pH and hormone secretion after PD.

Re-admissions are an objective tool to measure severity of long-term morbidity. Re-admissions may be caused by sequelae of tumour recurrence and late complications of the initial surgical procedure that require re-admission after PD. Data on re-admissions and the indications for re-admission after PD are limited but are needed to evaluate the long-term morbidity of the procedure.

Survival is the most important determinant of long-term outcome. Five-year survival after PD was poor varying from 1-25% for pancreatic carcinoma, and 6-50% for periampullary.
carcinoma\textsuperscript{10,11}. Decreased operative mortality resulted in a more optimistic view towards resection, and improved survival after PD has been reported. Patient selection as a result of a better diagnostic approach could have improved survival after PD. Therefore new data on survival and risk factors for poor survival are needed to evaluate the long-term outcome of PD.

At the time of diagnosis most patients (80\%) are no candidates for resection\textsuperscript{12}. At this stage palliation of symptoms such as jaundice or gastric outlet obstruction can be performed by bypass surgery. A hepaticoenterostomy relieves jaundice, and duodenum obstruction can be treated with a gastroenterostomy. Pain is another major symptom and is mostly treated with pain medication. However other therapeutic options are available. During bypass surgery a chemical splanchnectomy can be performed with injection of alcohol\textsuperscript{13}, or a thoracoscopic splanchnectomy can be performed. Also radiotherapy can offer pain relief\textsuperscript{14}. It is still unclear what the effects and side effects of these treatment modalities are.

The complex syndrome of cancer cachexia continues to be a major contributor to the morbidity and mortality of patients with advanced malignancy\textsuperscript{15,16}. Different types of nutritional support or hormone treatment have been used in an attempt to reverse this cachectic state and increase the lean body mass. Previous nutritional support or hormone treatment resulted only in an increase of weight due to an increase in fat rather than lean body mass. A pilot study showed that administration of eicosapentaenoic acid (EPA), an omega-3 fatty acid derived from fish oil, resulted in weight stabilisation\textsuperscript{17,18}. However, level one evidence is not available.

The limited prognosis forces physicians to carefully consider the risk of postoperative complications, mortality, long-term complications and survival of each treatment strategy in the different stages of the disease, and to carefully select patients and also the setting in which the different types of treatment are performed. The first part of the thesis covers issues concerning the resection of periamplillary and pancreatic carcinoma by means of PD. The second part of the thesis deals with aspects of long-term outcome after surgical resection, and the third part deals with the issues in palliation of symptoms such as pain and cachexia.

Part one
In chapter 2 the morbidity, mortality, and risk factors for complications after PD are discussed in a single centre study performed in the Netherlands. Also the inverse relationship between hospital volume and in-hospital mortality after PD in the Netherlands and its effect on centralisation are described in this chapter. In Chapter 3 the impact of hospital and surgeon volume on in-hospital mortality is described and the importance of a multidisciplinary approach in the management of complications after PD is clarified in a case history. In chapter 4 a meta-analysis of the available literature on hospital volume and mortality in pancreatic surgery is presented. In chapter 5 the indication, technique and the additional value of the PV/SMV resection in the presence of tumour invasion of this structure and its effect on morbidity and mortality is described.
Part two
Functional outcome in terms of intragastric and intraduodenal pH after pylorus preserving PD in comparison with healthy control subjects is described in chapter 6. In a non-malignant setting, functional outcome in patients after pylorus preserving PD or duodenum preserving resection of the head of the pancreas is analysed in comparison with non-operative chronic pancreatitis patients in chapter 7. Changes in proximal and distal gut hormone secretion in patients after pancreatic surgery are compared with non-operated patients with comparable exocrine pancreatic insufficiency and with healthy controls in chapter 8. Re-admissions after PD are an objective parameter to measure long-term outcome. Re-admission-rate and indications for re-admissions are discussed in chapter 9. Current survival after PD is discussed in chapter 10, this chapter also deals with the risk factors for poor survival after PD.

Part three
Pain management is an important part in the palliative treatment of patients with periampullary and pancreatic carcinoma. The effect of pain medication, intraoperative chemical splanchnectomy, and radiotherapy is discussed in chapter 11. The developments in the treatment of cachexia were stimulated by the positive effect of EPA. Chapter 12 describes the effect of a supplement of a high caloric supplement combined with EPA on weight loss and quality of life in pancreatic cancer cachexia.

References

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