DECISION MAKING IN THE TREATMENT OF PANCREATIC CANCER

a retrospective analysis

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a retrospective analysis

BESLUITVORMING BIJ DE BEHANDELING VAN HET PANCREASCARCINOOM

een retrospectieve analyse

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As disappointing as the results may be, we are unwilling to accept an uniform nonresection philosophy. An occasional patient with cancer of the pancreas is cured, the duration and quality of palliation are improved, and the chance of resecting a more favorable type of periampullary malignancy is not overlooked. The future of surgery for carcinoma of the pancreas hangs in the balance. Methods must be found to reduce the risk of pancreatic resection and improve the survival rate of patients who undergo surgery for pancreatic cancer if the procedure is to be more widely used in the future. (W.P. Longmire Jr., 1984)

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CHAPTER 1

GENERAL INTRODUCTION

1.1 PREFACE

Pancreatic cancer is a major and often frustrating disease in clinical gastroenterology. Diagnosis and treatment are very difficult; 90% of all patients diagnosed with pancreatic cancer die within one year after diagnosis has been made. The incidence of pancreatic cancer has increased steadily in the past 60 years, becoming the fourth leading cause of death in Western Europe and the USA. The aetiology of pancreatic cancer remains unclear. Some studies have found some influence of cigarette smoking; others find coffee consumption as an aetiological factor. Diet, diabetes mellitus, chronic pancreatitis, industrial exposure and alcohol consumption are mentioned as aetiological factors, but no consensus has been reached so far. It is possible that different methods of obtaining data and its subsequent analysis are the main reasons that a definitive aetiological factor has not been found. Further investigations in experimental models and a better understanding of oncogenes might result in improved knowledge of the aetiology of pancreatic cancer.[1-4]

When cancer of the pancreas or periampullary region have been diagnosed, surgical excision continues to be the only possibility for cure. However, the overall resectability rate is low, and long-term survival after intentional curative resection is 0-15% in cases of cancer of the head of the pancreas and up to 50% in cases of periampullary cancer.[5-8,14,19] Although several types of adjuvant treatments have been proposed, none of these have proven to be effective.[9-13] One of the major problems, however, remains to select those patients who will benefit from radical surgery, and as a consequence, how to palliate patients with irresectable cancer, aiming for maximal quality of life and low morbidity.

1.2 PALLIATIVE PROCEDURES

At the time when cancer of the head of the pancreas or periampullary region is confirmed by diagnostic modalities, only 5-25% of the patients with cancer of the head of the pancreas and about 90% of patients with periampullary cancer (duodenum, papilla of Vater, distal common bile duct) appear to have resectable tumors.[14-20] One of the major problems in the patient with an irresectable tumor is jaundice caused by obstruction of the common bile duct. The palliation of symptoms caused by biliary obstruction is the main goal for the treatment of this group of patients. Biliary drainage can be performed percutaneously, endoscopically and

surgically, each procedure with its pros and cons. Since the early 1980s, both percutaneous and endoscopic stenting of the common bile duct have become established procedures. Because of the limited life expectancy it is attractive to perform a non-surgical drainage procedure. However, the morbidity and mortality due to the procedure and readmissions in the hospital should be taken into account. A major study of Siegel et al. showed promising results of endoscopically placed endoprosthesis in a group of 277 patients with no mortality, acceptable morbidity and a success rate of 89%. The main problem of endoprostheses, clogging, occurred in one-third of the patients at three months; however, the mean survival time was only 129 days. Known early complications such as transient fever, cholangitis, bleeding and migration of the stent occurred in 21% of the patients; comparable results were found by others.[21-24] Late complications such as clogging of the endoprosthesis is a major drawback for stenting, especially in the group of patients with localized irresectable disease because of their expected longer survival than those patients with disseminated disease. Probably, stents have to be used in patients with advanced disease with a life expectancy too short to develop problems such as clogging of the stent.[25] In irresectable disease the question remains whether it is preferable to perform a surgical biliary bypass or an endoprosthesis. Three randomized controlled studies have been performed with no difference in morbidity, mortality and survival between an endoprosthesis or surgical biliary bypass.[26-28] The same result with respect to morbidity, mortality and survival were obtained in retrospective studies, with preference for endoscopically placed endoprosthesis. A cost analysis showed the endoscopically placed endoprosthesis to be the most inexpensive option to perform drainage of the biliary tract.[29-32] The advantage of a surgical bypass is a long-lasting relief of jaundice, but results in a longer initial stay in the hospital. Proper patient selection is important, for example, relatively young patients without metastases and a relatively good performance score will weigh the decision towards surgical bypass. A simple way to perform a bypass is the cholecystojejunostomy, but the results of this procedure are doubtful, with a high incidence of biliary sepsis and obstruction by tumor soon after surgery.[33,34] Better results are obtained after choledochojejunostomy, with equal patency after a simple loop reconstruction or a Roux-Y procedure.[34] If a patient with limited irresectable disease is operated on for biliary bypass, the question arises whether a gastroenterostomy has to be performed during the same procedure. However, the incidence of gastric outlet obstruction at the time of diagnosis is reasonably low ($\pm$ 5%). If duodenal obstruction is evident, only a small number of patients

have localized disease. Moreover, gastrojejunostomy has its own complications. In particular, delayed gastric emptying occurs frequently (± 30%) with longer hospitalization for the patients.[35,36] Percentages of gastric outlet obstruction in the course of the disease after initial surgical biliary bypass range from 10 to 37, in most cases considered a sign of terminal disease, but 9-16% of the patients in relatively good condition required a second operation to perform a gastrojejunostomy.[34,37-49]

If advanced disease is evident and life expectancy low, endoscopic biliary stenting seems the best option. In localized irresectable disease without metastases, discussion still continues on whether or not to perform a surgical bypass or biliary stenting, and if this bypass is performed, whether to combine this procedure with a gastroenterostomy to prevent gastric outlet obstruction or to wait and perform this operation at the moment symptoms of duodenal obstruction occur. In the majority of patients, metastases will be present at that time and the outlet obstruction is merely a terminal event.

1.3 PREOPERATIVE BILIARY DRAINAGE

Severe jaundice, as seen in almost all patients with cancer of the head of the pancreas or periampullary region, seems to jeopardize outcome after surgery with mortality and morbidity rates of 15-25% and 35-60% respectively. Complications such as liver and renal failure, wound haematoma, wound infection, fever and sepsis are common after surgery in jaundiced patients.[50-53] It is debatable whether preoperative relief of jaundice results in lower morbidity and mortality.[54-56] The optimal method of drainage, percutaneously or endoscopically, is also not yet clear. Some prospective studies performed to solve this problem are inconclusive and contradictory; however, the techniques used in these studies were percutaneously transhepatic drainage procedures.[57-62] Ellison concluded that preoperative drainage in the group of patients who subsequently underwent curative resection was better than in patients palliatively operated. Morbidity after resection was 40% as compared with 70% in the group without preoperative drainage; mortality was 28% and 60% respectively.[63] Only one report compared the endoscopical and percutaneous route of drainage of bile. Relief of jaundice was established in 81% of the patients treated by endoscopy and only in 61% when the transcutaneous route was used. Results concerning mortality and morbidity showed a marked advantage for drainage of bile by endoscopy.[64] Recalling the progress made in endoscopy with large bore

bile duct endoprostheses and the combined transhepatic/endoscopic approach, it is to be expected that morbidity and mortality of the procedure can be minimized, and consequently the advantage of preoperative drainage of bile can be optimally utilized.[65,66]

1.4 CURATIVE SURGICAL PROCEDURES

1.4.1 SURGICAL PROCEDURES : HISTORY

The first resection of a periampullary tumor has been described in 1899 by Halsted. He performed a local transduodenal excision with reimplantation of the common bile duct and pancreatic duct into the suture line of the duodenum.[67] En bloc partial pancreatoduodenectomy followed in 1912 by Kausch. The resection was a two stage procedure; first, a cholecystoenterostomy and ligation of the common bile duct; and second, a resection with pancreatoduodenal anastomosis.[68] Until 1935 the transduodenal resection was the most performed treatment, but after the initial report of Whipple, who described a two stage pancreatoduodenectomy, the interest in radical resections of periampullary cancers was revived. The original procedure of Whipple consisted of a cholecystogastrostomy and a gastrojejunostomy to relief jaundice and gastric outlet obstruction respectively. After a few weeks the distal part of the duodenum and the head of the pancreas were resected, the duodenum was closed and the pancreas was left alone without enteric anastomosis.[69] In 1941 the first one-step procedure was described by Trimble, who added a partial gastrectomy to the procedure.[70] The first attempt to perform a postpyloric resection of the duodenum with a jejunal loop reconstruction was described by Watson in 1944.[71] During the same period Whipple modified his first operative procedure into an one-stage resection with pancreatojejunostomy.[72] The operative technique and improved pre- and postoperative care resulted in a better outcome. The latest modification, widely used at the present time, was the reintroduction of the pylorus preserving pancreatoduodenectomy by Traverso and Longmire in 1978 leaving the pylorus intact and performing a pancreato-, a choledocho- and a duodenojejunostomy with one simple jejunal loop.[73]

1.4.2 SURGICAL PROCEDURES : RESECTABILITY, MORBIDITY, MORTALITY AND SURVIVAL

As described above, the only possible cure for cancer of the head of the pancreas and periampullary region lies in the radical resection of the tumor. Different types of resectional strategies are described, with all the pros and cons. Resectability criteria differ from center to center depending upon surgical experience and skill, but all agree that a resection is not indicated in case of distant metastases. Extended resections as proposed and executed by Fortner and others have not met with great success and have more or less been abandoned.[74-77] The amount of vascular invasion in the superior mesenteric artery and/or portal vein preoperatively diagnosed by angiography was, in the study of Ishiwaka, the most important reason to decide on whether or not to perform an extended resection. Nevertheless, this study was retrospective and only a small number of patients have been treated.[78] Generally, the local situation is best judged by the surgeon, in which tumor size, lymph node involvement and ingrowth in, for example, the portal vein or superior mesenteric artery are the main drawbacks for a resection. Tumor size itself is disputed for being a contraindication for resection.[79-83] Especially pancreatitis surrounding the tumor may be a confusing factor in measuring tumor size. In cases of cancer of the pancreatic head 5-25% will be resectable, and in cases of periampullary cancer 90% will be resectable.[14-20] Whether to perform a partial pancreatoduodenectomy or total pancreatectomy has been disputed. Total pancreatectomy might result in wider lymphadenectomy, eliminates the complicating factor of the pancreatojejunostomy but also causes brittle diabetes mellitus. Multicentricity of the tumor has been mentioned in most reports as the major reason to perform a total resection of the gland, especially to prevent tumor-containing resection margins. During the last few years it has become clear that the standard Whipple's procedure has resulted in less morbidity and mortality compared with the total pancreatectomy.[84-91]

Since 1978, when Traverso and Longmire performed a pylorus preserving pancreatoduodenectomy, the interest in this technique was revived. They reported less dumping, improved gastrointestinal function and reduced jejunal ulceration, with a less time-consuming operation and less bloodloss.[73] Radicality, especially of the duodenal resection margin, was doubted, however. Furthermore, prolonged hospital stay was reported because of delayed gastric emptying after this procedure. Overall, weight gain during follow-up and

a better quality of life are the results of multiple retrospective studies. In conclusion, the pylorus preserving pancreatoduodenectomy did earn its position in the treatment of cancer of the head of the pancreas and periampullary region, although never studied prospectively in comparison with the standard Whipple's procedure.[92-97]

The most important question to be asked when performing either one of the techniques of resection is how to reduce postoperative complications and mortality. The major problem after partial pancreatoduodenectomy is leakage of the pancreatojejunostomy resulting in pancreatic fistula's. As Trede reported in 1988, the complication rate concerning the anastomosis between the pancreatic remnant and the jejunum was 11% of which one-fifth was fatal.[98]

Several kinds of techniques are described for the anastomosis between the remnant of the pancreas and the jejunum, varying from one layer running sutures to two layers with or without using intrapancreatical stents. A very promising technique is the pancreato-gastrostomy. Advantages are the anatomic relation of the stomach to the pancreatic remnant, especially after a pylorus preserving resection and the possibility to control the pancreatic duct endoscopically. The pancreatic secretion is inactive in the stomach and therefore may prevent erosion of the anastomosis. Until now, no prospective comparative trial has been executed to prove the advantages of this technique.[99-104]

As shown in table 1, morbidity differs from 13% to 71%, pancreatic fistula's from 1% to 19% and mortality from 0% to 40%. It is noticed and shown in table 1 that morbidity and especially mortality have significantly decreased during the latest decade. Recently series reported 0% to 5% mortality, probably due to improved experience among surgeons and improved postoperative care.[8,14,19,105-116]

Reviewing the literature, the striking difference in results of survival after resection is apparent. This phenomenon is partially due to different forms of statistical calculations used, especially the complicated use of absolute and actuarial survival as well as the exclusion of postoperative death. The only accurate survival statistics, however, have to be calculated from the total number of patients with pancreatic or periampullary cancer, including those without resection or palliative surgery. As Gudjonsson et al. reported in 1978, only 0.4% 5-year survival was established from a study of approximately 15000 patients.[5] However, most available studies report overall 5-year survival of patients seen by the surgeon and thus do not include patients who did not come to surgery. As a consequence, only those patients are cited in most studies. Five-year survival figures after curative surgery for cancer of the head of the

pancreas range from 0% to 25%; periampullary cancer has a less dismal prognosis with 5-year survivals ranging from 4% to 50%. One report mentioned 5-year survival of 30.3%, but only tumors less than 2 cm in diameter of the head of the pancreas were analyzed (table 2).[8,14,19,106,107,109-111,113-121]

Table 1 : morbidity and mortality after curative surgery

author	year	n	morbidity %	pancreatic fistula %	mortality %
Howard[105]	1968	41	50	10	0
Aston[106]	1973	65	71	18	13.8-5.1[@]
Warren[107]	1975	348	52	8	15-10[#]
Piorkowski[108]	1982	55	56	5	14
Warren[109]	1983	61	NR	NR	13.9-3.4[$]
Lerut[110]	1984	58	19	15	10.6
Kairaluoma[14]	1984	40	33	NR	30-3[&]
Dunn[111]	1987	238	54.5	1	40-5.9[*]
Lygidakis[112]	1989	78	13	1	4
Ceuterick[113]	1989	79	46	11	5
Crist[114]	1989	88	59-36[+]	18	24-2[+]
Michelassi[19]	1989	133	NR	NR	19-5[**]
Kairaluoma[115]	1989	78	42-57[@@]	5	27-3[@@]
Trede[8]	1990	118	18	8	0
Cameron[116]	1993	92	52	19	0[++]

[@] : 1952 > 1962-1962 > 1972 ; [#] : 1942 > 1962-1962 > 1972 ; [$] : 1951 > 1960-1971 > 1980
[&] : < 1977-1977 > 1981 ; [*] : 1960 > 1970-1971 > 1980 ; [+] : 1969 > 1981-> 1982
[**] : < 1981-> 1982 ; [@@] : < 1977-> 1978 ; [++] : out of 145 resections ; NR : not reported
n : only patients with cancer of the head of the pancreas or periampullary region

The reason why periampullary cancer results in better survival is not yet clear. The most reasonable explanation seems to be the early onset of symptoms related to the strategic location of the tumor and therefore early detection and treatment. Others attribute this difference to earlier and more widespread lymph node involvement in pancreatic cancer; however, this also can be due to the later onset of symptoms.[19,106-110,113,118] Despite these depressing results, especially in cancer of the head of the pancreas, an improvement has occurred. It is most likely that this improvement is a direct result of proper patient selection, more experienced surgeons and lower mortality after resection.

It is stated that cancer of the pancreas is a rapidly metastasizing process. After resection a

high incidence of locoregional and distant recurrence has been found. Locoregional recurrence rates of 50-67% and distant metastases up to 100% are reported.[122-125] Until now there have been no reports on the surgical treatment of locoregional recurrence except for our own retrospective study as described in chapter 2.3.

As stated by Trede and Warshaw the attitude towards this disease remains the problem in treating cancer of the head of the pancreas and periampullary region. A fatalistic attitude has to be abandoned and a realistic and optimistic approach should become the keywords when reviewing and considering the increasing results of survival in the last decade.[18,126]

Table 2 : survival after curative surgery

author	year	n	period	5-YR survival head pancreas	5-YR survival periampullary
Aston[106]	1973	65	'52-'72	5.7	30-36.4
Warren[107]	1975	348	'42-'72	12.5	25-41.3
Cohen[117]	1982	96	'40-'80	0	24-38
Warren[109]	1983	61	'51-'80	3.4	NR
Lerut[110]	1984	58	'69-'85	6	50
Kairaluoma[14]	1984	40	'72-'81	0	42
Matsuno[118]	1986	36	'60-'85	8.1	29.6-41
Tsuchiya[119]	1986	91*	'66-'83	30.3	NR
Dunn[111]	1987	238	'60-'82	8	NR
Ceuterick[113]	1989	79	'78-'87	27	44
Crist[114]	1989	88	'69-'86	18	34
Michelassi[19]	1989	133	'46-'87	8.8	20-32
Kairaluoma[115]	1989	78	'68-'87	0	11-40
Trede[8]	1990	91	'85-'89	25	4-21
Geer[120]	1993	146	'83-'90	19	NR
Bakkevold[121]	1993	108	'84-'87	1	20**

*: only tumor size < 2 cm. ; **: only carcinoma of papilla of Vater ;
NR : not reported ; head pancreas : cancer of the head of the pancreas, survival in % ;
periampullary : cancer of the periampullary region, survival in %, survival range depending from tumortype i.e. duodenum, distal common bile duct and ampulla of Vater

1.4.3 PROGNOSTIC FACTORS

The ultimate goal of prognostic factors in cancer of the head of the pancreas and periampullary region is to provide reliable information about the effects on survival, whether to perform a resection and to select those patients with the lowest possible morbidity and

mortality. An optimal prognostic index must offer a decision tree on how to deal with the pancreatic cancer patient, even before considering any kind of invasive diagnostic modality or treatment option. However, until now no such a prognostic index is available. About 20 prognostic factors are given in the literature. Among these only a few do have consistent value for prognosis. Age, sex, performance score, duration of symptoms, weight loss, pain, bilirubin, CA 19-9, tumor size, TNM-stage, grade of differentiation of tumor, invasion of lymph- and bloodvessels, blood loss and blood transfusions are mentioned in the literature. Disputable factors are age and tumor size. In former days an age above 70 years was considered to be a contraindication for resection because of the high morbidity and mortality in this patients group of patients. Kairaluoma in 1987 and Cameron in 1993 reported no disadvantage in patients over 70 years of age per se. This will depend mainly on the performance score of the elderly patient.[116,127] Tumor size is still the most contradictionary prognostic factor. Questions arise on how to estimate tumor size, as a part of the tumor measured is the tumor-surrounding pancreatitis and how to define critical tumor size for performing a resection etc.. Until now, neither consensus has been reached nor is to be expected in the near future.[79-81] Better differentiation of the tumor results in greater survival, even when no resection is performed, probably as a result of a less aggressive behavior of the tumor. The stage of the disease seems a reliable prognostic factor, but this can be defined in different ways, even using the UICC directives.[128] In particular the N-stage is disputed, although most studies consider the prognosis to be worse if lymph node involvement exists. However, in cases of cancer of the head of the pancreas, it is defendable to divide the group of patients into one group without and one group with distant metastases (including lymph node metastases outside of the normal resection borders).[79-83,120] In addition to these considerations, it must be realized that the patient deserves an individual and objective decision making about the possible treatment options. The proper treatment is based on the state of the disease, bearing in mind all possible pros and cons. It is clear that, without the availability of a reliable prognostic index, a proper judgement is difficult and will be more or less dependent on the experience of the treating physician. Even with a reliable prognostic index it will remain very difficult to predict individual patients' survival.

1.5 CHEMO- AND RADIOTHERAPY

1.5.1 CHEMO- AND RADIOTHERAPY IN IRRESECTABLE CANCER

Chemotherapy has been used in locally advanced and metastatic pancreatic cancer with the intention of prolonging survival. The results obtained vary largely, depending upon the kind of chemotherapy used. Agents as 5-FU in combination with cyclophosphamide, methotrexaat, vincristine, adriamycin, mytomycin-C and CCNU are used in disseminated disease especially in phase I and phase II studies. In almost all of these studies some effect was noted, but truly significant differences are lacking.[129-134] Overall, no substantial effect of chemotherapy has been proven up till now for advanced cancer of the pancreas.[135,136] Hormonal therapy, especially the use of tamoxifen has been used with varying success. The best responders were elderly women with advanced disease, but this is likely to be accidental in these studies.[137-140] Immunotherapy has been used in clinical trials, but reliable data are not yet available.[141]
In the seventies, radiotherapy alone has been used to treat the locally advanced stages of pancreatic cancer with encouraging results.[142,143] During this time period, 5-FU was considered to be an effective radiosensitizer. Several in vitro and in vivo studies were published using 5-FU as a radiosensitizer in different forms of gastrointestinal malignancies. It seemed to be effective especially when 5-FU was given simultaneously with, and even continued 48 hours after, radiotherapy. Radiotherapy was given as split courses, varying in dose from 35-65 Gray, combined with 5-FU as bolus-injections of 500 mg/m^2/day; in following studies as continuous infusion in a dose of 25-35 mg/kg/day. Toxicity was reasonably low; mucositis, bone marrow depression and nausea are the normal side-effects, with good response to conservative treatment. Discontinuation of therapy is seldom reported.[144-149] The studies of the Gastro-Intestinal-Tumor-Study-Group (GITSG) earn special attention because of the thorough search by means of clinical studies what the best dosages of radiotherapy and 5-FU should be. A significant advantage of 40-60 Gray radiotherapy combined with 500 mg/m^2/day as bolus injections was shown as compared with the radiation-therapy-alone group of patients, with a median survival of 10 months versus 5.5 months respectively.[150,151] It seems that radiation therapy combined with 5-FU has significant influence on survival, even in loco-regional irresectable or disseminated disease. The results of these studies are confirmed by others with 50 Gray radiotherapy and 375 mg/m^2/day 5-FU

as bolus injection for locally advanced disease, resulting in a median survival of 10 months and even some long-term survivors.[152,153] Another therapeutic option is intra-operative radiotherapy eventually combined with external beam radiation. The most important result of this kind of treatment lies in reduction of pain in advanced stages of disease, with little or no effect on survival.[154-157]

1.5.2 CHEMO- AND RADIOTHERAPY AS ADJUVANT TREATMENT

As a consequence of the experiences with radiotherapy and/or 5-FU obtained in patients with locally advanced cancer of the pancreas and periampullary region, this regimen was also used after intentional curative surgery. The first evidence of influence on survival was described in the GITSG study in 1985 in which 21 patients received adjuvant radiotherapy and 5-FU treatment. Radiotherapy consisted of a split course of 2 times 20 Gray in 2 weeks each separated by 2 weeks, with 5-FU as a bolus of 500 mg/m^2/day during the first 3 days of every radiotherapy cycle of 2 weeks. The 5-FU treatment was continued 2 years after surgery, every week one bolus injection. Toxicity was reasonably low and the treatment was well tolerated. A significant benefit was obtained with median survival of 11 months in the control group and 20 months in the treated group respectively. One of the 22 control patients and 3 of the 21 treated patients were alive at 5 years.[13] Further evidence of this beneficial treatment protocol was reported again by the GITSG in 1987. Another 30 patients treated showed a median survival of 18 months, with 2 year survival of 46%, compared with 11 months median survival and 18% 2 year survival respectively if no adjuvant treatment was given.[12] A recent report of Foo et al. showed comparable results in 29 patients, median survival 22.8 months and 2 year survival of 48%.[158] Others claimed the same benefit of radiotherapy alone, but this was done only in a small study.[159] The most recent developments in adjuvant treatment for cancer of the pancreas consists of the proposal of preoperative and/or intraoperative radiotherapy to prevent local recurrence due to microscopical remnants of tumor cells after resection.[160]

1.6 OVERVIEW OF THE CONTENTS

The aim of the study was to retrospectively describe the last decade of pancreatic surgery in the University Hospital Rotterdam-Dijkzigt. A general introduction was given in chapter 1, with an overview of the literature. Palliative treatment in cases of irresectability or in cases of loco-regional recurrence is described in chapter 2. The major question was when and how to palliate a patient. In chapter 3 the results of treatment during the 10 years of surgery in the University Hospital Rotterdam-Dijkzigt is described, followed by the first toxicity results of a prospective randomized trial in collaboration with the EORTC (European Organization of Research and Treatment of Cancer) in which adjuvant treatment is administered. The adjuvant treatment consists of radiotherapy and 5-FU. The toxicity results of the first 77 treated patients are described. In chapter 4 the pylorus preserving pancreatoduodenectomy is described in a retrospective way, an appendix with the objectives of an already started prospective trial is added. In this trial the question is if the pylorus preserving pancreatoduodenectomy is as safe as the standard Whipple's procedure considering morbidity, mortality and survival. A prognostic index is described in chapter 5, completed with a decision tree how to handle with a patient with cancer of the head of the pancreas. The general discussion and conclusions are described in chapter 6. A summary of the contents (and a summary in Dutch) are given. At the end of each chapter references to the literature are given.

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CHAPTER 2

PALLIATIVE TREATMENT

2.1

GUIDELINES FOR THE APPLICATION OF SURGERY AND ENDOPROSTHESES IN THE PALLIATION OF OBSTRUCTIVE JAUNDICE IN ADVANCED CANCER OF THE PANCREAS

Summary of the original publication

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2.2

IS THERE A PLACE FOR GASTROENTEROSTOMY IN PATIENTS WITH ADVANCED CANCER OF THE HEAD OF THE PANCREAS ?

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2.3

TREATMENT OF LOCOREGIONAL RECURRENCE AFTER INTENTIONAL CURATIVE RESECTION OF PANCREATIC CANCER

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2.1

GUIDELINES FOR THE APPLICATION OF SURGERY AND ENDOPROSTHESES IN THE PALLIATION OF OBSTRUCTIVE JAUNDICE IN ADVANCED CANCER OF THE PANCREAS

2.1.1 INTRODUCTION

This retrospective study was set up to identify patient-related factors favoring the application of either surgery or endoprostheses in the palliation of obstructive jaundice in subsets of patients with cancer of the head of the pancreas or periampullary region. Of the patients with cancer of the head of the pancreas and periampullary region 70-90% develop jaundice caused by biliary obstruction.[1-4] Only 10-30% of the patients can be treated with intention to cure, thus, in the majority of patients palliation is the main goal of treatment in terms of relieving pain, cholestasis and duodenal obstruction.[5-8] In the palliation of obstructive jaundice surgical biliodigestive anastomosis has traditionally been performed. Surgical biliary bypass is associated with high mortality (15-30%) and morbidity rates (20-60%), but little recurrent obstructive jaundice (0-15%). Biliary drainage with endoscopically placed endoprostheses has a lower complication rate, but recurrent obstructive jaundice is seen in up to 20-50%.[5,9-18] The hospital readmissions as a result of recurrent obstructive jaundice may impair the quality of life. Long surviving patients may therefore benefit from a surgical bypass.

2.1.2 MATERIAL AND METHODS

Patients with advanced cancer of the head of the pancreas or periampullary region treated at the University Hospital Dijkzigt, Rotterdam, The Netherlands, between 1980 and 1990 were reviewed. In 148 patients data concerning morbidity, hospital stay after palliation of obstructive jaundice with endoscopic endoprostheses or surgical biliary bypass, readmissions in case of stent complications as clogging and the total hospitalization period were compared. These patients were stratified for long (>6 months) and short (<6 months) survival.
Thirty-five patients did not get any form of biliary drainage because of terminal disease, 5 patients only received external bile drainage.

2.1.3 RESULTS

Because of a longer initial hospital stay and higher early morbidity after surgical bypass in patients surviving less than 6 months, the higher late morbidity after endoprosthesis is cancelled. Total hospital stay was similar after surgical bypass or endoprosthesis, but in the

endoprosthesis group of patients late morbidity was significantly higher (table 1). Success rate of surgical bypass procedure was 93.2%, after endoprosthesis 95.2% respectively. Thirty-day mortality was comparable after the two procedures, 13.6% after surgical bypass and 12.7% after endoprosthesis respectively. Overall there were no differences in survival between the two groups of patients treated for their biliary obstruction. The data described suggest endoscopic placed endoprosthesis as the optimal palliation in patients surviving less than 6 months, a surgical bypass procedure seems the best option for patients surviving longer than 6 months. Prognostic criteria were obtained in this group of patients using Cox proportional hazards model. Advanced age, male sex, liver metastases and large tumor diameters were less favorable factors. One can calculate the risk of terminal disease before and after 6 months with these parameters.

Table 1 : morbidity and hospital stay in patients with survival shorter and longer than 6 months

	survival < 6 months		survival > 6 months	
	surgery (n=24) n (%)	endoprostheses (n=40) n (%)	surgery (n=20) n (%)	endoprostheses (n=23) n (%)
total morbidity	7 (29)	12 (30)	1 (5)	14 (61)*
early morbidity	7 (29)+	3 (7.5)	1 (5)	0 (0)
late morbidity	0 (0)	9 (23)*	0 (0)	14 (61)*
	days (range)	days (range)	days (range)	days (range)
initial stay	42.8 (10-87)	27.3 (3-66)*	27.3 (14-50)	20.0 (5-37)*
total stay	58.8 (12-156)	40.3 (12-93)*	53.5 (17-151)	56.1 (13-113)
readmissions (n)	1.7 (1-4)	2.0 (1-4)	2.8 (1-6)	3.0 (1-8)

* : p=0.05; # : p<0.05
early morbidity : < 1 week; late morbidity : > 1 week
stay : hospital stay

2.1.4 DISCUSSION

One of the major questions in palliation in patients with cancer of the head of the pancreas or periampullary region is by which technique a patient should be palliated for obstructive

jaundice. Endoprostheses are widely used, but quality of life is impaired because of the frequent readmissions for complications of the stent, especially clogging. Morbidity in the group of patients surviving longer than 6 months is significantly higher after endoprosthesis (61%) than after surgical bypass (5%). No difference in morbidity was found in patients surviving shorter than 6 months, early morbidity after surgical bypass was compensated for late morbidity in the endoprosthesis group of patients. Initial and total hospital stay was significantly shorter in the group of patients treated with endoprosthesis surviving less than 6 months. The frequent readmissions for complications of the endoprosthesis as clogging resulted in equal hospital stay in both groups of patients surviving longer than 6 months. Until now, no studies are available in which a differentiation has been made between short and long survival. Overall, there are no differences between the use of endoprosthesis or surgical bypass with respect to morbidity, mortality and survival.[12,14,15,17,18]

We conclude that in patients with survival shorter than 6 months, endoscopic biliary drainage is more favorable because it results in shorter hospitalization. Surgical biliary bypass, however, will be superior in palliation in patients surviving longer than 6 months, because of less late morbidity and a long lasting effect of bile drainage. The question remains which patients will die before and after 6 months, the Cox regression analysis showed four important prognostic factors in this irresectable group of patients, comparable with some other reports.[19-21] Age, sex, tumor diameter and livermetastases were of prognostic value. Male patients with liver metastases do have the shortest survival, female patients without livermetastases and a relatively small tumor do have the best chance to live longer than 6 months. If a patient has an irresectable tumor at laparotomy, one should consider these factors when the decision has to been made whether to perform a surgical bypass or not. Of course, the general condition of the patient should be taken into account. In the future, it is very well possible that the results of endoscopic biliary drainage will improve because of larger bore endoprosthesis and self expandable wall stents.[22] It is not yet clear if this techniques will replace the surgical bypass completely in case of irresectable pancreatic or periampullary carcinoma.

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2.2

IS THERE A PLACE FOR GASTROENTEROSTOMY IN PATIENTS WITH ADVANCED CANCER OF THE HEAD OF THE PANCREAS ?

2.2.1 INTRODUCTION

The number of patients with cancer of the head of the pancreas and the periampullary region is increasing.[1] About 10-15% can be treated surgically with the intention of cure, which results in a median survival time of 17-20 months.[2-4] Patients with advanced tumors carry a very bad prognosis. The median survival time of such patients is approximately 4-6 months and 90% will be dead within 1 year of the time from diagnosis.[4-6] In case of locally irresectable tumors without distant metastases, prolonged survival may be obtained by treatment with radiotherapy and 5-FU.[7] Since most patients cannot be cured, palliative therapy plays an important role in the treatment of these patients to relieve pain, cholestasis and obstruction of the duodenum. Biliary bypasses or biliary stents are obligatory procedures since they decrease morbidity.[8,9] There is still doubt, however, about the need for a bypass of the duodenum in those patients who are having problems with the passage of food. When vomiting minimizes the intake of food, it is common practice to perform gastroenterostomy. However, it remains uncertain as to whether prophylactic gastroenterostomy is a good palliation for a possible future obstruction of the duodenum. Not all patients develop gastric outlet obstruction, and even those patients who are treated prophylactically are not always secured against gastric outlet obstruction. This may be partly due to impairment of the innervation of the stomach caused by tumoral invasion. Therefore, the problem of the passage of food is also thought to be a functional problem rather than a matter of obstruction of the duodenum by tumor growth.

The aim of this study is to analyze the results of bypass procedures of the duodenum, performed on a prophylactic or therapeutic basis, in patients with advanced cancer in the pancreatic head.

2.2.2 MATERIAL AND METHODS

All the records of patients with advanced cancer of the head of the pancreas and periampullary region admitted to the Erasmus University Hospital between 1-1-1980 and 31-12-1990 were reviewed. Advanced cancer was defined as locally non-resectable tumors and/or distant metastases. The definitive diagnosis of pancreatic cancer was confirmed after pancreatic biopsy, biopsy of a metastatic lesion with evidence of a primary lesion in the head of the

pancreas or by autopsy. Patients with no histologically proven carcinoma but with obvious signs of cancer in the head of the pancreas, determined by radiological imaging techniques and a supportive clinical course, were also included. Excluded were patients who previously had gastric surgery. We obtained data about the techniques of bypass for the common bile duct and duodenum. A gastroenterostomy was made trans-mesocolic, isoperistaltic and with a single layer, running suture. Biliodigestive bypasses (BDB) were performed by surgical methods (cholecystoduodenostomies, choledochoduodenostomies and choledochojejunostomies) or other procedures, namely percutaneous drainage, nasobiliary drainage and stents in the common bile duct. We especially looked at pre- and postoperative problems of food intake in cases involving gastroenterostomy. We defined gastric outlet obstruction as problems with the passage of food leading to vomiting and causing dehydration and malnutrition, necessitating the parenteral administration of fluids. If the patient had preoperative signs of gastric outlet obstruction, we regarded the gastroenterostomy as having been performed for symptomatic reasons. Operative morbidity was measured by the incidence of surgical complications and by the number of days gastric suction was needed, the time elapsed until a normal diet could be resumed and the time spent in hospital after operation. Follow-up information regarding gastric outlet obstruction, metastases and hospital admissions concerning other palliative therapies was obtained. Data on metastases were obtained by histological examination of biopsy specimens, CT-scan or ultrasonography.

Statistical significance was determined by the use of the Chi-square test and Fisher's exact test for cross tables and analysis of variance and Student-Newman-Keuls test for normally distributed variables. For not normally distributed variables, rank tests were used (Mann-Whitney, Kruskal-Wallis). Analysis for time to event data was done by using Cox proportional hazards analysis. A p-value of less than 0.05 was considered to indicate a significant difference.

2.2.3 RESULTS

Patients

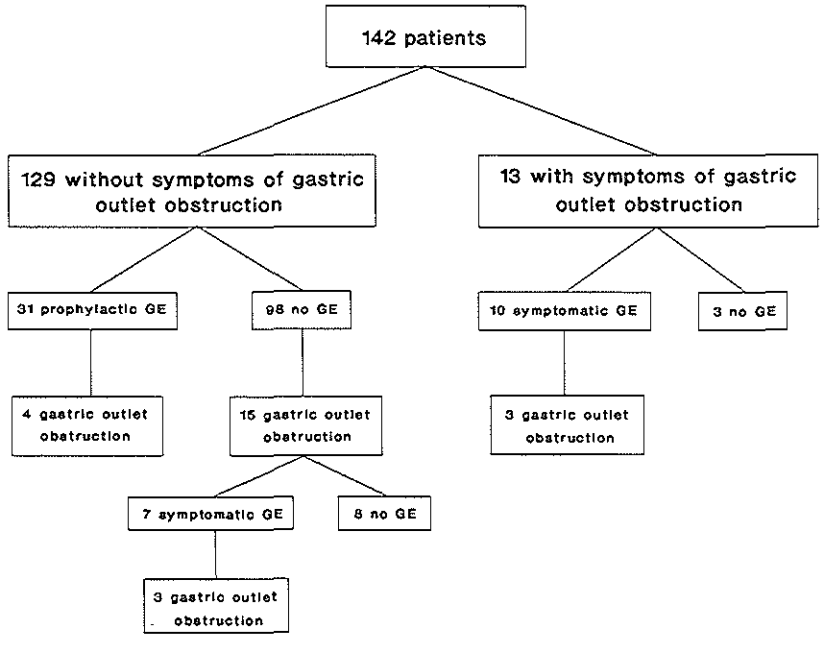
Between 1980 and 1990, 149 patients with advanced cancer of the head of the pancreas were admitted to the Erasmus University Hospital. Seven of these patients had previous gastric surgery and were excluded from further analysis. The remaining 142 patients were divided

according to the different options for palliative treatment. The characteristics of these patients are described in tables 1 and 2. Age was significantly higher in patients who did not have a laparotomy. There were no other differences in the various treatment groups with regards to sex and the presence of metastases. Diagnosis was proven histologically in 116 patients (82%).

Gastric outlet obstruction (figure 1)

Thirteen patients had symptoms of gastric outlet obstruction at admission. Of these, 10 underwent gastroenterostomy, 2 patients died soon after diagnosis and 1 refused further treatment. Hundred twenty-nine patients had no symptoms of gastric outlet obstruction at the

Figure 1 : occurrence of gastric outlet obstruction in 142 patients



time of diagnosis. Thirty one patients underwent prophylactic gastroenterostomy but in 4 patients this could not prevent gastric outlet obstruction. Of the remaining 98 patients without gastroenterostomy, 15 developed symptoms of gastric outlet obstruction. Cox proportional hazards analysis of these data showed no significant difference in time to occurrence of symptomatic obstruction between these groups, taking into account sex, age and presence of metastases as co-variables (table 3, p=0.401).

Table 1 : patient's characteristics according to different bypass procedures

	n	♀/♂	mean age (range)	M0	M1
no bypass	28	13/15	61.5 (36-80)	15	13
GE	4	1/ 3	56.8 (49-74)	2	2
BDB	66	27/39	65.3 (37-89)	43	23
GE + BDB	44	22/22	60.8 (38-88)	28	16
total	142	63/79	63.0 (36-89)	88	54

GE = gastroenterostomy, BDB = biliodigestive bypass (stents, drains and surgical methods), M0 = no metastases, M1 = metastases, n = number

Table 2 : patient's characteristics according to surgical bypass procedures

	n	♀/♂	mean age (range)	M0	M1
no laparotomy	49	17/32	67.8*(36-89)	34	15
laparotomy	31	17/14	61.6 (41-77)	18	13
SBDB	14	6/ 8	57.4 (37-77)	6	8
prophylactic GE	9	5/ 4	59.1 (38-73)	4	5
symptomatic GE	11	4/ 7	60.9 (49-74)	9	2
prophylactic GE + SBDB	22	13/ 9	62.7 (41-88)	13	9
symptomatic GE + SBDB	6	1/ 5	55.3 (40-76)	4	2
total	142	63/79	63.0 (36-89)	88	54

GE = gastroenterostomy, SBDB = surgical biliodigestive bypass, M0 = no metastases, M1 = metastases, n = number, * $p < 0.05$

These 15 patients who developed gastric outlet obstruction at a later stage all required hospitalization. Seven underwent gastroenterostomy, which was successful in only 4 cases.

Table 3 : development of gastric outlet obstruction in the 129 patients without symptoms at the time of diagnosis

	n	gastric outlet obstruction	median follow-up range (days)	person-years follow-up
no GE	98	15 (15.3%)	137 (7-589)	48.1
prophylactic GE	31	4 (12.9%)	168 (12-1569)	22.7

GE = gastroenterostomy, n = number

Two of these 7 patients had postoperative complications; in one patient the gastroenterostomy never functioned and he died after 21 days, the other patient had an anastomotic leakage and a relaparotomy was necessary. The other 8 patients did not receive a gastroenterostomy due to their terminal condition. The median survival of these patients was 13 days after the development of gastric outlet obstruction versus 58 days for the 7 patients with a gastroenterostomy. In the group with a prophylactic gastroenterostomy, four patients developed gastric outlet obstruction. The median survival of these patients was 28 days after the development of gastric outlet obstruction.

Morbidity and mortality

One hundred elective laparotomies were performed in 93 patients. A comparison of post-operative morbidity between the various treatment groups showed a significantly higher rate of complications after a surgical biliodigestive bypass ($p=0.013$), also in combination with a prophylactic gastroenterostomy ($p=0.015$), compared with the other operative procedures. In-hospital mortality was not significantly different after the various palliative operations (table 4). The fact as to whether a gastroenterostomy was performed prophylactically or when symptoms of gastric outlet obstruction had arisen did not have a significant influence on the number of days during which gastric suction was needed, nor did it affect the time at which oral liquids or a normal diet could be taken, or the number of days spent in the hospital postoperatively (table 5).

Survival

All patients died in the follow-up time. Median survival of all patients was 4.5 months with a mean of 6.3 months (range 0.2 - 51.6 months). Patients with a biliodigestive bypass ($n=110$) had a significantly prolonged survival time in comparison to patients without a

biliodigestive bypass (n=32) (p=0.024); median survival of 5.1 months and 2.4 months respectively. There was no statistical difference between patients with or without a biliodigestive bypass as regards the occurrence of metastases. Other palliative procedures had no effect on survival. Neither was there a difference in survival between patients who did and those who did not develop gastric outlet obstruction.

Hospital admissions

The number of hospital admissions during survival time is the same in all groups and averages 2 admissions per patient. The percentage of days of survival spent in hospital is not significantly different in the various groups.

Table 4 : morbidity and mortality after 100 elective laparotomies in 93 patients

	n patients	n laparotomies	in-hospital mortality	post operative complications	
laparotomy	31	37	6 (16.2%)	4 (10.8%)	- 2 woundinfections - GI-bleeding - perforation of the small bowel
SBDB	14	15	1 (6.7%)	7*(46.7%)	- 2 bile-leakage - 2 iab - 2 fascia dehiscence - gastric retention
prophylactic GE	9	9	1 (11.1%)	2 (22.2%)	- non functional GE - pancreatitis with pancreaticocutaneous fistula
symptomatic GE	11	11	3 (27.3%)	1 (9.1%)	- non functional GE
prophylactic GE + SBDB	22	22	4 (18.2%)	9*(40.9%)	- 3 non functional SBDB - 3 iab - 2 SBDB anastomosis leakage - fascia dehiscence
symptomatic GE + SBDB	6	6	2 (33.3%)	1 (16.7%)	- SBDB anastomosis leakage - iab
total	93	100	17 (17%)	24 (24%)	

GE = gastroenterostomy, SBDB = surgical biliodigestive bypass, GI = gastro-intestinal, iab = intra-abdominal bleeding, * $p < 0.05$ compared to the other procedures, n = number

Table 5 : post-operative dietary problems in patients after a prophylactic or symptomatic gastroenterostomy

	gastric suction median days (range)	DGE n	start of liquid diet after operation median days(range)	start of normal diet after operation median days(range)
prophylactic GE n=31	3 (1-42)	5	5 (2-42)	8 (5-43)
symptomatic GE n=17	5 (1-12)	5	7 (1-37)	12 (3-65)

DGE = delayed gastric emptying (the inability to tolerate oral fluids 8 days or more after operation).

2.2.4 DISCUSSION

The correct palliative treatment for patients with advanced pancreatic cancer remains uncertain. Since it is known that biliary bypass for jaundice decreases morbidity, the debate focuses on whether or not to perform a gastroenteric bypass. This may be done prophylactically at initial diagnostic laparotomy, or when symptoms of gastric outlet obstruction have arisen. The choice between these options is mainly determined by the incidence of symptoms of gastric outlet obstruction occurring during the course of the disease. In a review of the literature we found an incidence of obstruction ranging from 3 to 50%.[4,8,10-13] Sarr and Cameron reported in a review of 3327 patients an incidence of 16%.[9] In our study, 25% of the patients developed symptoms of gastric outlet obstruction. Most authors state, therefore, that a prophylactic gastroenterostomy is obligatory.[8,9,14] We agree that if these symptoms could be prevented by adding a gastroenterostomy to a diagnostic laparotomy or a surgical biliary bypass procedure without any increase in morbidity or mortality, it would be rational to do so. However, adding a gastroenterostomy to a laparotomy or a surgical biliodigestive bypass most likely increases morbidity and mortality.[15-21] Furthermore, most patients never develop symptoms of gastric outlet obstruction and therefore should never be operated upon.

Few authors have reported on the frequency of gastric outlet obstruction after a prophylactic gastroenterostomy has been performed.[22] In our study, the incidence of gastric outlet obstruction after prophylactic gastroenterostomy was not significantly lower in comparison to the frequency of obstruction in patients who did not receive gastroenterostomy. Postoperative

morbidity was higher in patients who underwent gastroenterostomy, whether or not combined with a surgical biliodigestive bypass. Delayed gastric emptying following gastroenterostomy is thought to be the main cause of postoperative morbidity. Doberneck et al. defined delayed gastric emptying as the inability to tolerate oral fluids for 8 days or more after operation.[23] They found delayed gastric emptying in 16% after prophylactic gastroenterostomy and in 57% after gastroenterostomy performed for symptomatic reasons. Other authors reported percentages of delayed gastric emptying after bypass surgery of the duodenum ranging from 14 to 29%.[12,14,19] We found delayed gastric emptying in 16% of the patients after a prophylactic gastroenterostomy and in 29% after a gastroenterostomy performed for symptomatic reasons. There was no difference in the number of days in which gastric suction was needed postoperatively between these patients. The exact pathophysiological mechanism of gastric outlet obstruction is uncertain. The main reason is obviously the impingement upon the duodenum by tumor growth. A bypass of the duodenum should solve this anatomical obstruction. However, not all patients are cured by gastroenterostomy. This implies that other mechanisms must be involved, such as infiltration of the splanchnic nerves by tumor cells with subsequent functional impairment of gastric motility.

Our results indicate that prophylactic gastroenterostomy does not prevent future gastric outlet obstruction and furthermore increases morbidity and therefore should not be performed. A gastroenterostomy performed for symptomatic reasons should be considered carefully since the success rate is low and is accompanied by a considerable incidence of morbidity and mortality. It is our opinion that palliative surgery in patients with advanced cancer of the head of the pancreas should be prevented at the extreme since the postoperative problems are unacceptably high, especially considering that these patients have only a few months to live. Finally, it is necessary to learn more about the anatomical or functional rational of gastric outlet obstruction in cancer of the head of the pancreas in order to improve the treatment of these symptoms.

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2.3

TREATMENT OF LOCOREGIONAL RECURRENCE AFTER INTENTIONAL CURATIVE RESECTION OF PANCREATIC CANCER

2.3.1 INTRODUCTION

In the last few years pancreatic cancer has become one of the major causes of death from neoplastic disease, due to an increase of incidence and a mortality rate of 99%.[1,2] Even after surgical treatment, the 5-year survival rate ranges from 0 to 15%.[2,4,5] However, patients with a periampullary carcinoma, i.e. carcinoma of the ampulla of Vater, the distal common bile duct or duodenum, show a better 5-year survival (20-40%).[4,5] Although pancreatic cancer is a rapidly metastasizing process, it is confined to the upper abdominal region at an early stage of the disease.[6,7] The reported incidence of local recurrence is as high as 50 to 67%.[8,9] It is important to know if locoregional recurrence can occur without distant metastases, if one considers treatment for these recurrences. So far there have been no reports of clinical presentation, treatment and survival of patients with locoregional recurrence of pancreatic cancer. In order to answer the question if (surgical) treatment is meaningful for these patients, we analyzed our data regarding incidence, symptoms and treatment of patients with locoregional recurrence after intentional curative resection of pancreatic- and periampullary carcinomas, over a period of 11 years.

2.3.2 MATERIALS AND METHODS

Between 1978 and 1988, 108 patients underwent an intentional curative resection for carcinoma of the pancreas or periampullary region at the University Hospital of Rotterdam. The patient population existed of 57 men and 51 women with a mean age of 59 years (range 27-78 years). A resection was considered curative when all macroscopic tumor tissue could be completely removed and when no lymph node metastases or distant metastases outside the resection specimens could be detected. The type of resection that was performed depended on the localization of the tumor. Table 1 shows the localization of the carcinomas and the type of resection that was performed in all patients who underwent an intentional curative resection. Hospital mortality was defined as the mortality rate during the postoperative period in hospital. Locoregional recurrence was defined as tumor recurrence at the site from which the primary tumor was resected, in adjacent structures or in the area of lymph drainage in the direct surroundings of the surgical area. The diagnosis of locoregional recurrence was made by ultrasonography and CT-scan. In 56% of the cases tumor recurrence was confirmed by

histological examination of tissue specimens obtained by transcutaneous punction, operation or autopsy. The follow-up period ranged from 2 months to 10 years after resection of the primary tumor (mean duration 25 months). The patients were followed postoperatively by patient interview, physical examination, ultrasonography and CT-scan, every 3-6 months after resection.

The records of all patients with locoregional recurrence were reviewed for clinical presentation, treatment and survival. Survival rates were assessed by computerized life table analysis according to Kaplan and Meier.[10] To compare the survival rates of the different subgroups of patients the Logrank test was used. Cumulative recurrence rate was calculated according to the life table method (Kaplan-Meier).[11]

Table 1 : tumor localization and type of resection

Localization and type of resection	Intentional curative resection n (%)	Locoregional recurrence n (%)
Pancreatic head:	54 (50)	19 (56)
-Whipple	34 (32)	11 (32)
-Pylorus preserving Whipple	9 (8)	2 (6)
-Total pancreatectomy	11 (10)	6 (18)
Pancreatic body/tail:	3 (3)	0 (0)
-Resection of the tail	2 (2)	-
-Total pancreatectomy	1 (1)	-
Periampullary carcinoma:	51 (47)	15 (44)
-Whipple	37 (34)	15 (44)
-Pylorus preserving Whipple	13 (12)	-
-Total pancreatectomy	1 (1)	-

n = number, % = percentage of total of the subgroup

2.3.3 RESULTS

Incidence and disease-free interval.

Locoregional recurrence was found in 34 of the 108 patients, all within a period of three years

after resection of the primary tumor. The cumulative recurrence rate in the first year after resection was 20%, in the second year 35%, and after three years 56%. The group of patients with locoregional recurrence existed of 19 men and 15 women, with ages ranging between 32 and 72 year (mean age 58 years). Table 1 shows the different sites of primary carcinoma and the type of resection that was performed in the 34 patients with locoregional recurrence. In 11% of all resected patients and in 26% of the patients with locoregional recurrence microscopical remnants of the tumor were found at the line of resection on histological examination of the resection specimens. Positive lymph nodes were found in 32% of the resected specimens of all resected patients and in 44% of the patients with locoregional recurrence. Hospital mortality was 7%.

Symptoms.

Most of the patients with locoregional recurrence presented with upper abdominal pain or pain diffuse in the abdomen (68%) and weight loss (59%). In five patients other symptoms have led to the diagnosis: two patients presented with icterus, one with nausea, one with a palpable mass at the site of the abdominal incision, and one patient was analyzed because of an abnormal finding on routine ultrasound examination.

Distant metastases.

Distant metastases were proven in 16 of the 34 patients (47%) with locoregional recurrence, by ultrasound and computertomographical examination. Five patients had liver metastases, three patients had abdominal metastases, one had metastases of the lung, and seven patients had metastases at other sites or at multiple sites. In 18 patients (53%) distant metastases could not be demonstrated.

Treatment.

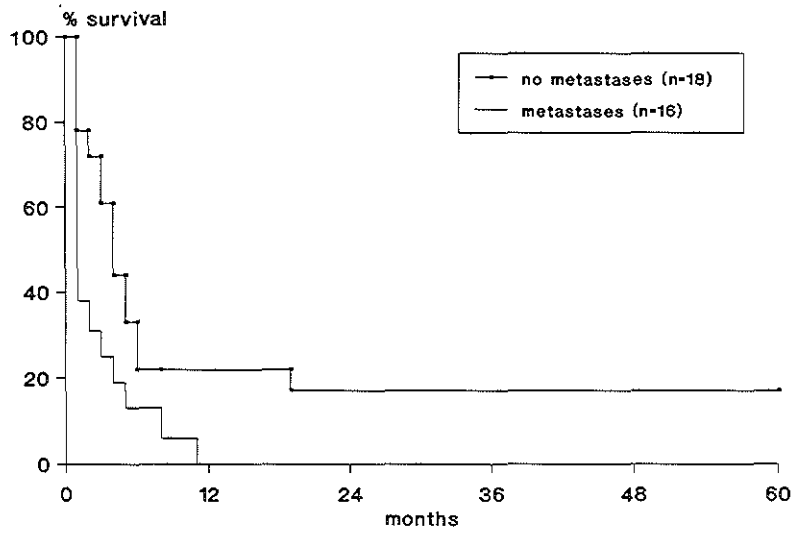
Eight patients with locoregional recurrence without distant metastases underwent laparotomy. In two cases the tumor recurrence could be resected radically, in one patient the resection turned out to be irradical, after which radiation- and chemotherapy were given. In five other patients surgical treatment could only be palliative. Two patients were treated by chemotherapy alone. Six patients with locoregional recurrence without distant metastases were not treated because of their poor physical condition, and two patients wished not to receive further treatment.

Survival.

After the diagnosis locoregional recurrence was established, the 1-, 2- and 5-year survival

rates for these patients were resp. 12%, 8% and 8%. Survival was significant better for the group of 18 patients without distant metastases (1-, 2- and 5-year survival rates resp. 22%, 17% and 17%), compared to the group of 16 patients with distant metastases (1-year survival rate 0%), p=0.02.(Figure 1)

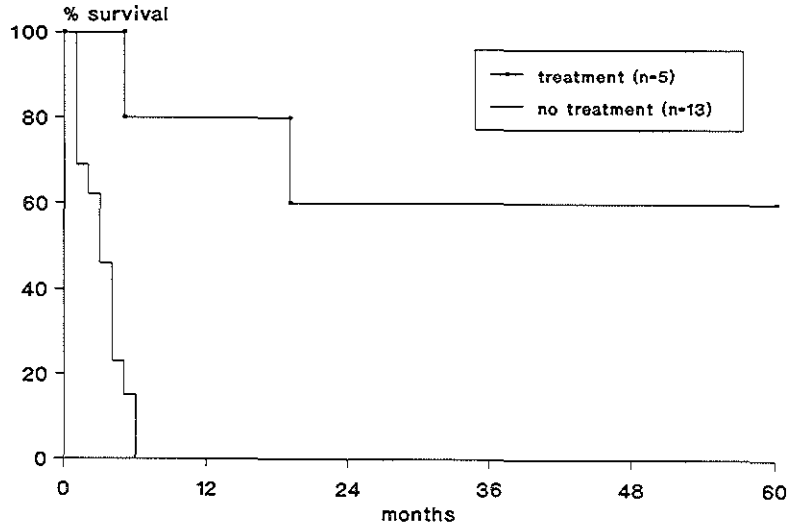
Figure 1 : cumulative survival rate for patients with locoregional recurrence with and without distant metastases



The 5 patients without distant metastases who could be treated did have a mean survival of 33 months (range 6-74 months), which is significant better than for the patients without distant metastases who were not treated (0.4-7 months, mean 4 months), p=0.002. (Figure 2) The 2 patients in which recurrence of the tumor could be radically resected were both alive at the end of the study, respectively 6.2 years after resection of the recurrent tumor at the jejuno-jejunostomy, and 3.2 years after resection of recurrent tumor at the site of the abdominal incision. The patient who received a combined treatment (irradical resection with adjuvant radiation and chemotherapy) was also alive at the end of the study, 2.3 years after treatment of the recurrent tumor. The 2 patients who were treated by chemotherapy alone died resp. 6

and 20 months after the diagnosis of locoregional recurrence was established.

Figure 2 : cumulative survival rate for patients with locoregional recurrence in absence of distant metastases; treated vs untreated patients



2.3.4 DISCUSSION

The reported incidence of local recurrence in pancreatic cancer is 50-70%.[8,9] In colorectal cancer, the local recurrence rate ranges between 6% and 20%. The great majority of these patients present within two years after resection of the primary tumor. Five-year survival after reoperation for local recurrence in colorectal cancer has been reported.[12] It is surprising that there are no reports about surgical treatment of local recurrence of pancreatic cancer.
Some authors attribute local recurrence to intrapancreatic multifocal cancers, or to microscopic cancer infiltration within regional lymphatic vessels, nerve or loose connective tissue, and they recommend total or regional pancreatectomy.[7,13] However, a better survival rate for patients after total or regional pancreatectomy was not found.[14,15] Since at an early stage dissemination is often restricted to the locoregional area, adjuvant treatment after resection of

pancreatic tumors might prevent locoregional recurrence.[6,7] According to some series radiotherapy was effective, but this was not always confirmed by others.[16,17] Chemotherapy alone has little or no effect on survival rates.[18,19] In a randomized study of the Gastrointestinal Tumor Study Group, a significant better 2-year survival rate for the group of patients treated by a combination of radiotherapy and 5 FU-chemotherapy was seen, compared to the control group without adjuvant therapy.[19,20] The study of Cubilla et al. suggests that insufficient regional lymph node clearance of the traditional Whipple's procedure might account for local recurrence.[21] Ishiwaka et al. found a significant decrease of the cumulative death rate from local recurrence when an extended dissection of the regional or juxta-regional lymph nodes together with the neighboring connective tissue was performed as an addition to a routine Whipple's operation.[22] However, the extended procedure has not succeeded in decreasing the number of deaths due to distant metastases nor those due to distant metastases plus local recurrence. The mean follow-up period in this study was only 25 months, due to the poor survival rate. The high cumulative recurrence rate of 56% in three years was mainly caused by the fact that many patients died early during the follow-up period.

Since the presenting symptoms, upper abdominal pain and weight loss, are relatively late symptoms of a locally expanding tumor process, and since only in 29% of the patients a palpable mass in abdomen could be found by physical examination, it is important to check patients regularly in the first years after resection by ultrasonography and CT-scan.

Compared to the whole group that underwent an intentional curative resection of a pancreatic tumor, a considerably higher percentage of patients in the group with locoregional recurrence had microscopical remnants of the tumor at the line of resection (11% resp. 26%) or positive lymph node metastases in the resection specimens (32% resp. 44%). This indicates that patients with microscopical remnants of the tumor or with a local metastasizing process are predisposed to develop locoregional recurrence. When locoregional tumor recurrence was diagnosed, there was no evidence of distant metastases in as much as 53% of the patients in our series. The 1- and 2-year survival rates for these patients without distant metastases were significant better than for patients with locoregional recurrence and distant metastases. Although these two groups are in different stages of the disease and therefore not comparable, the difference in survival rates indicates that within the whole group of patients with locoregional tumor recurrence, there is a subgroup with a better prognosis. Five patients in the group with locoregional recurrence without distant metastases could be treated with

curative intent. Survival in the treated group was significant better than in the untreated group, although there was a bias in favor of the treated group, because treatment with curative intent was not possible for all patients. Yet, in the treated group a five-year survival was seen, which indicates that if possible, treatment can improve survival. In case of locoregional recurrence of pancreatic cancer in absence of distant metastases, long-term survival was seen after surgical treatment in our series. Although there was no comparable group of patients without treatment, it seems that treatment, especially resection of locoregional recurrence favors the survival rate. It can be concluded that in case of locoregional recurrence after intentional curative resection of pancreatic- and periampullary cancer, (surgical) treatment should be considered in those cases without distant metastases.

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CHAPTER 3

SURGERY, ADJUVANT TREATMENT

3.1

CARCINOMA OF THE PANCREAS AND PERIAMPULLARY REGION: PALLIATION VERSUS CURE

A review of 310 patients

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3.2

TOXICITY OF ADJUVANT TREATMENT WITH RADIOTHERAPY AND 5-FU AFTER CURATIVE RESECTION FOR CANCER OF THE HEAD OF THE PANCREAS AND PERIAMPULLARY REGION EORTC PROTOCOL 40891

J.H.G. Klinkenbijl, A.M. Treurniet-Donker, T. Sahmoud, A. Magotteaux, J. Jeekel on behalf of the EORTC

3.1 British Journal of Surgery 1993:80;1575-1578

3.2 Submitted

3.1

CARCINOMA OF THE PANCREAS AND PERIAMPULLARY REGION: PALLIATION VERSUS CURE

A review of 310 patients

3.1.1 INTRODUCTION

In patients with cancer of the head of the pancreas, pancreatoduodenectomy (Whipple's procedure) is the treatment of choice in most centers. However, the tumor proves to be irresectable in many cases and 90% of all patients admitted for pancreatic cancer die within one year. Obviously the only chance of prolonged survival lies in radical tumor resection. After surgical treatment with curative intention, a five-year survival of only 0-15% has been found and $\pm$ 80% of the patients die within two years after resection. Efforts to improve survival by extending the resection to a total pancreatectomy or to a regional extended pancreatectomy as described by Fortner did not meet with great success.[1-5]

The question therefore arises whether surgical resection is the best treatment for pancreatic cancer. The operative mortality and morbidity are high and these operative risks should be weighed against expected gain in survival. The operative mortality over the years 1981-1986 reported in a recent review of 2398 pancreas resections from different centers was still 16%, nevertheless, improvement has been made during the last years, even 0% mortality has been reported.[6,7]

Operation for cancer of the pancreas could be potentially radical if the process is still confined to the resection area. Preoperatively an attempt should be made to select patients who have a limited tumor process without distant metastases or lymph node involvement outside the resection area. At present no techniques are available to identify such patients accurately. In a previous study we could identify one general risk factor for operative mortality indicating that patients over 70 years of age have an operative mortality of 27% compared to 3% in patients younger than 70 years of age.[8,9]

In this study the results of treatment of pancreas and periampullary cancer in 310 patients admitted within a relatively short period from 1977-1988 were statistically analyzed to determine the influence of preoperative symptoms, drainage of bile, tumor size, tumor-containing resection margins and lymph node involvement on the outcome of surgical resection in cancer of the head of the pancreas and periampullary region. This study is a retrospective analysis of data with all its limitations. Prospective randomized trials are clearly needed in pancreatic cancer.

3.1.2 MATERIAL AND METHODS

Between 1977-1988 310 patients were admitted to the department of surgery of the University Hospital Dijkzigt, Rotterdam, for cancer of the head of the pancreas or periampullary region. Standard preoperative investigation included ultrasonography, computed tomography (CT), endoscopic retrograde cholangiography (ERCP) or percutaneous transhepatic cholangiography (PTC) and optional angiography of coeliac artery and superior mesenteric artery.
The mean age of these patients was 62.6 years (range 26-89 years), 180 men and 130 women. Cancer of the head of the pancreas was diagnosed in 226 patients. 59 (26%) patients were not operated at all because of distant metastases or a bad World Health Organization performance rating.
Clinical history, preoperative diagnostic procedures, intraoperative and pathological findings and follow-up data were analysed using the log rank test, the Cox regression model and Kaplan Meier life tables.
The standard operation for resectable cancer was a Whipple's procedure. A jejunal loop was used for reconstruction, with an end-to-side or end-to-end pancreatojejunostomy with a one-layer inverting running suture. An end-to-side choledochojejunostomy was constructed on the same jejunal loop, also with a one-layer running suture. Stents were not used for the pancreatic duct and only in few cases for the bile duct.
In case of a positive frozen section of pancreatic resection margin, a subtotal or total pancreatectomy was carried out. Pancreatic resection was performed by a limited number of surgeons. Operative mortality was defined as death during the first admission to hospital.
Tumor node metastases (TNM) staging after operation was defined in the Union International Contra la Cancrum 1987 system with a modification for the N-stage, stage N1a indicating positive lymph nodes within the resection specimen and N1b outside the resection specimen.

3.1.3 RESULTS

Of a total of 242 operations for cancer of the head of the pancreas (n=167) or periampullary region (n=75) a radical resection with curative intent could be performed in 106 (34%) patients: 50 patients with cancer of the head of the pancreas (30% resection rate) and 56 patients with cancer in the periampullary region (75% resection rate). In 19 (6%) patients a

palliative i.e. non-radical resection was performed. Non-radicality was shown postoperatively by pathological examination, stage T3 pancreatic cancer (n=7) and T4 periampullary cancer (n=3), N1b (n=8) or M1 (n=1). Stage T4 periampullary cancer resembles stage T3 pancreatic cancer, with tumor extending directly to any of the stomach, spleen, colon or adjacent large vessels. In 34 patients with infiltration of tumor into vital organs or distant metastases in lymph nodes or liver, the operation was limited to an explorative laparotomy. To treat or prevent biliary or gastric outlet obstruction, a drainage procedure, i.e. a choledochojejunostomy and/or a gastrojejunostomy was performed in 83 (37%) patients. Preoperative stent drainage was established by means of PTC or ERCP in 88 (39%) patients with cancer of the head of the pancreas. In 16 (7%) patients stenting was undertaken during operation as a palliative procedure when none had been placed before surgery and no resection was possible. In patients with cancer of the periampullary region, a stent was placed before operation in 28 (33%) patients and during operation in 6 (9%) patients. In total 138 (45%) patients received an endoprosthesis. In 38 patients no treatment other than stenting was possible. In 40% of all patients (n=125) malignancy was cytologically or histologically confirmed before operation.

Cancer of the head of the pancreas

Presenting symptoms in 226 patients with cancer of the head of the pancreas are listed in table 1.

Table 1 : symptoms and signs in numbers and percentages in patients with cancer of the head of the pancreas or periampullary region

symptoms & signs	head of pancreas		periampullary	
	n	%	n	%
pain	157	70	40	48
weight loss	173	77	57	68
gastric stasis	67	30	16	19
jaundice	160	71	61	73
altered defecation	72	32	22	26
alkaline phosphatase ↑	142	63	68	81
gamma-glutaryl-trans ↑	168	74	56	67
LDH ↑	78	35	22	26
coagulation disorders	38	17	24	29

n = number, % = percentage of the total of the subgroup

Pain, weight loss, jaundice, an elevated alkaline phosphatase and gamma-glutamyl-transferase were the main signs in patients with cancer of the head of the pancreas. Of patients with pain, distant metastases were found in 97 (62%) during preoperative investigation and, as a consequence no operation or surgical drainage procedure was performed. Coagulation disorders were all the result of vitamin K deficiency. In 54 (24%) patients tumor size was estimated before surgery by ultrasonography, CT and ERCP: in 15 patients the tumor was smaller than 3 cm. in diameter. The surgical procedures performed are shown in table 2. Tumor in the resection margin was found in 20 patients with cancer of the head of the pancreas (11 patients after palliative Whipple's resection and 9 patients after curative resection).

Table 2 : surgical procedures performed

	head of pancreas		periampullary		total	
	n	%	n	%	n	%
no operation	59	26	9	11	68	22
expl. laparotomy	30	13	4	5	34	11
drainage procedure	74	33	9	11	83	27
palliative resection	13	6	6	7	19	6
curative resection	50	22	56	67	106	34
-Whipple resection	30	13	41	49	71	23
-PPPD	8	4	14	17	22	7
-total panc.	12	5	1	1	13	4
(tumorcontaining resection margin)	(9	18)	(4	7)	(13	12)
total	226	100	84	100	310	100

n = number, % = percentage of the total of the subgroup

Periampullary cancer

Eighty-four patients were admitted for cancer of the periampullary region, defined as cancer in the ampulla of Vater (n=59), distal common bile duct (n=13), or duodenum (n=12). Weight loss, jaundice, an raised levels of alkaline phosphatase and gamma-glutamyl-transferase were the main presenting features in this group of patients.(table 1)

Surgical procedures are listed in table 2. Six patients with periampullary cancer had tumor

growth in the resection margin (2 after palliative resection and 4 after curative resection).

Postoperative Complications.

Cancer of the head of the pancreas

After resection, 14 (22%) reexplorations were needed, 10 (16%) for intraabdominal bleeding, one (2%) for leakage of the pancreaticojejunostomy and 3 (5%) for various reasons. Two wound abscesses were drained on the ward, one intraabdominal abscess was treated conservatively, as were 12 other minor complications. Non-surgical, i.e. cardiac, respiratory and urinary tract complications occurred in 45 (27%) patients.

Periampullary cancer

In this group, 14 (19%) reexplorations were carried out, 4 (5%) for intraabdominal bleeding, 2 (3%) for intraabdominal abscess, 3 (4%) for leakage of the pancreatojejunostomy and 5 (7%) for other reasons. In one patient leakage of the pancreatojejunostomy was treated conservatively, as were 8 other minor complications. Non-surgical complications occurred in 23 (31%) patients.

Preoperative drainage

No preoperative drainage for jaundice was performed in 170 patients; 116 had an endoprosthesis inserted for preoperative biliary drainage. Postoperative laparotomy for bleeding occurred in 2 patients who underwent stenting before operation and in 14 with no stent (chi-2=4.60, 1 d.f., p=0.03), probably due to disturbance of coagulation as a result impaired liver function.

Operative Mortality.

In hospital mortality after all surgical interventions was 11%. Patients aged over 70 years had a higher operative risk.(table 3) However, this was significant only in overall mortality after all surgical interventions for patients with cancer of the pancreatic head; following resection the difference was not significant. During the last two years of study the operative mortality rate after curative resection has fallen to 2% (n=1) in the last 40 resections.

Table 3 : in-hospital mortality after operation for pancreatic and periampullary cancer

	in-hospital mortality						
	total		age years < 70		age years ≥ 70		p
	(n=242)		(n=164)		(n=78)		
site of tumor	n	%	n	%	n	%	
head of the pancreas							
overall (n=167)	21	13	9	7	12	27	<0.05
after resection (n=50)	4	8	3	7	1	14	n.s.
periampullary region							
overall (n=75)	5	7	1	2	4	17	<0.001
after resection (n=56)	3	5	0	0	3	23	<0.001
total	26	11	10	6	16	21	n.s.

n = number, % = percentage of the total of the subgroup, p = p-value between <70 years of age and ≥70 years of age; log rank test, n.s. = not significant

Pathology

Histological investigation of resection specimen margins revealed a high proportion containing tumor, 18% in cancer of the head of the pancreas and 7% in that of the periampullary region. A tumor-containing resection margin was found in 5 of 10 pylorus-preserving pancreatic resections, but no duodenal resection margins containing tumor were found. Almost all tumors were moderately to poorly differentiated adenocarcinomas. In 56 (72%) patients of 78 patients with liver metastases and in 11 (50%) patients of 22 patients with peritoneal carcinomatosis histological confirmation of the metastases was obtained.

Survival and prognostic factors

Cancer of the head of the pancreas

Overall survival in the group of patients with cancer of the head of the pancreas was 23% at 1 year and 3% at 5 years with a median survival time (MST) of 5.1 months. There were significant differences in survival depending on treatment. When no resection was performed,

1-year survival was significantly shorter compared to palliative resection, 11% and 39% respectively. The longest survival was achieved after intentional curative resection, with survival rates of 56%, 28% and 11% at 1, 2 and 5 years respectively (MST 13.3 months) ($p = < 0.001$, Figure 1). Involvement of local lymph nodes (N1a) did not influence survival after intentional curative resection. In 36 patients with stage N0 and 14 patients with stage N1a cancer, a 1-year survival rate of 61% and 35% and a 2-year survival rate of 28% and 20% respectively were observed ($p=0.43$). Higher age ($p=0.01$) or pain ($p=0.003$) were of prognostic value for overall survival in pancreas cancer, as well as a gamma-glutamyl-transferase level above 250 U/l ($p<0.02$) and a lactate dehydrogenase concentration (LDH) greater than 320 U/l ($p<0.002$). Tumor dimension measured in the resection specimen directly after operation did not have significant prognostic value. In contrast, tumor size measured before operation showed an unexpected trend ($p=0.08$): patients with larger tumors had a trend towards improved survival. A positive resection margin was found in 11 patients after palliative and in 9 patients after curative resection. Following resection with curative intent, survival was not influenced by microscopical tumorgrowth in the resection margin ($p=0.48$). After multivariate analysis of the prognostic factors significant on univariate analysis, age above 70 years, pain and a LDH level over 320 U/l remained of significant value for prognosis as independent factors.

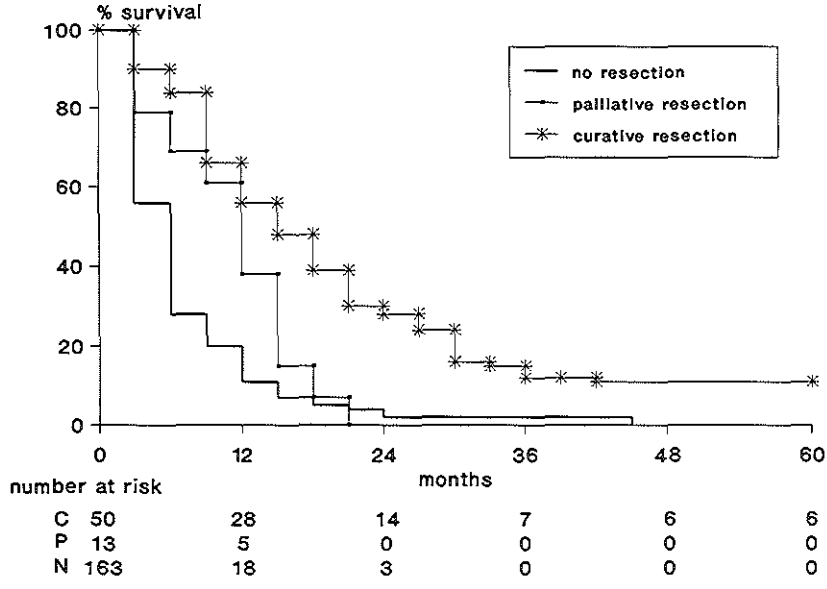
Cancer of the periampullary region

The overall survival rate at 1 year was 65%, at 2 years 45% and at 5 years 28%. Significant improvements in survival were found in this group of patients after both palliative and curative resection compared with no resection ($p<0.001$). After resection with curative intend, survival rates of 78%, 64% and 43% were obtained at 1, 2 and 5 years respectively (median survival of 54.8 months).

There was no difference in survival between 40 patients with stage N0 and 16 with stage N1a cancer, with a 1-year survival rate of 82% and 65%, a 2-year rate of 70% and 50%, and a 5-year rate of 43% and 42% respectively ($p=0.43$). However, comparison of survival in these two groups of patients with Greenwood confidence intervals suggests that a significant difference would be found if more patients were included. Age ($p=0.01$) was a significant prognostic factor for overall survival. Pain ($p=0.83$) and raised gamma-glutamyl-transferase ($p=0.77$), and lactate dehydrogenase level ($p=0.31$) had no influence on survival. Tumor containing resection margins ($p=0.23$) and tumor size ($p=0.24$) had no prognostic value.

Multivariate analysis showed that only an age above 70 years was of prognostic value as an independent factor in periampullary cancer.

Figure 1 : survival related to treatment; no resection, palliative or intentional curative resection in patients with cancer of the head of the pancreas



p<0.001; log rank test, N=no resection, P=palliative resection, C=curative resection

3.1.4 DISCUSSION

Only a small proportion of patients with pancreatic cancer will survive for more than three years after resection. Apparently the tumor process has metastasized beyond the resection area in most patients at the time of surgery, and this cannot be recognized adequately before or during operation. Better selection criteria therefore would be needed to achieve successful

curative surgery. In this retrospective study, an attempt has been made to identify variables that might predict outcome or help to select appropriate patients for surgery. The authors accept the limitations of the method, but prospective controlled studies are currently lacking. The chosen defenition of operative mortality is reliable as it includes all deaths related to operation, not only those occurring in the 30-day period. The operative mortality rate after resection was 8% in patients with cancer of the head of the pancreas. The lack of any difference between those aged more or less than 70 years probably reflects careful selection for operation in the older patients. In periampullary cancer in patients aged under 70 years, there were no postoperative deaths, which is significantly different from the mortality rate of 23% found in patients over 70 years of age ($p<0.001$).[8,9] The operative mortality rate decreased progressively in the last 2 years of study to 2% in the most recent 40 resections. A similar low operative mortality has been reported by others.[7]

Surgical drainage procedures for irresectable tumors carry a high operative mortality rate (about 10%) and should therefore be performed only in the presence of gastric or duodenal obstruction when endoscopic stenting for jaundice is impossible. In this situation, when an operation has to be performed, the addition of gastroenterostomy is advised by some authors.[10-13] The present authors' opinion is that bilioenteric anastomosis should not be combined with gastroenterostomy if the patient has no duodenal obstruction.[14]

Preoperative relief of jaundice by stenting the common bile duct by means of ERCP or PTC resulted in a significant reduction in the number of postoperative laparotomies for bleeding ($p=0.03$), and fewer cases of abscess and anastomotic leakage. Jaundice should be treated as early as possible before operation.[9,15] Resection should be performed only in the non-jaundiced patient.

Non-radical resection was demonstrated in 19 patients by pathological examination, which showed tumor cells in regional lymph nodes outside the resection specimen or even distant metastases. Despite this non-radicality, the prognosis of these patients after palliative resection was significantly better than that in those who underwent surgical drainage or explorative laparotomy. Resection margins that appeared to contain tumor in the definitive pathological resection specimen did not appear to influence survival in the present study. Attempts to avoid non-radical resection by extending the area of excision have not been very promising so far.[5] Recently, however, a study from Japan showed significantly reduced local recurrence rates after extended clearance of regional (R2) lymph nodes.[26]

In the present series of 310 patients admitted for pancreatic or periampullary cancer, potentially curative resection could be performed in only 106 patients (34%). After intentional curative resection for cancer of the head of the pancreas, 56% of patients survived for more than 1 year, and 2- and 5-year survival rates were 28% and 11% respectively. These survival data are similar to those encountered in other studies.[16-25] In a recent review of 4100 pancreas resections for cancer, a 5 year survival of 4% was found.[6]

In the present study, independent prognostic factors for overall survival were found for patients with cancer of the head of the pancreas. Age above 70 years, pain and lactate dehydrogenase level greater than 320 U/l correlated with a decreased survival rate. In periampullary cancer, only age above 70 years remained as independent prognostic factor. In both forms of cancer, tumor size had no prognostic value. Thus, a larger tumor does not necessarily imply a worse prognosis; in the present study, a larger preoperative tumor diameter showed a trend towards a better patient survival rate ($p=0.08$). Tumor infiltration in locoregional lymph nodes (N1a) resected together with the primary tumor did not appear to be of prognostic value in the group of patients with cancer of the head of the pancreas.

In conclusion, pancreatic resection should be performed if technically possible, irrespective of tumor size or tumor infiltration in locoregional lymph nodes (in patients with cancer of the head of the pancreas). Non-radical resection may benefit selected patients, especially during the first year after resection. Although the present study suggests that surgical resection for cancer of the head of the pancreas is largely a palliative procedure, curing only a small proportion of patients, it is a good operation in centres with low operative mortality rates. As postoperative morbidity and mortality are increased in jaundiced patients and in those aged over 70 years, preoperative drainage of bile by endoscopic stenting of the distal common bile duct should be carried out in patients with jaundice and great caution is advised in the elderly.

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3.2

TOXICITY OF ADJUVANT TREATMENT WITH RADIOTHERAPY AND 5-FU AFTER CURATIVE RESECTION FOR CANCER OF THE HEAD OF THE PANCREAS AND PERIAMPULLARY REGION; EORTC PROTOCOL 40891

3.2.1 INTRODUCTION

The incidence of cancer of the pancreas has increased in recent years and is at present the fourth cause of death from cancer in the U.S.A. The prognosis of this kind of cancer is one of the most dismal of all cancers. Until now the only potentially curative therapy is radical surgical resection. After potentially curative resection the one-year survival is 50% to 60%, two year survival 15% to 25% and five-year survival 0% to 20%. In patients with a periampullary carcinoma, located either in the ampulla of Vater, distal common bile duct or duodenum, a much better survival is obtained after surgical resection with a five-year survival of 15% to 40%.[1,6,14,16,18-22,24]

To obtain better survival a number of studies have been performed with radiotherapy, chemotherapy or combined modalities.[3-5,8-10,12,23]

The concept of local and systemic adjuvant treatment in pancreas cancer is interesting, for it can benefit those patients, who have microscopic metastases at the time of operation, which is the case in more than 90% of the operated patients. Metastases occur in the early stage of the disease predominantly at the local and locoregional level with spread along the lymph nodes around pancreas in the hepato-duodenal ligament, mesenterium of transverse colon, in para-aortal lymph nodes, omentum, and in peritoneum and liver.[2,17] Distant metastases in liver and lung are seldom seen without local or intraabdominal tumor spread and are characteristic of late recurrence.

Radiotherapy combined with 5 fluorouracil as adjuvant treatment has been studied by GITSG in a trial in which 14 institutes participated.[13] The high incidence and the large group of participants should guarantee sufficient accrual. However this was not the case, for which explanation was not given. Radiotherapy consisted of a split course of 40 Gy, two courses of 20 Gy with an interval of 2 weeks. 5-FU was given concomitantly during the first week of radiotherapy and during 2 years thereafter. Two-year survival of 21 patients who received adjuvant treatment was 43%, which was significantly better than the control group, in which a two-year survival was 18% ($p < 0.03$). The five-year survival in the treated group was 19% and in the control group 4.5%. This randomized controlled trial demonstrated for the first time that prolonged survival can be obtained by adjuvant treatment after surgical resection of pancreas cancer, however, only demonstrated in a relatively small number of patients. The survival in the control group is comparable to the survival described in other studies.[1,6,14-

[16,18-22,24] The randomized GITSG trial has been discontinued after the intake of these 43 patients because of low accrual. At present no other randomized adjuvant trial in pancreas cancer has been reported in the U.S.A. or in Europe. In addition another 30 patients were treated with the same adjuvant treatment of irradiation and 5-FU, with similar results (2-year survival: 46%).[11]

Aim of this report is to show the low toxicity after radiotherapy and 5-FU as adjuvant treatment after curative resection for cancer of the head of the pancreas and periampullary region.

3.2.2 MATERIAL AND METHODS

A prospective randomized trial was started in september 1987 in collaboration with the EORTC with two groups of patients to study the effect of adjuvant treatment of loco-regional radiotherapy and 5-FU treatment in pancreatic cancer. A stratification was made in two groups of patients: cancer in the pancreatic head and cancer in the periampullary region. Eligibility criteria are carefully described in the protocol. Patients were randomized recruited from 22 centers in Europe. Before randomization an eligibility checklist is checked. All the data were collected in a central database in the EORTC Data Center.

The only modification in the treatment schedule as compared with the GITSG study is a reduction in the 5-FU therapy, as 5-FU therapy is limited to the periods of radiation therapy. Patients with periampullary carcinoma were also eligible for this study, as it is quite possible that these patients may also benefit from this adjuvant treatment. In many respects the behavior is similar to that of pancreatic cancer and the surgical resection is similar in the two types of cancer. A Whipple's procedure, pylorus preserving pancreatoduodenectomy or a total pancreatectomy is the method of choice for resection. The adjuvant treatment must start within 8 weeks after resection.

Radiation therapy

Three or four fields technique is preferred to opposite AP-PA fields. Dose in liver, kidneys and spine must not exceed the tolerance of these normal tissues. Megavoltage photon irradiation of at least 6 MV energy is used. All fields are treated daily. The absorbed daily dose is 2 Gy, 5 fractions a week during 2 weeks. After an interval of two weeks, the treatment is repeated, the total absorbed dose is 40 Gy.

Chemotherapy

Chemotherapy is started on the same day prior to radiotherapy and consists of 25 mg/kg/24 hours 5-FU with a maximum dose of 1500 mg a day. Depending on toxicity the second cycle consists of 0, 3 or 5 days of 5-FU administration. No 5-FU treatment during the second cycle of radiotherapy was given in case of grade 3 or 4 toxicity, 3 days of 5-FU in case of grade 1 or 2 toxicity and 5 days of 5-FU when no toxicity occurred. Toxicity is scored as proposed by the World Health Organization (table 1).

Table 1 : recommendations for grading toxicity according to the World Health Organization (WHO)

grade toxicity	0	1	2	3	4
mucositis	none	soreness	erythema	ulcers	alimentation not possible
nausea/vomiting	none	nausea	vomiting	vomiting	intractable vomiting
			therapy +		
diarrhea	none	transient	tolerable	intolerable	hemorrhagic dehydration
constipation	none	mild	moderate	distention	distention and vomiting
drug fever	none	< 38 °C	38 °C-40 °C	> 40 °C	fever with hypotension
cutaneous	none	erythema	pruritus	ulceration	exfoliative dermatitis
hairloss	none	minimal	moderate	alopecia	nonreversible alopecia
infection	none	minor	moderate	major	major with hypotension
WBC ($x10^9$/l)	> 4	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
platelets ($x10^9$/l)	> 100	75-99	50-74	25-49	< 25

3.2.3 RESULTS

Between september 1987 and june 1993, 153 patients were randomized to the EORTC trial 40891 (76 patients in the control arm and 77 patients in the radiotherapy/5-FU arm). Among the 77 patients randomized to the treatment arm, data are available for 47 patients. The reason for missing data in 30 patients is shown in table 2. Six patients refused treatment after randomization. In 7 patients there were other reasons for not starting treatment, in 3 patients postoperative complications, in 2 the discovery of distant metastases, in one renal dysfunction prohibiting radiation therapy and one patient found to be ineligible because of metastatic prostate cancer. Total dose of radiotherapy is shown in table 3, only 5 patients did not receive

Table 2 : available treatment data

	n	
total number of patients	77	
available data	47	
no available information after randomization	14	
too early (randomized after march 1993)	3	
patients refused treatment	6	
problems before start treatment	7	
postoperative complications[#]		3
metastases[*]		2
renal dysfunction		1
found to be ineligible (metastatic prostate cancer)		1

[#] : one patient had lung embolism and died 25 days after surgery, one patient had severe bleeding and fever with relaparotomy, one peri-operative death due to septic shock
[*] : liver metastases in one patient and supra-clavicular nodes in the other

Table 3 : total dose of radiotherapy

total dose (Gray)	n
20	2[*]
30	1
34.8	1
39.2	1
40	42

[*] : 2 patients who had only one course, n = number

Table 4 : percentage of 5-FU actually given relative to the maximum theoretical dose

dose percentage	n	%
≤ 50	4	8
51-70	4	8
71-90	28	60
91-100	5	10
> 100	6	13

n = number, % = percentage of total number

the full dose of 40 Gy. Total dose of 5-FU varied between 3000 mg and 16000 mg with a median of 12000 mg. When corrected for the body weight, the total dose varied between 30 mg and 208 mg with a median of 130 mg/kg body weight. We considered the maximum theoretical dose of 5-FU in the protocol to be 25 mg x body weight in kg x a maximum of 9 days taking into account that a total daily dose should not exceed 1500 mg. So the maximum theoretical dose was limited to 13500 mg (1500 mg x 9 days (4 days for the first course and a maximum of 5 days for the second course)). The total given dose of 5-FU expressed as a percentage of the maximum theoretical dose varied between 22% and 118% with a median of 88% (table 4). The toxicity results are given in table 5, a very low number of toxicities were seen, the highest WHO grade of toxicity was grade 3. Nausea and vomiting were the most frequent occurring toxicity, it is not yet clear if this complication is due to the radiotherapy or the 5-FU administration or the disease itself. All but one toxicities were easily managed with conservative methods. Mild leucopenia occurred in 15 patients and was completely reversible after discontinuation of therapy at the end of the cycle. One patient developed severe upper abdominal pain at the end of the first radiotherapy course due to a duodenal ulcer, it was treated by antacids and H2-blockers. After six weeks this patient still had duodenal ulceration, reason for discontinuation of therapy. Life-threatening toxicities did not occur.

Table 5 : toxicity after radiotherapy and 5-FU therapy, graded according the WHO (table 1), numbers of patients are given

grade toxicity	0	1	2	3	4	missing data
performance status	41	5	-	1	-	-
mucositis	46	-	1	-	-	-
nausea/vomiting	26	16	2	3	-	-
diarrhea	40	5	1	-	-	1
constipation	44	2	-	1	-	-
drug fever	45	2	-	-	-	-
cutaneous	43	4	-	-	-	-
hairloss	45	1	1	-	-	-
infection	47	-	-	-	-	-
WBC ($x10^9/l$)	32	14	1	-	-	-
platelets ($x10^9/l$)	43	3	-	-	-	1

number of patients

3.2.4 DISCUSSION

Survival in case of cancer of the head of the pancreas and even in the periampullary region is dismal, with 2-year survival of 15-25%. If the tumor is resectable, the incidence of local recurrence is high independent of the type of resection performed, up to 80%, in most cases combined with distant metastases.[1,6,14-16,18-22,24] To improve survival all therapeutic modalities have been used, radiotherapy, chemotherapy and combinations of both in case of irresectable and resectable disease with varying success.[3-5,8-10,12,23] The first study showing some effect of adjuvant treatment was the GITSG trial.[13] Two-year survival was 43% after adjuvant treatment, significantly better than after surgery alone (18%,$p<0.03$). Another 30 patients were treated with the same treatment schedule with comparable results.[11]

To subscribe to the former results in a larger group of patients we initiated a prospective randomized trial in 1987 in collaboration with the EORTC to study the effect of adjuvant treatment with radiotherapy and 5-FU. The only modification compared to the GITSG trial is a reduction in 5-FU therapy, the 5-FU treatment is limited to the first week of each radiation cycle. The results presented here are the first data on toxicity after adjuvant treatment in such a large consecutive series of patients. From 77 patients randomized for adjuvant treatment, data of 47 patients are available. When using prerandomization, one of the problems is patients' refusal of treatment. Nevertheless, it seems to be ethically correct to prerandomize, of course depending on the ethical committee in the different centers participating. The total dose of radiotherapy could be given in all patients but two. The median total administrated dose of 5-FU was 88% of the maximum theoretical dose. Of course, when radiotherapy was discontinued, 5-FU was also discontinued. Overall toxicity was low, the highest WHO-grade of toxicity was 3, but all mild toxicities were treated with conservative methods. No life-threatening toxicities occurred in the 47 treated patients. These results of toxicity are reassuring. Nearly all patients could be treated postoperatively with the adjuvant regimen. Although retrospectively, 2 other recent studies confirm our toxicity results after adjuvant treatment with radiotherapy and 5-FU.[7,25]

In conclusion, radiotherapy combined with 5-FU as adjuvant treatment after resection of cancer of the head of the pancreas and periampullary region is very well tolerated. The results on locoregional recurrence and survival of this treatment regimen have to be awaited.

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CHAPTER 4

PYLORUS PRESERVING PANCREATODUODENECTOMY

THE ADVANTAGES OF PYLORUS PRESERVING PANCREATODUODENECTOMY IN MALIGNANT DISEASE OF THE PANCREAS AND PERIAMPULLARY REGION

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4.1 INTRODUCTION

Since Whipple et al. in 1935 described the first resection of the head of the pancreas for malignant disease many modifications have been reported.[1] Watson et al. described the first pylorus preserving pancreatoduodenectomy (PPPD) in 1944.[2] However, this technique was not applied until Traverso and Longmire in 1978 used the PPPD in two patients.[3] The expected advantages of the PPPD above the standard Whipple's resection with partial gastrectomy were less dumping, improved gastrointestinal function and reduced jejunal ulceration. On the other hand, prolonged hospital stay because of delayed gastric emptying has been reported. Furthermore, in malignant disease, radicality of the PPPD has been argued with respect to the duodenal resection margin.[4-9]

We reviewed the hospital charts of patients with cancer of the pancreas head or periampullary region after resection by means of standard Whipple's procedure or pylorus preserving pancreatoduodenectomy during the period 1984-1990. Both treatment modalities were compared with respect to radicality of the resection, morbidity and mortality.

Aim of this study was to establish whether PPPD is a safe and radical procedure in malignant disease of the head of the pancreas and periampullary region, with acceptable morbidity and mortality compared to the standard Whipple's procedure.

4.2 MATERIAL AND METHODS

From 1984 to 1990 113 patients underwent a Whipple's resection or pylorus preserving pancreatoduodenectomy (PPPD), 13 patients for a benign disease like pancreatitis or villous adenoma of the pancreas or duodenum and 4 patients for malignant disease of other origin than pancreas head or periampullary region. Ninety-six patients underwent Whipple's resection or PPPD for cancer of the head of the pancreas or periampullary region. None of these patients underwent total pancreatectomy. In 4 patients a resection was performed despite of tumor growth in lymph nodes outside the resection area (N1b) and in one patient with livermetastases. These patients were excluded for analysis.

This study concerned 91 patients with cancer of the head of the pancreas (n=50) or periampullary region (n=41), 34 women and 57 men with a mean age of 60 years. In 45 patients a standard Whipple's resection with partial gastrectomy was performed, in 46 patients

a pylorus preserving pancreatoduodenectomy (PPPD). In the group of patients with cancer of the head of the pancreas (n=50) 25 PPPD resections and 25 standard Whipple's resections were performed. In the group of patients with periampullary cancer (n=41) 21 PPPD resections and 20 Whipple's resections were performed.

For reconstruction after the standard Whipple's resection a Roux-en-Y jejunal loop was used with an end-to-side or end-to-end pancreatojejunostomy with a one layer inverting running suture of pancreatic tissue to the jejunum. An end to side choledochojejunostomy was constructed on the same jejunal loop, also with a one layer running suture. An end-to-side gastrojejunostomy was constructed with the other part of the Roux-en-Y jejunal loop. Only one jejunal loop was used after PPPD with an end-to-side one layer running inverting pancreatojejunostomy and an end-to-side choledochojejunostomy. Finally an end-to-side duodeno-enterostomy with an one layer running suture was performed on the same jejunal loop. Stents were never used for the pancreatic or bile duct. Postoperatively prophylactic antacid medication by ranitidine was given to all patients after PPPD and in selected cases after standard Whipple's procedure.

Operative mortality was defined as death during the first admission period. T.N.M. Staging (UICC 87) was used, with a modification for the N-stage. Stage N1a indicating positive lymph nodes within the resection specimen and stage N1b indicating positive lymph nodes outside the resection specimen. During follow up locoregional and/or distant metastases were demonstrated by means of ultrasound and/or computertomography with or without fine needle aspiration biopsy or histology. Median follow up was 25 months, ranging from 1 month to 67 months.

Data on location of tumor, blood loss and duration of operation were obtained. Postoperatively information on days of gastric suction, days of liquid nutrition and days of normal nutrition, occurrence of ulcer disease and gastric stasis were obtained. Pathological examination of the resection specimen was performed with special attention to the resection margins. All resection margins were reviewed by one pathologist. During follow up in the outpatients department, information on nutritional status, weight, ulcer disease with or without medication, locoregional recurrence and distant metastases was obtained.

In table 1 data on gender, age, tumor localization and TNM staging of both treatment groups are presented. There were no significant differences between the two groups with respect to any of these parameters.

Quantitative data were compared using Mann-Whitney's test. The Chi-square test was used in case of qualitative data. Survival was calculated and compared using life-table methods (Kaplan Meier, logrank test). The limit of statistical significance was considered to be $p \leq 0.05$ (two-sided).

Table 1 : various patients characteristics according to treatment

		treatment	
		PPPD	Whipple
characteristic		n (%)	n (%)
gender	male	30 (64)	27 (61)
	female	17 (36)	17 (39)
age mean (range)	years	62 (41-79)	60 (27-78)
localization	head	26 (55)	24 (55)
	periamp.	21 (45)	20 (45)
T-stage	T1	9 (19)	13 (29)
	T2	34 (72)	24 (55)
	T3	4 (9)	7 (16)
N-stage	N0	34 (74)	28 (65)
	N1a	12 (26)	15 (35)

n = number, % = percentage of the total of the subgroup

4.3 RESULTS

Median duration of the operation performed in the PPPD group of patients was 210 minutes (range 160-270 minutes) with a median blood loss of 1800 ml (range 850-3050 ml). In the group of patients with a standard Whipple resection median operation time was 255 minutes (range 180-335 minutes) and median blood loss was 2500 ml (range 1400-3600 ml). This difference was significant for duration of operation and blood loss. In-hospital mortality was 2% (1/47) after PPPD and 5% (2/44) after standard Whipple's resection. Morbidity after resection did not differ significantly with respect to days of gastric suction, start of liquid meals, normal meals and complaints of duodenal or gastric ulceration. Postoperative complications and reexplorations were similar in both groups of patients, leakage of the pancreaticojejunostomy occurred 2 times in the group of patients after PPPD, 5 times after standard Whipple resection. Hospital stay was significantly shorter after PPPD than after Whipple's resection (median 14 days (range 8-85 days) and median 19 days (range 9-184

days)(table 2). The TNM classification was similar in both groups of patients. Review of the duodenal resection margins in the group of patients after PPPD revealed in 2 patients tumor containing resection margins, after standard Whipple resection in 2 patients a tumor containing duodenal resection margin was found. Considering all the resection margins, including pancreas and common bile duct, no differences were observed. In patients after standard Whipple's procedure or PPPD with cancer of the head of the pancreas significantly more tumor containing resection margins were found compared to the patients with

Table 2 : direct postoperative course according to treatment

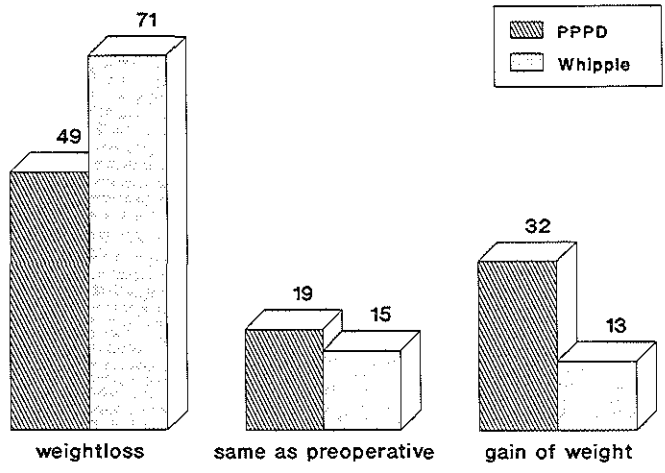
	PPPD (n=47) median (range) days	Whipple (n=44) median (range) days
gastric suction	4 (1-39)	4 (1-45)
liquid diet	7 (1-39)	7 (3-45)
normal diet	9 (2-39)	9 (6-71)
hospital stay	14 (8-85)	19 (9-184)*
	n (%)	n (%)
ulcer disease	3 (6)	1 (2)
antacid medication	30 (64)	18 (41)*
abscess wound	2 (4)	1 (2)
abscess intra-abdominal	5 (11)	3 (7)
bleeding	2 (4)	2 (5)
leakage pancreatojejunostomy	2 (4)	5 (11)
relaparotomy	11 (23)	17 (39)

*: $p<0.05$ (Mann-Whitney's test), n = number, % = percentage of the total of the subgroup

periampullary cancer ($p=0.02$). During follow up, with a mean duration of follow up of 25 months (range 1-67), no differences were found with respect to complaints of ulcer disease. Significantly more patients after PPPD received antacid medication as this was prescribed routinely. Weight changes after operation during follow up in the outpatients department were significantly more favorable after PPPD (figure 1). Locoregional recurrence was found 8 times after PPPD and 11 times after Whipple's resection. No influence was seen of tumor containing resection margins in case of local recurrence: in 5 out of 13 patients local recurrence was found in case of tumor containing resection margins, in 14 out of 75 patients

when the resection margins were negative. Calculated by life-table methods, differences were

Figure 1 : weight changes during follow up in the out-patients department



Data given are percentages of patients. Postoperative deaths are excluded. Mann-Whitney's test overall p=0.02.

Table 3 : number of patients with local recurrence, livermetastases, other metastases or peritonitis carcinomatosa according to localization

	head of pancreas n=50	periampullary n=41	significance (log rank)
local recurrence	13 (36)	6 (11)	p=0.04
liver metastases	18 (43)	5 (15)	p<0.01
other metastases	13 (55)	7 (21)	p=0.06
peritonitis carcinomatosa	12 (31)	1 (5)	p<0.01

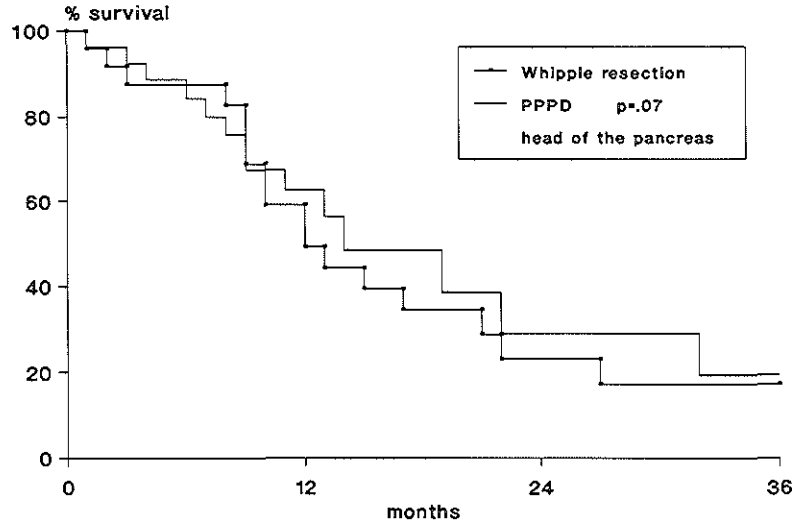
( ) : Cumulative (life-table) percentage at 3-years, n = number

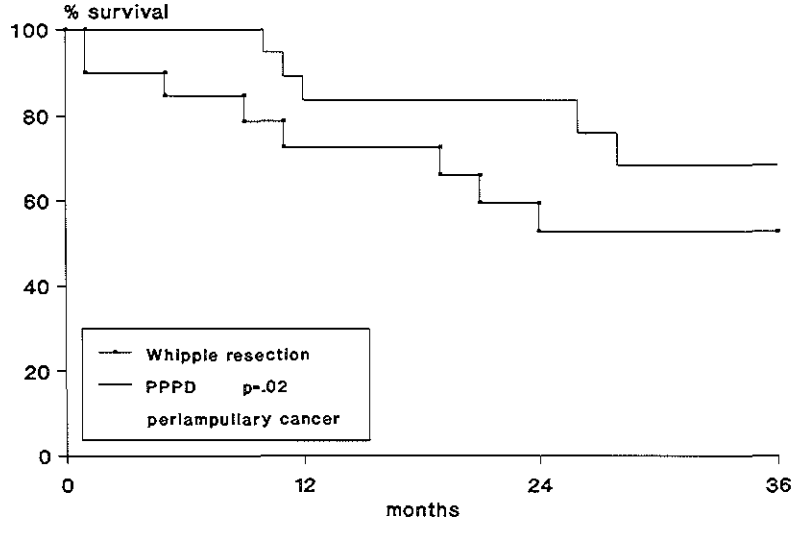
not significant. Local recurrence was found after a mean follow up of 11 months (range 3-38 months). Liver metastases were found after a mean of 10 months (range 3-19 months) in 13 patients after PPPD and in 10 patients after Whipple's resection. Metastases elsewhere and

peritonitis carcinomatosa were found in 18 patients after PPPD and 15 patients after Whipple's resection, a mean of 12 months and 11 months respectively (range 2-29 months and 2-38 months)(table 3). In patients with cancer of the head of the pancreas local recurrence, livermetastases, metastases elsewhere and peritonitis carcinomatosa were found significantly more, survival was also significantly shorter in this group of patients irrespective of type of resection performed(figure 2).

No difference in survival was found after PPPD or standard Whipple's procedure with a one year survival of 56% for both groups of patients and two year survival of 38% after PPPD and 26% after Whipple's procedure ($p=0.18$). Cause of death was recurrence of disease in 35 patients, 3 patients died of other causes than malignancy. Eleven patients are alive with local recurrence of disease and/or distant metastases.

Figure 2 : survival according to treatment for patients with cancer of the head of the pancreas (upper panel) and periampullary region (lower panel)





4.4 DISCUSSION

Presently the standard procedure for malignancy of the head of the pancreas or periampullary region is the Whipple's resection.[1] To reduce postoperative morbidity and mortality Traverso and Longmire in 1978 reintroduced the pylorus preserving pancreatoduodenectomy after Watson proposed this technique first in 1944.[2,3] Expected advantages of this procedure were less dumping, improved gastrointestinal function and reduced jejunal ulcera. Postoperative gain of weight and a better quality of life were reported.[4,5,8,10-13] Some authors doubted radicality of PPPD, others mentioned a prolonged hospital stay mainly as a result of delayed gastric emptying.[7,14-16] Grace et al. reported in 1990 that PPPD is a safe and radical procedure with less morbidity and mortality in patients with benign and malignant disease in the periampullary region.[9] During the study period we were in the unique situation to compare the two techniques in a comparable group of patients. Duration of operation and blood loss during operation were significantly less after PPPD. Operative mortality of both procedures was not significantly different. In particular no great differences were observed with respect to gastric emptying and complaints of ulcer disease, claimed to be disadvantages of PPPD. Moreover, hospital stay was significantly shorter after PPPD. Surgical complications and the need for reexplorations were similar in both groups of patients.

As discussed before, irradicality and locoregional recurrence might be expected more frequently after PPPD. However, in our series no difference was observed in tumor containing resection margins, all reviewed by one pathologist. Locoregional recurrence was observed in 11 patients (20%) after Whipple's procedure, in 8 patients (17%) after PPPD, in similarly staged patients according to the TNM staging. During follow up in the out-patient department ulcer disease occurred equally in both groups. More patients in the PPPD group received antacid medication because it was given routinely as prophylaxis. Gain of weight appeared to be significantly better in patients after PPPD. No difference in survival was observed between the two groups of patients after intentionally curative resection. There was also no difference in postoperative in-hospital mortality, respectively 2% after PPPD and 5% after standard Whipple's procedure. In conclusion, PPPD can be a radical and safe procedure for cancer of the head of the pancreas and periampullary region. No difference in morbidity and mortality was found between the two procedures. Advantage of the PPPD is an easier and less time consuming operation, with less blood loss and a shorter hospital stay. During follow up gain

of weight appears better after PPPD. Therefore, quality of life seems to be better, which is especially of importance when life expectancy is so low.

4.5 APPENDIX

As a result of the retrospective study as shown in this chapter, a prospective randomized multicenter study has already started. The objective of this trial is to compare the pylorus preserving pancreatoduodenectomy and the standard Whipple's procedure in a prospective randomized study. A comparison will be made in operative blood loss, length of operation, peri-operative mortality, postoperative morbidity, hospital stay and long-term results.
The patients will be randomized during operation as soon as it is evident that both techniques are feasible. After operation the first information form will be completed. The second information form will be completed after discharge from the hospital or in case of in-hospital death. During scheduled visits to the outpatient department follow-up inquiries will be made.

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CHAPTER 5

PROGNOSTIC INDEX

PROGNOSTIC INDEX IN CANCER OF THE HEAD OF THE PANCREAS

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submitted

5.1 INTRODUCTION

Despite efforts to diagnose cancer of the head of the pancreas in an earlier stage of disease and decreasing morbidity and mortality after resection, there is still a bad prognosis with a 5-year survival rate ranging from 0% to 20%.[1-7] More radical resections as proposed by Fortner only increased morbidity and mortality and did not change survival rate.[8] The most recent trend in surgery of carcinoma of the head of the pancreas is a more limited resection with preservation of the pylorus instead of a partial resection of the stomach as described by Whipple. Survival, however, is not modified by this technique and remains dismal.[9-11] Nevertheless, resection of the tumor is the only possible way to cure patients with pancreatic carcinoma, but it has been difficult to select those patients who will benefit from surgery. In previous studies a number of prognostic factors have been mentioned as age, sex, duration of symptoms, size of the tumor, TNM-stage, blood loss etc., without being conclusive. A large tumor and/or microscopical tumor in the resection margin does not per se imply a worse survival rate.[6,7,12-20]

In order to select patients who will benefit from surgical treatment and to predict overall survival after resection, a multivariate analysis has been performed in 203 patients with cancer of the head of the pancreas admitted to the University Hospital Rotterdam-Dijkzigt during the period 1977 to 1988. The overall group of patients and the patients after resection have been analyzed separately. A decision tree is suggested to determine proper patient selection based on the independent prognostic factors.

5.2 MATERIAL AND METHODS

Between January 1977 and December 1988 226 patients with cancer of the head of the pancreas were admitted to the University Hopital Rotterdam-Dijkzigt. Fifty-nine patients had distant metastases or a performance scale of 3 or 4 according to the WHO classification at the time of diagnosis. A palliative procedure as explorative laparotomy, biliary and/or gastric bypass or palliative resection was performed in 117 patients; 59 patients underwent no operation at all. Fifty patients underwent an intentional curative resection. Twenty-three patients with unknown M-stage of disease were excluded from analysis. The mean age of all the patients included was 62 years (sd 11 years, range 32-88 years), 122 men and 81 women.

Information on history, preoperative diagnostic procedures, intraoperative data, pathological examination and follow-up was obtained and statistically analyzed using the method of Kaplan and Meier, the log rank test and Cox's proportional hazards model; statistical significance in the Cox's model was defined as a p-value <0.10.[21,22] Pain is considered to be pain in the back and/or upper abdomen. Preoperative diagnostic procedures consisted of ultrasound and computertomography of the abdomen, endoscopic retrograde cholangiopancreatography (ERCP) and in some patients a percutaneous transhepatic cholangiography (PTC). Liver and renal function were evaluated as lactate dehydrogenase (LDH), gamma-glutamyl-transpeptidase, aspartate-aminotransferase (ASAT), alanine-aminotransferase (ALAT) and bilirubine. Pathological anatomical examination was done revealing tumor size, TNM-stage and differentiation of the tumor. Four grades of differentiation were found: good, moderate, bad or undifferentiated. Cox's proportional hazards model was used also for deriving a prognostic index. With this multivariate technique a linear combination of significant prognostic factors can be calculated, which relates the outcomes of the combination of these factors with survival. The survival function for an individual patient can be written as: $S(t) = \{S_0(t)\}^{\exp\{\text{index i}\}}$, where $\text{index}_i = \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_p x_{ip}$ is the prognostic index for the individual patient i with outcomes $x_{i1}, x_{i2}, \ldots, x_{ip}$ for p prognostic factors; $\beta_1, \beta_2, \ldots, \beta_p$ are estimated constant values. $S_0(t)$ is the baseline survival function for all prognostic outcomes equal zero. All calculations were done with the personal computer program STATA 3.0.[Computer Research Center, Santa Monica, California, 1992] In-hospital mortality was defined as death during the first admission period in the hospital, including the thirty-day mortality. T.N.M. staging after operation was defined as proposed by the UICC 1987, with a modification for the N-stage, stage N1a indicating tumor containing lymph nodes within the resection specimen and N1b outside the resection specimen.[23] Resection was performed as a standard Whipple procedure (n=30), total pancreatectomy (n=12) or pylorus preserving pancreatoduodenectomy (n=8).

5.3 RESULTS

The analysis of the patients'records consists of two parts: 203 patients with cancer of the head of the pancreas with known M-stage and a subgroup of 50 curatively operated patients. Median survival time was 5 months; 1-year, 2-year and 5-year percentages of survival were

Table 1: univariate analysis of 20 factors in 203 patients with cancer of the head of the pancreas. *: only patients after resection, palliative resections included

factor	n	grouping	median survival time (months)	1-year survival %	p-value
overall	203		5.1	24	-
age	146	< 70 years of age	5.7	27	0.004
	57	≥ 70 years of age	3.3	12	
sex	122	male	4.8	19	0.24
	81	female	5.4	29	
pain	60	no	9.1	37	0.0008
	143	yes	4.1	17	
weight loss	27	≤ 4 kg.	5.0	24	0.96
	176	> 4 kg.	5.1	23	
gastric obstruction	145	no	5.5	25	0.16
	58	yes	3.5	18	
jaundice	59	no	4.1	17	0.04
	144	yes	5.5	26	
diabetes	167	no	4.8	24	0.99
	36	yes	5.1	21	
gallbladder	128	not palpable	5.2	24	0.06
	45	palpable	5.5	19	
	21	earlier removed	2.3	12	
gamma-GT	42	≤ 35 U/l	4.5	18	0.40
	161	> 35 U/l	5.1	25	
LDH	137	≤ 320 U/l	5.4	25	0.01
	66	> 320 U/l	3.4	19	
drainage of bile	117	no	4.2	20	0.01
	86	yes	6.1	28	
duration of operation	158	≤ 4 hours	4.1	18	0.0003
	45	> 4 hours	9.8	42	
blood loss	163	≤ 2000 ml.	4.2	19	0.002
	40	> 2000 ml.	9.4	41	
tumor size*	15	≤ 3.5 cm.	9.8	40	0.09
	39	> 3.5 cm.	5.2	16	
resection margin*	41	negative	13.3	51	0.58
	20	positive	12.3	50	
T-stage	25	T1	9.7	44	<0.0001
	40	T2	9.5	45	
	85	T3	4.8	16	
	53	Tx	2.5	7	
N-stage	43	N0	15.3	56	<0.0001
	24	N1a	9.7	36	
	26	N1b	2.5	8	
	110	Nx	3.8	10	
M-stage	109	M0	9.5	39	<0.0001
	94	M1	2.5	5	
tumor differentiation	137	good/moderate	5.2	24	0.28
	66	bad/undifferentiated	4.1	23	
blood transfusions	184	≤ 5 units	4.6	22	0.22
	19	> 5 units	9.4	34	

24%, 8% and 3% respectively. In-hospital mortality overall was 10%. Twenty potential prognostic factors have been analyzed in an univariate analysis for all patients (table 1). Tumor size and resection margins were not significant factors. Using Cox's proportional hazards model, only four factors in the overall group of patients were independent prognostic factors: age under 70 years(=0) or 70 years and above(=1), pain (no=0,yes=1), LDH ≤ 320 U/l(=0) or > 320 U/l(=1) and nonmetastatic(=0) or metastatic disease(=1) (table 2).

Table 2: Cox's proportional hazards model for 4 prognostic factors in 203 patients with cancer of the head of the pancreas.

factor	n	grouping	coëfficient ± SE	p-value
age	146	< 70 years of age	.56 ± .17	0.001
	57	≥ 70 years of age		
pain	60	no	.53 ± .18	0.004
	143	yes		
LDH	137	≤ 320 U/l	.55 ± .16	<0.001
	66	> 320 U/l		
M-stage	109	M0	1.32 ± .17	<0.001
	94	M1		

It appears that M-stage has the strongest prognostic impact, while age, pain and LDH each have a smaller and similar contribution to survival. The related Kaplan Meier survival curves of these 4 factors are shown in figure 1. The prognostic index for an individual patient can now be calculated as: index= .56 x age(0 or 1) + .53 x pain(0 or 1) + .55 x LDH(0 or 1) + 1.32 x M-stage(0 or 1). For example, a patient with pain, under 70 years of age, LDH below 320 U/l and M1-stage has an index value of .53 + 1.32 = 1.85. For all possible (2^4=16) outcomes of the prognostic factors a separate survival curve can be calculated. Figure 2 shows these curves for extreme values of the index (index=0 and index=2.96) and two intermediate values (index=.57 and index=1.64). Using this method three regions of different survival results can be distinguished. The first region has a relatively good prognosis (M0 and at most one of the other 3 factors present), the third region has a poor prognosis (M1 and at least one of the other 3 factors present) and the second region has a relatively moderate prognosis (all other cases). Thus, it is possible to predict survival outcome of a patient with minimal diagnostic modalities as LDH measurement and an ultrasonography of the abdomen.

Figure 1: **Kaplan Meier survival curves for 4 prognostic factors age, pain, LDH and M-stage of disease in 203 patients with cancer of the head of the pancreas.**

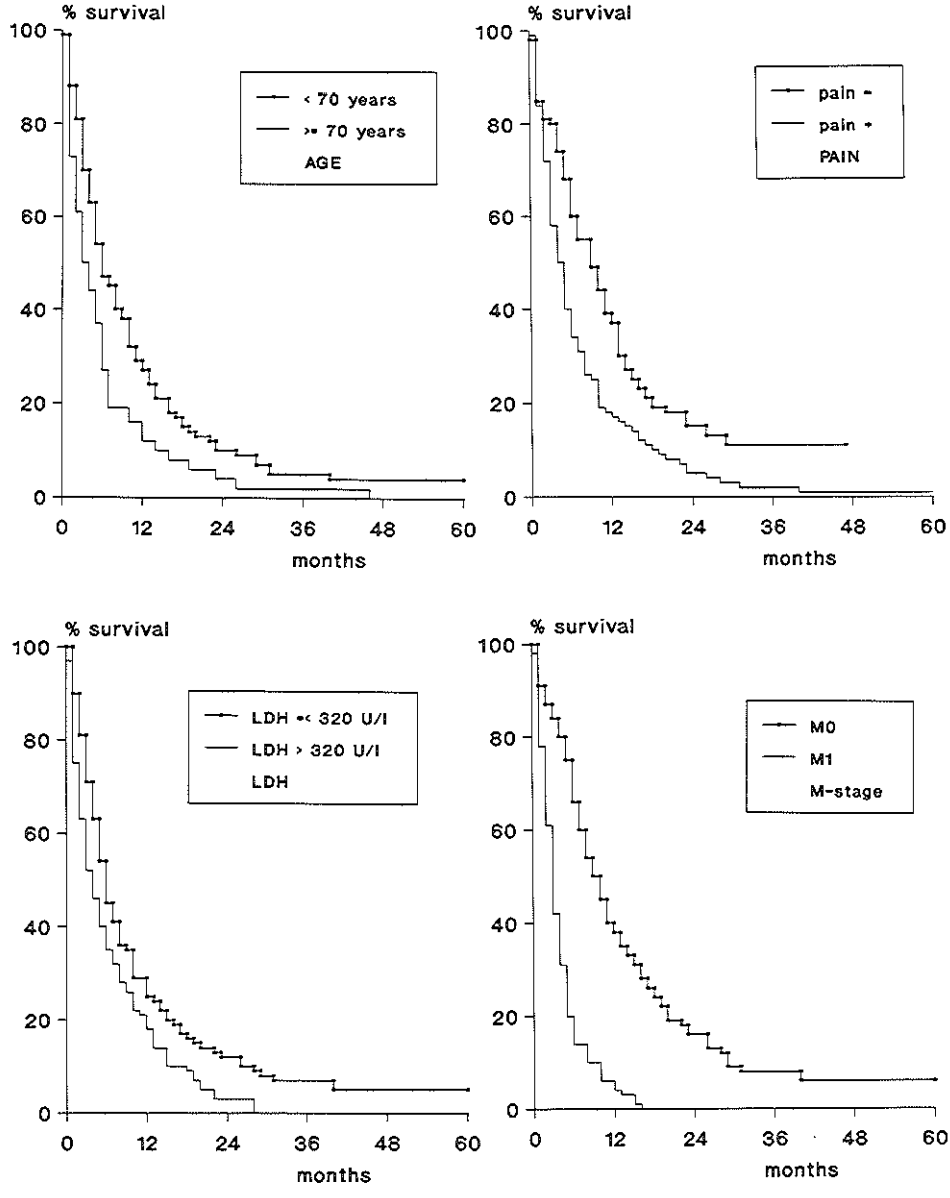
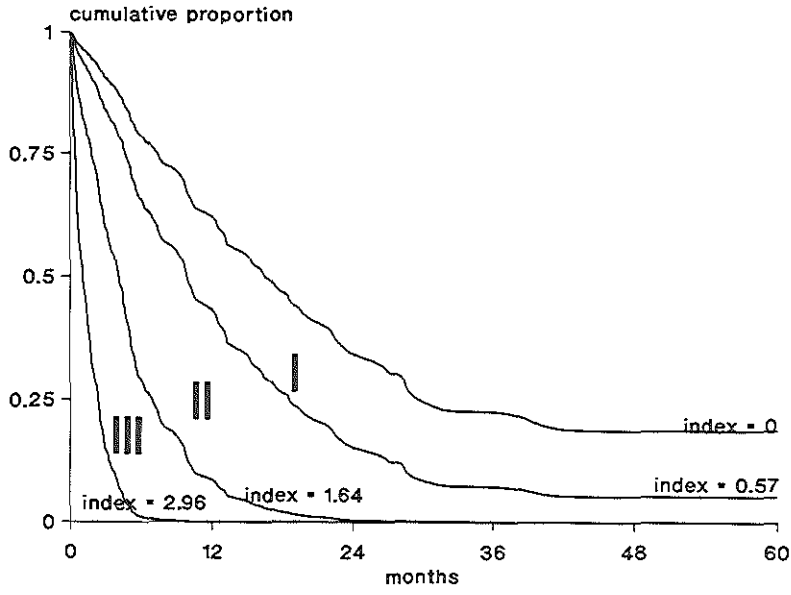


Figure 2: prognostic index and 3 regions of survival in 203 patients with cancer of the head of the pancreas.



region I : M0 and at most one of the other 3 factors present (age, pain, LDH)
region III : M1 and at least one of the other 3 factors present (age, pain, LDH)
region II : all other cases

If a resection was performed, the same procedure as described above can be used. Median survival time was 13 months; 1-year, 2-year and 5-year percentages of survival after resection were 54%, 26% and 8% respectively. In-hospital mortality was 8%. The same 20 factors were analyzed univariately for the patients after resection (n=50); in table 3 the grouping, median survival, 1-year-survival and corresponding p-value of the most important factors is given. Only LDH ≤ 320 U/l(=0) or > 320 U/l(=1), duration of operation 4 hours or less (=0) or longer than 4 hours.(=1) and differentiation of tumor divided in good/moderate(=0) or bad/undifferentiated(=1) have been found of independent prognostic value (table 4). The Kaplan Meier survival curves of these 3 prognostic factors are shown in figure 3. In the same way as depicted above, the prognostic index can be calculated in the resected group of patients: index= .86 x LDH(0 or 1) + .97 x duration of operation(0 or 1) + .60 x

differentiation(0 or 1). For example a patient with LDH over 320 U/l, duration of operation less than 240 min. and a bad differentiation has an index value of .86 + .60 = 1.46. Again, for all possible (2^3=8) outcomes of the prognostic factors a survival curve can be drawn. In figure 4 the index=0, index=2.43 and an intermediate value of the index (index=1.46) are shown. This results in two regions of prognosis after resection. The first region with a relatively good outcome (at most one factor present) and a second region with a relative poor outcome (two or three factors present) after resection.

Table 3: univariate analysis of 3 prognostic factors in 50 patients with cancer of the head of the pancreas after curative resection.

factor	n	grouping	median survival time (months)	1-year survival %	p-value
overall	50		13.3	54	-
LDH	33	≤ 320 U/l	17.4	61	0.03
	17	> 320 U/l	11.3	38	
duration of operation	15	≤ 4 hours	26.9	75	0.03
	35	> 4 hours	10.4	43	
tumor differentiation	31	good/moderate	17.4	61	0.12
	19	bad/undifferentiated	7.6	39	

Table 4: Cox's proportional hazards model for 3 prognostic factors in 50 patients with cancer of the head of the pancreas after curative resection.

factor	n	grouping	coëfficient ± SE	p-value
LDH	33	≤ 320 U/l	.86 ± .35	0.017
	17	> 320 U/l		
duration of operation	15	≤ 4 hours	.97 ± .39	0.016
	35	> 4 hours		
tumor differentiation	31	good/moderate	.60 ± .33	0.072
	19	bad/undifferentiated		

Figure 3: **Kaplan Meier survival curves for 3 prognostic factors LDH, duration of operation and tumordifferentiation in 50 patients with cancer of the head of the pancreas after resection.**

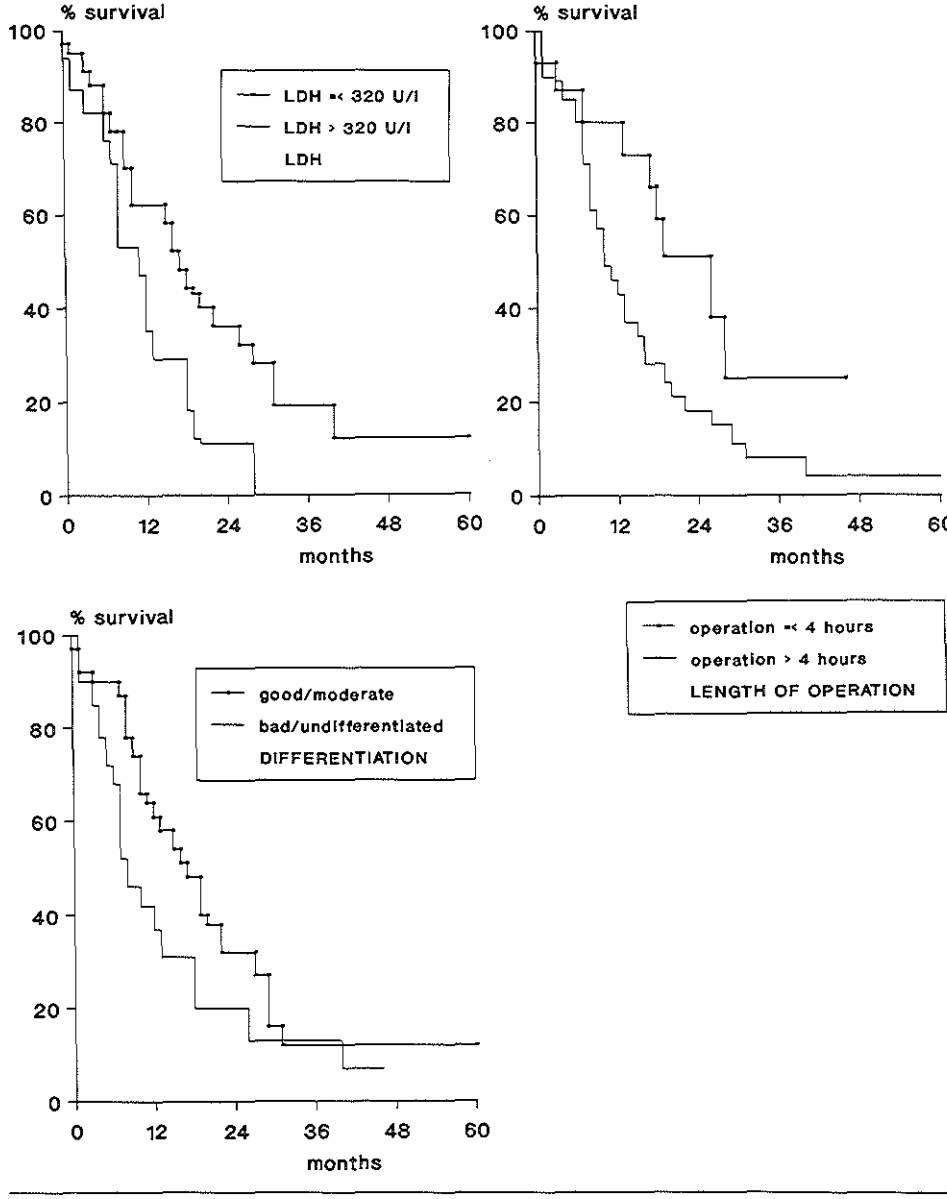
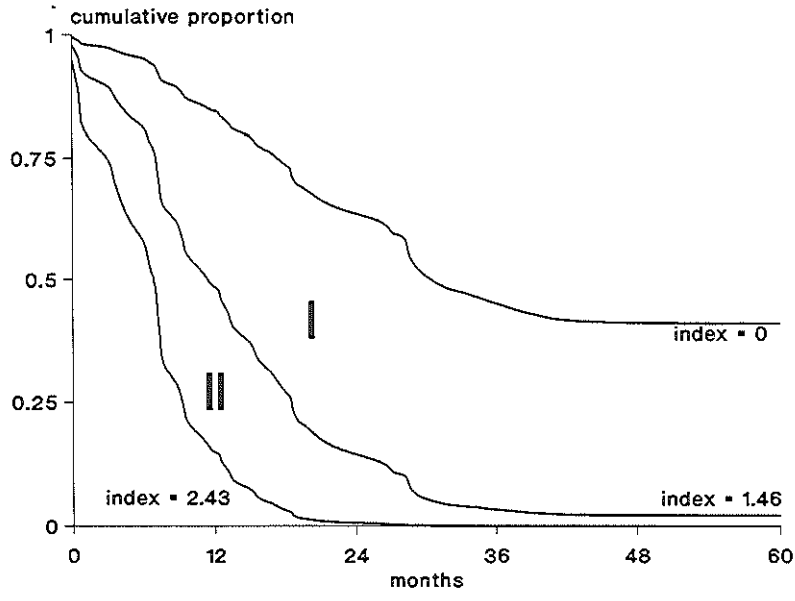


Figure 4: prognostic index and 2 regions of survival in 50 patients with cancer of the head of the pancreas after curative resection.



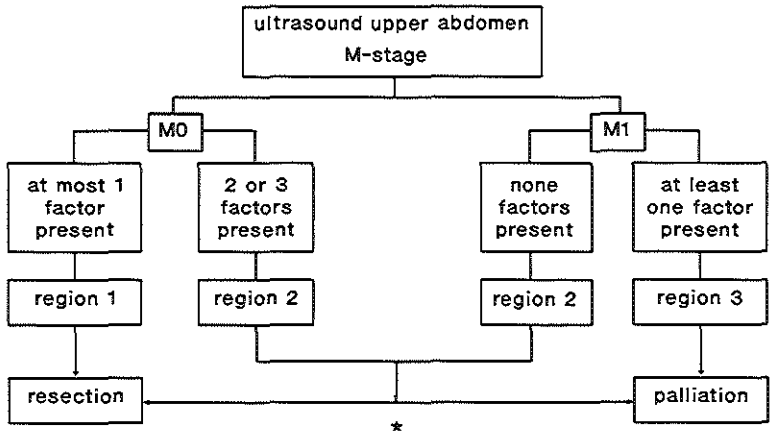
region I : at most one of the factors present
region II : two or three factors present

A decision tree can be made using these results with minimal diagnostics to decide whether to perform an explorative laparotomy and eventually a resection in cases of cancer of the head of the pancreas.(figure 5)

5.4 DISCUSSION

In cases of cancer of the head of the pancreas, the only possible curative treatment lies in resection of the tumor. However, it has been difficult to select those patients who will benefit from resection. Despite earlier diagnosis, declining morbidity and operative mortality, the overall prognosis has remained dismal for the last 2 decades.[1-5] More radical or less radical resections as the pylorus preserving pancreatoduodenectomy did not change prognosis.[8-11] A proper patient selection is important to obtain indications for chance of survival after

Figure 5: decision tree for patients with cancer of the head of the pancreas.



* = depending on the performance score and other diseases jeopardizing survival during and after operation
factors : age (< 70 years or ≥ 70 years), presence of pain, LDH (≤ 320 U/l or > 320 U/l)

resection.

We searched for prognostic factors in two groups of patients: in the total group of 203 patients with cancer of the head of the pancreas and in a subgroup of 50 patients after resection. We tried to link these factors with proper patient selection for resection.

Twenty possible prognostic factors have been analysed univariately. Age, pain, jaundice, LDH level, drainage of bile preoperatively, duration of operation, blood loss and TNM-stage appeared to be of prognostic value. Striking but not significant factors were tumor size (measured postoperatively by the pathologist) and microscopical irradicality, although these factors are mentioned in the literature as being significant for prognosis.[6,15-17] However, some authors did not find these factors significant, especially if analysed multivariately.[3,18] Tumor size itself is very difficult to measure before and during the operation.

Performing a multivariate analysis, only 4 factors were independent prognostic factors: age, pain, LDH level and M-stage of disease. Age is disputed for its prognostic value, but for the entire group of patients it was a strong prognostic factor.[12-14,16,20] No explanation was found

for the prognostic value of back and/or upper abdominal pain and LDH; however, it is possible that advanced disease will give more pain because of tumor ingrowth in the celiac plexus and will decrease liver function as a result of microscopical metastases in the liver. Until now, no literature is available to subscribe to this hypothesis. M-stage of disease is an expectable strong prognostic factor, easy to diagnose with ultrasound or computertomography.[15,17] Combining the independent factors using Cox's proportional hazard model with a prognostic index score, a division in survival time can be made depending on the presence of the four factors mentioned shown in figure 2. As a result, by calculating the index score survival time can be estimated. Consequently a decision can be made on whether or not to perform a explorative laparotomy with or without a resection. The decision tree as proposed in figure 5 is easy to follow, even very early in the treatment of the patient with cancer of the head of the pancreas. If the index score results in an outcome in region II, it is questionable on whether or not to perform a resection, depending on secondary factors as performance score and coexisting diseases jeopardizing survival.

The same analysis was conducted in 50 patients after resection and only three univariate significant prognostic factors were found: LDH level, duration of operation and differentiation of the tumor. Tumor size and microscopical irradicality were not significant. Lymph node stage is disputed for its prognostic value. Absence of lymph node involvement seems to be favourable but this is not found in all studies.[3,6,16,18,19] We did find a slight advantage for N0-stage in univariate analysis, but in multivariate analysis no significance was found. This is probably a result of our modified lymph node staging system in which lymph nodes within the resection specimen are separately staged as N1a lymph nodes. Again, no explanation other than the hypothesis mentioned before can explain the influence of an elevated LDH level. Differentiation of the tumor was a significant factor in multivariate analysis; good or moderate diferentiation results in better survival than poorly or badly differentiated tumors.[3,6,14,16] Estimation of survival after resection can be done in the same way as depicted before, using Cox's proportional hazards model and calculating the index score as shown in figure 4. When at most one of the significant prognostic factors (LDH $>$ 320 U/l, duration of operation longer than 4 hours or poor/bad differentiation) is present a more favourable outcome in survival will be the result as compared with two or three positive factors. The stage of disease is not an independent prognostic factor as a result of this analysis, realising that M1-stage and N1b-stage are not found in the curatively resected group of patients. As shown in this study

a thorough search for N1b lymph nodes and distant metastases is important as a first step before treatment.

In conclusion the treatment of a patient with cancer of the head of the pancreas starts with a search for distant metastases, for example by ultrasound investigation of the abdomen. If negative, three factors are of importance, age (< 70 years or ≥ 70 years), presence of pain and LDH (≤ 320 U/l or > 320 U/l). Calculating the prognostic index using the index score: index= .56 x age(0 or 1) + .53 x pain(0 or 1) + .55 x LDH(0 or 1) + 1.32 x M-stage(0 or 1), it is possible to estimate the probability of survival. If the outcome results in region I, a resection is advised when technically possible, in region II the decision depends on secondary factors as performance scores and jeopardizing diseases whether or not to perform a resection. In region III, and thus in metastatic disease, no resection must be performed. If a curative resection is performed, survival depends on three factors, LDH (≤ 320 U/l or > 320 U/l), duration of operation (≤ 4 hours or > 4 hours) and differentiation of the tumor (good/moderate or poor/bad differentiation). Estimation of survival is calculated by using the index= .86 x LDH (0 or 1) + .97 x duration of operation (0 or 1) + .60 x differentiation (0 or 1). If the outcome results in region I, a substantial survival is possible, with 2-year survival rate of 20% to 65%. Survival will be worse if the outcome results in region II, only a few patients will survive for more than 2 years after resection.

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CHAPTER 6

GENERAL DISCUSSION AND CONCLUSIONS

6.1 INTRODUCTION

In case of cancer of the head of the pancreas a fatalistic attitude has been shown by physicians and surgeons. The tumor proves to be unresectable in many cases and 90% of all patients admitted die within one year. The only realistic treatment that might cure the patient lies in radical surgery, i.e. a pancreatoduodenectomy. Long-term survival after intentional curative resection is 0-15% in cases of cancer of the head of the pancreas and up to 50% in cases of periampullary cancer.[1-6] The most frustrating problem is the inability to select those patients with pancreatic cancer who will benefit from radical surgery. Therefore, an accurate assessment of the stage of disease has to be achieved with a minimum of invasive techniques. If there is doubt about resectability or the presence of distant metastases, an explorative laparotomy has to be performed. If the tumor has proven to be irresectable or distant metastases have been found, a palliative procedure has to be performed, with the lowest possible morbidity and optimal comfort for the patient. However, the major purpose in treating patients with pancreatic cancer is to avoid misunderstandings about treatment possibilities and a fatalistic attitude by physicians. Misunderstanding and nihilism will lead to undertreatment of a small group of patients that otherwise could have been treated curatively.

6.2 PALLIATIVE PROCEDURES

The optimal palliative procedure in cases of irresectable cancer of the head of the pancreas or periampullary region is not yet known with respect to obstructive jaundice and gastric outlet obstruction. If obstructive jaundice is present, surgical and non-surgical methods are available with their pros and cons. Because of the limited life expectancy it seems attractive to perform a non-surgical drainage procedure; however, the quality of life is impaired because of the frequent readmissions for complications related to the endoprosthesis. These complications are transient fever, cholangitis, bleeding and migration of the stent in $\pm$20% of the patients. But the main problem is clogging of the endoprosthesis, occurring in about one-third of the stents within 3-4 months.[7] As a consequence, it seems reasonable to assume that a differentiation between short-term (<6 months) and long-term (>6 months) survivors will help to decide to perform a non-surgical or a surgical bypass. As described in **chapter 2.1** the morbidity in our group of patients surviving longer than 6 months was significantly

higher after endoprosthesis (61%) than after surgical bypass (5%). There was no difference in morbidity in patients surviving less than 6 months; the early morbidity after surgical bypass was compensated for by late morbidity in the patients treated with an endoprosthesis. For patients surviving less than 6 months, initial and total hospital stay was shorter after the use of an endoprosthesis; for those surviving longer than 6 months, this benefit diminished as a result of frequent readmissions for clogged endoprosthesis. In earlier studies, no difference in survival, morbidity or mortality were found in favor of either non-surgical or surgical bypass. However, in none of these studies was a differentiation made in short- and long-term survivors.[8-10] In order to predict survival shorter or longer than 6 months, a Cox's proportional hazards model was used in our study. Age, sex, tumor diameter and liver metastases were of prognostic value in this group of patients, comparable with some other reports.[11,12] A young female patient without liver metastases and a relatively small tumor has the best chance of surviving more than 6 months; a male patient, irrespective of age, with liver metastases has the shortest rate of survival. Bearing in mind these prognostic factors at laparotomy and finding an irresectable tumor, one should consider whether or not to perform a surgical bypass. As a matter of course, the general condition of the patient should be taken into account. In conclusion, in patients with survival less than 6 months, endoscopic biliary drainage is more favorable because it results in shorter hospitalization. Surgical biliary bypass, however, will be superior in palliation in patients surviving longer than 6 months, because of less morbidity and a long-lasting effect of bile drainage. Whether the surgical bypass will be completely abandoned because of the progress in the endoscopic use of large bore endoprostheses or self-expandable wall stents is not yet clear.[13,14]

Should we perform a gastroenteric bypass if irresectability is shown at the initial explorative laparotomy? In **chapter 2.2** we described a study of a group of 142 patients with irresectable disease. The incidence of gastric outlet obstruction reported in the literature varies between 3% to 50%; 25% of our patients developed symptoms of gastric outlet obstruction.[15,16] Does these figures indicate that a prophylactic gastroenterostomy should be performed at the time of the initial explorative laparotomy? The procedure in itself will lead to increased morbidity and mortality while most of the patients will not benefit of it because gastric outlet obstruction has shown to be a terminal event of the disease in most patients.[17-19] The main problem of a gastroenterostomy is delayed gastric emptying with an incidence of 14% to 29%; we found it in 16% of the patients with a prophylactic gastroenterostomy and in 29% after a

gastroenterostomy performed for symptomatic reasons.[16,20] A prophylactic gastroenterostomy does not prevent future gastric outlet obstruction and furthermore increases morbidity and therefore should not be performed. Notwithstanding these results, it is stated that surgical palliation can be performed with acceptable morbidity and mortality.[21]

Another problem in the palliation of patients with cancer of the head of the pancreas and periampullary region is the high incidence of locoregional recurrence after a former resection. Is it worthwhile to palliate these patients as well, and does this treatment turns out to be a proper palliation. In order to solve this question, we studied 108 patients after intentional curative resection and searched for symptoms and signs of locoregional recurrence(**chapter 2.3**). Locoregional recurrence is reported in the literature to be as high as 50-70%.[22,23] Thirty-four patients out of 108 patients developed locoregional recurrence in our series, 53% without signs of distant metastases. Survival in this group of patients was significantly better than in the group with distant metastases as expected, but 5 patients could be treated with curative intent resulting in better survival. However, there is a bias in favor of the treated group, because treatment with curative intent was not possible in all patients. One patient survived for more than five years after the second resection. Although this favorable result was achieved in only one patient, overall survival after second intervention seems better than after no treatment at all if locoregional recurrence is present without distant metastases.

6.3 CURATIVE SURGICAL PROCEDURES

In **chapter 3.1** a retrospective analysis consisting of 310 patients with cancer of the head of the pancreas (n=226) or periampullary region (n=84) was described. In only 34% of the 310 patients was a curative resection possible; 30% in cases of cancer of the head of the pancreas and 75% in cases of periampullary cancer, comparable with other studies.[24,25] Overall mortality was 8%, mortality decreased progressively in the last 2 years of the study to 2% in the last 40 resections.[4] Preoperative relief of jaundice seems to be efficient in lowering postoperative complications, as supported by others.[26,27] A resection should only be performed in the non-jaundiced patient. One-, two- and five-year survival after curative resection in cases of cancer of the head of the pancreas was 56%, 28% and 11% respectively. In cases of periampullary cancer these figures were 65%, 45% and 28% respectively.[1-6] Microscopical irradicality did not influence survival (p=0.48) which argues against more

extended resections. Extended resections as proposed by Fortner and others did not meet with great success and are more or less abandoned.[28,29] Ishikawa described a retrospective study in which portal vein invasion appeared to be of prognostic value and therefore in selected cases an extended resection was performed.[30] Even tumor size did not influence survival; moreover, there was a trend towards longer survival in cases of larger tumors ($p=0.08$). No explanation was found for this remarkable result.[11,31] Pancreatitis surrounding the tumor may be partially responsible for this phenomenon.

The standard Whipple's procedure, a one-stage pancreatoduodenectomy with partial gastrectomy, was the procedure of choice in case of resection of a pancreatic or periampullary tumor. In 1978, after the first description of a pylorus preserving technique in 1944, this procedure was introduced again with less morbidity and mortality compared with the standard Whipple's procedure.[32,33] The radicality of this procedure was doubted but less dumping, improved gastrointestinal function, reduced jejunal ulcera and a better gain of weight were reported.[34,35] In our retrospective study (**chapter 4**) comparing the pylorus preserving pancreatoduodenectomy and the standard Whipple's procedure performed in the same period the mortality and survival of both groups of patients were similar. No differences were found with respect to delayed gastric emptying, jejunal ulceration, microscopical irradicality, locoregional recurrence and reexplorations due to surgical complications. The duration of the operation and blood loss during the operation were less, weight gain during follow up was better after pylorus preserving pancreatoduodenectomy. There are no reports of prospective randomized studies comparing both techniques; therefore such a trial was started in our institute in collaboration with other centers in the Netherlands. The aim of the trial is to compare the pylorus preserving pancreatoduodenectomy and the standard Whipple's procedure with respect to operative blood loss, length of operation, postoperative morbidity, hospital stay, in-hospital mortality and long-term results as locoregional recurrence and survival.

6.4 ADJUVANT TREATMENT

The promising results of the GITSG studies using radiotherapy and 5-FU as adjuvant treatment after resection for cancer of the pancreas have resulted in a prospective randomized trial initiated in our institute in collaboration with the EORTC(**chapter 3.2**).[36,37] The original treatment schedule is used, with a modification of the 5-FU therapy; 5-FU therapy is limited

to the first week of each radiation cycle. The treatment schedule consists of 40 Gray of radiotherapy delivered as a split course; 2 times 2 weeks (fractions 2 Gray/day) with a separation of 2 weeks. 5-FU is administered in a dose of 25 mg/kg/24 hours with a maximum dose of 1500 mg/day. Depending on toxicity the second cycle consists of 0, 3 or 5 days of 5-FU treatment. Preliminary results of this trial of the first 153 randomized patients with regard to tolerance of radiation therapy and 5-FU treatment were promising. All but 2 patients received the total dose of radiation therapy; 5-FU could be administered in the minimum dose in 88% of patients. Overall toxicity was low; the worst WHO toxicity grade shown was three. All mild toxicities were easily managed with conservative methods. No life-threatening toxicities occurred. Only two other reports of more or less comparable adjuvant treatment, although retrospectively, confirmed these results.[38,39] The results on locoregional recurrence and survival can be given after the total number of 200 patients have been randomized and the follow up of 2 years is completed.

6.5 PROGNOSTIC INDEX

Despite earlier diagnosis, declining morbidity and mortality after resection and increasing survival, it still is very difficult to select those patients who will benefit from resection. To select these patients a search for prognostic factors was done and was described in **chapter 5**. In 203 patients with cancer of the head of the pancreas only four, out of twenty analyzed, items were independent prognostic factors; age ($< \geq 70$ years), the presence of pain, LDH ($\leq > 320$ U/l) and M-stage (M0 or M1) of disease. Age, tumor size and microscopical irradicality are disputed for their prognostic value.[40,41] Our results showed no influence on survival of larger tumors (> 3.5 cm.) or tumor containing resection margins. Using the Cox's proportional hazards model with a prognostic index score results in three possible regions of survival. Depending on the result of the index score one can decide to perform an explorative laparotomy and/or a resection. Using this method a decision tree can be made, with minimal invasive diagnostics it is possible to decide how to deal with a patient. The same procedure was used in patients after curative resection; LDH ($\leq > 320$ U/l), duration of operation ($\leq > 240$ minutes) and differentiation of tumor (good/moderate or bad/undifferentiated) were of independent prognostic value. Using Cox's proportional hazards model, 2 possible regions of survival were calculated. When not more than one of the independent prognostic factors

is present, a more favorable outcome in survival will be the result. No explanation was found for the influence of pain and LDH; however, it is possible that advanced disease will cause more pain by ingrowth in the celiac plexus and will decrease liver function as a result of microscopic liver metastases that cannot be detected by current diagnostic modalities. The influence on survival of tumor containing lymph nodes is debatable; we did find a slight advantage for N0-stage in univariate analysis, but in multivariate analysis no significance was found. Possibly as a result of our modified lymph node staging system, N1a nodes being nodes within the resection specimen and thus removed during resection.[42,43] If other or stronger prognostic factors, as DNA ploidy, will become available is not yet clear, but a thorough search for such prognostic factors is mandatory to select patients with the best outcome of intentional curative treatment.[44,45]

6.6 CONCLUSIONS

In cases of irresectable cancer of the head of the pancreas or periampullary region, biliary drainage is the first step in palliation. In patients surviving less than 6 months, endoscopic biliary drainage is more favorable because it results in shorter hospitalization. If a patient will survive for more than 6 months, depending on prognostic factors as age, sex, tumor diameter and metastases, a surgical bypass will be the superior procedure because of the long-standing effect of drainage and less morbidity. A prophylactic gastroenterostomy does not prevent future gastric outlet obstruction; it increases morbidity. If performed in symptomatic cases, it should be considered once more because of the high incidence of morbidity and mortality. The success rate of a gastroenterostomy is low and therefore it should not be routinely performed. In both palliative procedures, the general condition of the patient should be taken into account whether to palliate surgically or not.

The best treatment option for cancer of the head of the pancreas and periampullary region is resection, irrespective of tumor size or tumor infiltration in locoregional lymph nodes. Irradical resection may benefit patients in selected cases, especially during the first year after resection. Although the cure rate of a radical resection remains low, a resection is the method of choice in centers with low operative mortality. Postoperative morbidity and mortality seems to be higher in the jaundiced patient, one should consider preoperative biliary drainage. Although retrospectively studied a pylorus preserving pancreatoduodenectomy seems to be a

radical and safe procedure; no difference in morbidity and mortality was found as compared to the standard Whipple's procedure. The advantages of the pylorus preserving technique were a less time consuming operation, with less blood loss and a shorter hospital stay. During follow up weight gain and, as a consequence, quality of life appears to be better after a pylorus preserving pancreatoduodenectomy. To subscribe and prove the results of the retrospective study, a randomized prospective study was initiated and started to compare the standard Whipple's procedure and the pylorus preserving pancreatoduodenectomy.

The first successful adjuvant treatment schedule was reported by the GITSG; a modified treatment schedule is used in a prospective randomized study in collaboration with the EORTC. Radiotherapy administered as a split course of 2 times 2 weeks with a split of 2 weeks combined with 5-FU in a dose of 25 mg/kg/day (maximum 1500 mg/day) during the first week of each radiation cycle resulted in very low toxicity. This treatment regimen is very well tolerated. The results concerning locoregional recurrence and survival have to be awaited until the total number of 200 patients have been randomized and the follow up of 2 years is completed.

In cases of locoregional recurrence of pancreatic cancer without the presence of distant metastases, one should consider a relaparotomy and eventually, if possible, a second resection. It could be possible that radiotherapy and 5-FU administration can be of benefit in this patients group. It seems that treatment favors the survival of this group of patients.

It is still very difficult to select those patients who will benefit from resection. To select these patients a multivariate analysis was performed. The treatment of the patient with cancer of the head of the pancreas will start with a search for distant metastases by ultrasound investigation of the abdomen. It appeared that anamnestic and laboratory results, especially age, pain and LDH, are mandatory. Combining these results using the Cox's proportional hazards model reveals a survival outcome in three regions depending on the outcome of the four independent prognostic factors. Whether to perform an explorative laparotomy and/or a resection can be decided using a decision tree as given in chapter 5. If a resection is performed, survival can be predicted depending on LDH, length of operation and differentiation of the tumor.

However, the most important topic in therapeutic modalities in cases of pancreatic cancer is the necessity to change the attitude of the physician from a fatalistic into a realistic and more optimistic approach. Real long-term survivors do exist and in selected cases even cure can be obtained.

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SUMMARY

Chapter 1

The introduction gives some reflections of palliative, curative and adjuvant treatment of cancer of the head of the pancreas and periampullary region taken from the current literature. An overview of the contents is given.

Chapter 2

Palliative treatment of cancer of the pancreas is still a controversial problem with respect to drainage of bile and the treatment of gastric outlet obstruction. In chapter 2.1 guidelines are described for the application of surgery and endoprosthesis in the palliation of obstructive jaundice in advanced cancer of the pancreas. The study was set up to identify patient-related factors favoring the application of either surgery or endoprostheses in the palliation of obstructive jaundice in subsets of patients with cancer of the head of the pancreas or periampullary region. In the palliation of obstructive jaundice, surgical biliodigestive anastomosis has traditionally been performed. Surgical biliary bypass is associated with high mortality (15-30%) and morbidity rates (20-60%), but little recurrent obstructive jaundice (0-15%). Biliary drainage with endoscopically placed endoprostheses has a lower complication rate, but recurrent obstructive jaundice is seen in up to 20-50% of the patients. Data of patients with advanced cancer of the head of the pancreas or periampullary region treated at the University Hospital Dijkzigt, Rotterdam, The Netherlands, between 1980 and 1990 were reviewed. The data concerning morbidity and hospital stay after palliation of obstructive jaundice with endoscopic endoprostheses or surgical biliary bypass were compared in 148 patients. These patients were stratified for long (>6 months) and short (<6 months) survival. In short-term survivors, higher late morbidity after endoprostheses was offset by higher early morbidity and longer hospital stay after surgical bypass. In long-term survivors there was no difference in hospital stay between the two groups, but late morbidity was significantly higher in the endoprostheses group. These data suggest endoscopic endoprostheses as the optimal palliation for patients surviving less than 6 months and surgical biliary bypass for those surviving more than 6 months. This policy necessitates the development of prognostic criteria, which were obtained by Cox's proportional hazards survival analysis. Advanced age, male sex, liver metastases and large tumor diameters were unfavorable prognostic factors. Using

these factors the risk of short or long survival can be predicted. It is hoped that the application of these data may allow a rational approach towards optimal palliative treatment of this form of malignant obstructive jaundice.

There remains doubt about the necessity for gastroenterostomy in patients with advanced cancer of the pancreatic head, either performed prophylactically or when the passage of food becomes impossible. The records of 142 patients admitted for advanced pancreatic cancer to the University Hospital Dijkzigt, Rotterdam over a period of 11 years were reviewed. We concentrated especially on the pre- and postoperative intake of food in cases involving gastroenterostomy, and the morbidity and mortality associated with abdominal surgery in these patients. Of 129 patients without symptoms of gastric outlet obstruction at the time of diagnosis, 31 underwent prophylactic gastroenterostomy. This did not prevent gastric outlet obstruction in 4 patients. Of the remaining 98 patients, 15 developed gastric outlet obstruction. Cox's proportional hazards analysis showed no significant difference in the interval to the occurrence of a symptomatic obstruction between these two groups, taking into account other co-variables. Postoperative complications and mortality due to a gastroenterostomy were high, ranging from 9-41% and 11-33%, respectively. Our results do not significantly indicate that prophylactic gastroenterostomy might prevent future gastric outlet obstruction; and therefore, as it also increases morbidity, it should not be performed. A gastroenterostomy for symptomatic reasons should be considered carefully as the success rate is low and is accompanied by a considerable incidence of morbidity and mortality.

During follow up after a former resection, a second palliative problem can arise, namely locoregional recurrence and/or distant metastases. In order to analyse the results of treatment of patients with locoregional recurrence after intentional curative resection of pancreatic cancer, a retrospective study was performed. During the period 1978-1988, 108 patients underwent an intentional curative resection of the pancreas. In 34 patients locoregional recurrence occurred, all within a period of three years (cumulative recurrence rate 56%). Sixty-eight percent of the patients showed signs of upper abdominal pain, and 62% had weight loss. Survival was significant better ($p=0.02$) for the group of 18 patients without distant metastases (1-year survival 22%) than for the 16 patients with distant metastases (1-year survival 0%). Five patients without proven distant metastases were treated by resection or chemotherapy. The mean survival was 33 months (range 6-74) for the treated group, and for the untreated group 4 months (0.4-7 months), $p=0.002$.

In this retrospective study the longest survival was seen after radical resection of locoregional tumor recurrence. Therefore we recommend treating patients with locoregional recurrence without distant metastases after intentional curative resection of pancreatic cancer.

Chapter 3

In chapter 3, both a review of 10 years of pancreatic surgery in the University Hospital Rotterdam-Dijkzigt and the preliminary results of a prospective randomized study of adjuvant treatment are described. A retrospective study of 310 patients with cancer of the head of the pancreas and periampullary region was performed. Preoperative bile drainage by placing a stent reduced postoperative complications, especially bleeding ($p=0.03$). A highly significant difference in operative mortality was found in patients with periampullary cancer under and over 70 years of age, mortality rate 0% and 23% respectively ($p<0.001$). In the last 2 years of the study mortality after resection decreased to 2%. Tumor containing resection margins did not influence survival after resection ($p=0.48$). Neither tumor dimension in both types of cancer nor presence of tumor in locoregional lymph nodes (N1a) in cancer of the head of the pancreas resected with the primary tumor were of prognostic value. After palliative resection the median survival time was significantly better than when no resection was performed, 10.1 months versus 3.9 months ($p<0.001$). In conclusion, even a palliative resection may benefit some patients. Preoperative bile drainage seems to be indicated in jaundiced patients. Resection should be performed, irrespective of tumor size provided that operative mortality is sufficiently low.

Radiotherapy and 5-fluorouracil adjuvant treatment after resection of cancer of the head of the pancreas and periampullary region was first demonstrated by the Gastro Intestinal Tumor Study Group (GITSG) in 1985, with promising results. In 1987 we initiated, in collaboration with the EORTC (European Organization of Research and Treatment of Cancer), a comparable trial with a modification in the 5-FU treatment; 5-FU administration is limited to the periods of radiation therapy. The aim of this report is to demonstrate the low toxicity of this treatment regimen in the first 77 treated patients in the complete group of 153 randomized patients. Radiation therapy consisted of 2 cycles of 20 Gy as a split course, 5-FU is administered during 4 days of the first radiation course in a dose of 25 mg/kg/day, 0, 3 or 5 days during the second course depending on toxicity during the first course. Data were

available for 47 of the 77 treated patients. Only 5 patients did not get the full dose of 40 Gy; the total dose of 5-FU administered was 88% of the theoretical maximum dose. The worst grade of toxicity was grade 3 (World Health Organization,WHO), all toxicities were easily managed with conservatives methods and completely reversible after completion of adjuvant treatment. In conclusion, adjuvant treatment with radiotherapy and 5-FU is very well tolerated after resection of cancer of the head of the pancreas or periampullary region. The results of this EORTC adjuvant treatment protocol on locoregional recurrence and survival have to be awaited until the intake of 200 patients is reached and follow up of 2 years is completed.

Chapter 4

The pylorus preserving pancreatoduodenectomy was reintroduced in 1978 as a resection technique for cancer of the head of the pancreas and periampullary region. Aim of the retrospective study was to establish whether the pylorus preserving pancreatoduodenectomy (PPPD) is a safe and radical procedure in malignant disease of the head of the pancreas and periampullary region, without increased morbidity and mortality compared to the standard Whipple's procedure. During the period 1984-1990 a Whipple's procedure (n=44) or PPPD (n=47) was performed in 91 patients. In-hospital mortality was 2% after PPPD and 5% after Whipple's procedure. The median duration of the resection procedure and median blood loss in the PPPD group were 210 minutes and 1800 ml respectively. After Whipple's procedure these figures were 255 minutes and 2500 ml, both significantly different ($p<0.01$) as compared to PPPD. No difference was found during follow up with respect to days of gastric suctioning, start of liquid diet, normal diet, complaints of for ulcer disease, postoperative complications, recurrence of disease and survival. In all patients an intentional curative resection was performed with comparable TNM staging. The number of tumor containing duodenal or gastric resection margins did not differ in both groups of patients (2 patients after PPPD, 2 patients after Whipple's procedure). Hospital stay was significantly ($p=0.02$) shorter after PPPD, median 14 days compared to median 18 days after Whipple's procedure. The advantages of the PPPD are an easier and less time-consuming operation, with less blood loss, a shorter hospital stay and a better weight gain ($p=0.02$) during follow up. In conclusion, PPPD is a safe and radical procedure for cancer in the head of the pancreas or periampullary region with the same survival and appearance of locoregional recurrence and distant

metastases as after standard Whipple's resection. Until now, no prospective randomized studies have been published to prove the retrospective results of the pylorus preserving pancreatoduodenectomy. Therefore, a prospective randomized multicenter trial is initiated and started in 1993 at the University Hospital Rotterdam-Dijkzigt. A comparison will be made in operative blood loss, length of operation, postoperative morbidity, hospital stay, in-hospital mortality and long-term results as locoregional recurrence and survival.

Chapter 5

In order to determine independent prognostic factors in patients with cancer of the head of the pancreas we performed a multivariate analysis of a group of 203 patients admitted during the period 1977-1988 to the University Hospital Rotterdam-Dijkzigt.
Univariate and multivariate analyses in the overall group of patients result in four independent prognostic factors; age ($<$ 70 years or $\geq$ 70 years), presence of pain, LDH ($\leq$ 320 U/l or $>$ 320 U/l) and M-stage of disease (M0 or M1). Tumor size and microscopical irradicality are of no prognostic value. A prognostic index is calculated using Cox's proportional hazards model revealing three possible regions of survival. A resection has to be considered if the prognostic index calculated results in region I; a palliative procedure has to be considered if the prognostic index is in region III. If the patients' prognostic index appears in region II performance of a resection will depend on secondary factors as coexisting diseases jeopardizing postoperative survival. After curative resection in 50 patients again a prognostic index can be calculated, with three factors: LDH ($\leq$ 320 U/l or $>$ 320 U/l), duration of operation ($\leq$ 4 hours or $>$ 4 hours) and differentiation of the tumor (good/moderate or poor/bad), while for these patients two regions of survival are distinguished. A decision tree is proposed to determine the treatment of the patient with cancer of the head of the pancreas.

Chapter 6

In this chapter the results of the studies performed are discussed and conclusions are given. In palliative treatment of an irresectable carcinoma of the head of the pancreas or periampullary region, an endoprosthesis has to be used for biliary drainage in patients surviving shorter than 6 months. A surgical bypass is the method of choice if a patient will

survive for more than 6 months. Survival will depend mainly on age, sex, tumor diameter and the presence of liver metastases. A gastroenterostomy should not be routinely performed; it is questionable whether it should be performed in cases of symptomatic gastric outlet obstruction, because this symptom is nearly always a terminal event in the course of the disease. As a matter of course the general condition of the patient will be the main indication of the kind of palliation suitable for that particular patient. The only possible cure lies in radical resection; it should only be performed in centers with experienced surgeons providing low operative mortality. Retrospectively the pylorus preserving pancreatoduodenectomy seems to have equal or even better results than the standard Whipple's procedure regarding postoperative morbidity, mortality, quality of life and survival. To prove the retrospective results of the pylorus preserving pancreatoduodenectomy compared with the standard Whipple's procedure a prospective randomized trial has been started. The possible effect on survival of adjuvant treatment is studied in a prospective randomized study in collaboration with the EORTC. The first results on toxicity are promising; the treatment is very well tolerated. The effect of this treatment on locoregional recurrence and survival has to be awaited until the total number of patients has been randomized and follow up is completed. If locoregional recurrence occurs during the course of the disease, one should consider treatment, especially if no distant metastases are present. The search for prognostic factors is important, for it can help to decide which patients should be operated on by using a decision tree. After resection it can provide some information about the chance of survival. However, the most important topic in therapeutic modalities in cases of pancreatic cancer is the necessity to change the physician's attitude from a fatalistic into a realistic and optimistic approach. Real long-term survivors do exist, and in selected cases even cure can be obtained.

SAMENVATTING

Hoofdstuk 1

In de algemene introductie wordt een beschouwing gegeven over de palliatieve, curatieve en adjuvante behandeling van het pancreaskop- en periampullair carcinoom aan de hand van de literatuur. Een overzicht van de inhoud wordt beschreven.

Hoofdstuk 2

De palliatieve behandeling van het pancreascarcinoom blijft een controversieel onderwerp voor wat betreft het verhelpen van icterus en passagestoornissen van de maag. In hoofdstuk 2.1 worden richtlijnen gegeven voor de toepassing van chirurgie en endoprothesen bij de palliatie van obstructieve icterus bij het inoperabele pancreascarcinoom. De studie is verricht om patiëntgebonden factoren te vinden ten voordele van chirurgie of endoprothesen bij de palliatie van het pancreaskop- en periampullair carcinoom. Traditioneel is de chirurgische behandeling van icterus door middel van een biliodigestieve anastomose. De chirurgische bypass resulteert in hoge mortaliteit (15-30%) en morbiditeit (20-60%), maar nagenoeg geen recidief obstructie (0-15%). Endoscopisch geplaatste endoprothesen geven minder aanleiding tot complicaties, maar recidief obstructie wordt gezien in 20-50%. De patiënten met een inoperabel pancreaskop- en periampullair carcinoom, behandeld in het Academisch Ziekenhuis Rotterdam-Dijkzigt, van 1980 tot en met 1990 werden onderzocht. Bij 148 met een endoprothese of chirurgische bypass behandelde patiënten werd een vergelijking gemaakt met betrekking tot morbiditeit en opnameduur ten gevolge van de behandeling. De patiënten werden gestratificeerd tussen lange (>6 maanden) en korte (<6 maanden) overleving. In de groep kort levende patiënten werd de hoge late morbiditeit gecompenseerd door hogere morbiditeit en langere opnameduur in de groep chirurgisch behandelde patiënten. Bij de lang overlevende patiënten trad dit niet op, maar de late morbiditeit was significant hoger in de met endoprothesen behandelde groep patiënten. Deze uitkomst suggereert dat de endoprothese de ideale behandeling is voor de patiënt die korter dan 6 maanden overleeft en de chirurgische bypass gereserveerd dient te blijven voor de groep die langer dan 6 maanden overleeft. Om dit onderscheid te kunnen maken moeten prognostische factoren gezocht worden om de overleving te voorspellen, door middel van de Cox's regressie analyse methode werden deze gevonden. Hogere leeftijd, mannelijk geslacht, levermetastasen en grote tumordiameter waren

ongunstige prognostische factoren. Door het toepassen van deze regressieanalyse kon de overleving korter of langer dan 6 maanden geschat worden. Door middel van deze studie hopen wij op een rationele overweging met betrekking tot het behandelen van maligne icterus.
Bij patiënten met een inoperabel pancreaskopcarcinoom blijft twijfel bestaan of het noodzakelijk is een gastroenterostomie aan te leggen, profylactisch of therapeutisch. Er werden 142 patiënten met een inoperabel pancreaskopcarcinoom bestudeerd welke gedurende een periode van 11 jaar behandeld werden in het Academisch Ziekenhuis Rotterdam-Dijkzigt. Met name de pre- en postoperatieve voedselinname en de morbiditeit en mortaliteit als gevolg van de gastroenterostomie werden bestudeerd. Bij 129 patiënten werden geen symptomen van gestoorde voedselpassage ten tijde van het stellen van de diagnose gevonden, 31 van hen ondergingen een profylactische gastroenterostomie. Het aanleggen van de gastroenterostomie kon bij 4 patiënten niet voorkomen dat er toch obstructieverschijnselen van de maag optraden. Van de 98 overblijvende patiënten ontwikkelden er 15 maagretentie in het beloop van de ziekte. Er werd geen verschil gevonden tussen het optreden van maagretentie in beide groepen, rekening houdend met andere variabelen en gebruik makend van het Cox's regressie model. De postoperatieve complicaties en mortaliteit van een gastroenterostomie waren hoog, respectievelijk variërend van 9-41% en 11-33%. Omdat een profylactisch aangelegde gastroenterostomie de morbiditeit verhoogt en niet voorkomt dat er toch maagretentie op de lange duur optreedt moet een degelijke profylactische bypass niet aangelegd worden. Bij symptomatische maagretentie moet zorgvuldig overwogen worden of daadwerkelijk een gastroenterostomie verricht moet worden, daar dit een aanzienlijke morbiditeit en mortaliteit voor de patiënt betekent.
Een tweede palliatief probleem is het ontstaan van locoregionaal recidief en/of afstandsmetastasen na eerdere in opzet curatieve resectie. Om de resultaten van behandeling van recidief tumor te bezien werd een retrospectieve studie verricht. In de periode van 1978 tot en met 1988 ondergingen 108 patiënten een in opzet curatieve resectie. Binnen een periode van drie jaar trad een locoregionaal recidief bij 34 patiënten op (cumulatief recidief percentage van 56%). Bovenbuikspijn en gewichtsverlies waren de optredende symptomen van recidief bij respectievelijk 68% en 62% van de patiënten. De overleving was significant beter ($p=0.02$) in de groep van 18 patiënten zonder metastasen op afstand (1-jaars overleving 22%) dan in de groep van 16 patiënten met afstandsmetastasen (1-jaars overleving 0%). Vijf patiënten zonder afstandsmetastasen werden door middel van re-resectie of de combinatie van

radiotherapie en chemotherapie behandeld. De gemiddelde overleving was 33 maanden (spreiding 6-74 maanden) in de behandelde groep, slechts 4 maanden (0.4-7 maanden) in de onbehandelde groep, $p=0.002$. In deze retrospectieve studie werd de langste overleving gevonden na radicale resectie van het tumorrecidief. Wij adviseren behandeling in plaats van een expectatief beleid bij patiënten zonder aanwijzingen voor metastasen op afstand na een eerdere curatieve resectie.

Hoofdstuk 3

In dit hoofdstuk wordt een retrospectieve studie over 10 jaar pancreaschirurgie in het Academisch Ziekenhuis Rotterdam-Dijkzigt en de eerste resultaten van een prospectief gerandomiseerde studie omtrent de adjuvante behandeling van het pancreaskop- en periampullair carcinoom beschreven. De retrospectieve studie behelst 310 patiënten met pancreaskop- of periampullair carcinoom. Het preoperatief plaatsen van een endoprothese om de bestaande icterus op te heffen heeft een lager aantal postoperatieve complicaties tot gevolg, met name postoperatieve bloedingen ($p=0.03$). De mortaliteit van resectie bij patiënten ouder dan 70 jaar met een periampullair carcinoom was significant hoger dan bij patiënten jonger dan 70 jaar, respectievelijk 23% en 0% ($p<0.001$). Tijdens de laatste twee jaren van de studie daalde de mortaliteit tot 2%. De overleving werd niet beïnvloed door microscopische irradicaliteit na resectie ($p=0.48$) of door tumorgrootte bij beide typen carcinoom. Wel bleken tumorbevattende lymfklieren in het resectiepreparaat (N1a) bij het periampullair carcinoom een negatieve prognostische waarde te hebben. Een palliatief uitgevoerde resectie, dat wil zeggen een macroscopisch irradicale resectie, heeft bij geselecteerde patiënten wel degelijk zin, de overleving was significant beter na een palliatieve resectie, namelijk 10.1 maanden mediane overleving ten opzichte van 3.9 maanden mediaan zonder resectie ($p<0.001$). Concluderend dient preoperatieve drainage van gal en als het technisch mogelijk is een resectie van de tumor uitgevoerd te worden, onafhankelijk van de grootte van de tumor. Vanzelfsprekend moet daarbij de operatieve mortaliteit zo laag mogelijk zijn.
De eerste veelbelovende resultaten van adjuvante behandeling met radiotherapie en 5-FU na resectie van pancreaskop- en periampullaire carcinomen werd in 1985 beschreven door de Gastro Intestinal Tumor Study Group (GITSG). In 1987 initiëerden wij, in samenwerking met de European Organization of Research and Treatment of Cancer (EORTC), een vergelijkbare

studie met een gemodificeerde dosis 5-FU. De 5-FU behandeling werd beperkt gehouden tot de perioden van radiotherapie. Het doel van de onderhavige analyse van de eerste 77 behandelde uit de gehele groep van 153 gerandomizeerde patiënten was het demonstreren van de lage toxiciteit van de behandeling. De radiotherapie bestaat uit 2 cycli van 2 weken, 20 Gray per 2 weken, 2 Gray per dag, gescheiden door een periode van 2 weken. De 5-FU wordt in een dosis van 25 mg/kg/dag gedurende de eerste 4 dagen van de eerste bestralingscyclus gegeven, tijdens de tweede bestralingscyclus wordt 0, 3 of 5 dagen 5-FU toegediend, afhankelijk van de toxiciteit tijdens de eerste cyclus. Gegevens waren beschikbaar van 47 van de 77 behandelde patiënten. Slechts 5 patiënten kregen niet de gehele dosis van 40 Gray, 88% van de theoretisch maximale dosis 5-FU kon gegeven worden. De hoogste graad van toxiciteit volgens de score van de World Health Organization (WHO) was graad 3, alle voorkomende bijwerkingen konden eenvoudig met conservatieve maatregelen behandeld worden. Concluderend is de verdraagzaamheid van de adjuvante behandeling na resectie van een pancreaskop- of periampullair carcinoom met radiotherapie en 5-FU zeer goed. De verdere resultaten met betrekking tot locoregionaal recidief en overleving van deze studie worden afgewacht tot het totale aantal patiënten van 200 is gerandomiseerd en de follow-up van 2 jaar is afgerond.

Hoofdstuk 4

In 1978 werd de pylorussparende pancreatoduodenectomie gereïntroduceerd als mogelijke resectietechniek voor het pancreaskop- en periampullair carcinoom. Het doel van de retrospectieve studie was het aantonen dat de pylorussparende techniek (PPPD) een veilige en radicale procedure is bij maligniteiten van de pancreaskop en periampullaire regio, met een vergelijkbare morbiditeit en mortaliteit als bij de standaard Whipple procedure. Tijdens de periode 1984 tot en met 1990 werden 44 standaard Whipple procedures en 47 pylorussparende resecties uitgevoerd bij 91 patiënten. De mortaliteit tijdens opname was 2% na PPPD en 5% na een Whipple procedure. De gemiddelde duur van de operatie en het bloedverlies in de PPPD groep waren respectievelijk 210 minuten en 1800 milliliter. Bij een Whipple procedure lagen de gemiddelden significant hoger ($p<0.01$), respectievelijk 255 minuten en 2500 milliliter. Tijdens de follow-up werd geen verschil tussen beide ingrepen gevonden voor wat betreft de dagen dat een maagsonde nodig was, het starten van vloeibare maaltijden, het

starten van een normaal dieet, ulcusklachten, postoperatieve complicaties, recidief van tumor en overleving. Bij alle patiënten kon een curatieve resectie uitgevoerd worden met vergelijkbare TNM stagering. Het aantal keer dat er microscopische irradicaliteit bestond was in beide groepen gelijk (2 maal in de PPPD groep, 2 maal na een Whipple resectie). De totale opnameduur was significant ($p=0.02$) korter na PPPD, gemiddeld 14 dagen ten opzichte van 18 dagen na een Whipple resectie. Voordelen van de PPPD zijn een kortere operatie, met minder bloedverlies, een kortere opnameduur en een betere gewichtstoename ($p=0.02$) tijdens de follow-up. Concluderend is de pylorussparende pancreatoduodenectomie een veilige en radicale ingreep bij pancreaskop- en periampullaire carcinomen met eenzelfde overleving en optreden van locoregionaal recidief als bij de standaard Whipple procedure. Tot nu toe zijn er geen prospectief gerandomiseerde studies beschreven waarin bovenstaande resultaten getoetst zijn. Daarom zijn wij een multicenter studie gestart in 1993. Hierin wordt het peroperatieve bloedverlies, de duur van operatie, de postoperatieve morbiditeit, de opnameduur, de mortaliteit tijdens opname en lange termijn resultaten als locoregionaal recidief en overleving van de pylorussparende techniek van resectie vergeleken met de standaard Whipple procedure.

Hoofdstuk 5

Om onafhankelijke prognostische factoren te vinden bij patiënten met een pancreaskopcarcinoom werd een multivariabele analyse verricht bij een groep van 203 patiënten. De patiënten werden allen behandeld gedurende de periode 1977-1988 in het Academisch Ziekenhuis Rotterdam-Dijkzigt. Vier onafhankelijke prognostische factoren werden na univariate en multivariate analyse gevonden in de gehele groep patiënten; $<$ of $\geq$ 70 jaar, aanwezigheid van pijn, LDH waarden $\leq$ of $>$ 320 U/l en de M-stagering (M0 of M1). De grootte van de tumor en microscopische irradicaliteit waren niet van prognostische betekenis. Door middel van het Cox's regressiemodel werd de prognostische index berekend. Met behulp van deze index kan de kans op overleving berekend worden, met als resultaat drie mogelijke regio's van overleving. Een in opzet curatieve resectie moet worden overwogen als de patiënt in regio I valt; een palliatieve procedure als patiënt in regio III valt. Wanneer de index valt in regio II, zal afhankelijk van bijkomende secundaire factoren welke een hoger operatierisico geven, een resectie of alleen een palliatieve procedure overwogen moeten

worden. Na curatieve resectie bij 50 patiënten werd opnieuw de prognostische index berekend met behulp van 3 factoren; LDH (≤ 320 U/l of > 320 U/l), operatieduur (≤ 4 uur of > 4 uur) en tumordifferentiatie (goed/matig of slecht/ongedifferentieerd), met twee mogelijke regio's van overleving. Er wordt een beslisboom voorgesteld welke de werkwijze bij de patiënt met een pancreascarcinoom kan vereenvoudigen, deze bestaat uit een aantal eenvoudig te verkrijgen parameters.

Hoofdstuk 6

De algemene discussie en de conclusies van de verrichte studies worden in dit hoofdstuk beschreven. Bij de patiënt met een inoperabel pancreaskop- of periampullair carcinoom die korter dan 6 maanden zal overleven is een endoprothese de methode van keuze wanneer drainage van gal nodig is. Wanneer de kans het grootst is dat een dergelijke patiënt langer dan 6 maanden overleeft zal een chirurgische biliaire bypass aangelegd moeten worden. De genoemde overleving kan worden berekend met behulp van een aantal prognostische factoren, namelijk leeftijd, geslacht, tumordiameter en het al of niet aanwezig zijn van levermetastasen. Een gastroenterostomie moet niet profylactisch aangelegd worden. Wanneer symptomatische maagretentie aanwezig is blijkt dit vrijwel altijd een symptoom van terminale ziekte te zijn. Vanzelfsprekend blijft de algehele conditie van de individuele patiënt de belangrijkste factor wanneer besloten moet worden wat voor soort palliatie uitgevoerd zal gaan worden. Radicale chirurgisch resectie is de enige kans op overleving bij het pancreaskop- en periampullair carcinoom. Belangrijk is dat een resectie alleen uitgevoerd moet worden in centra welke ervaren chirurgen op dit gebied hebben en dientengevolge een lage mortaliteit kunnen garanderen. Retrospectief lijkt de pylorussparende pancreatoduodenectomie dezelfde of zelfs betere resultaten op te leveren dan de standaard Whipple procedure voor wat betreft de postoperatieve morbiditeit, mortaliteit, kwaliteit van leven en overleving. Om de retrospectieve resultaten te toetsen is een prospectief gerandomiseerde studie gestart die de pylorussparende techniek en de standaard Whipple techniek vergelijkt. Het mogelijk effect van radiotherapie en 5-FU als adjuvante therapie wordt bestudeerd in een prospectief gerandomiseerde studie in samenwerking met de EORTC. De eerste resultaten met betrekking tot de bijwerkingen van de behandeling zijn veelbelovend, de therapie is zeer goed te verdragen. Het effect van de adjuvante behandeling op het locoregionale recidief en overleving is nog niet bekend, hiervoor

moeten eerst de benodigde 200 patiënten gerandomiseerd zijn en de follow-up van 2 jaar afgewacht worden. Wanneer er sprake is in het beloop van de ziekte na eerdere resectie van een locoregionaal recidief zonder aantoonbare afstandsmetastasen dient behandeling overwogen te worden door middel van reresectie. Het zoeken naar prognostische factoren bij het pancreascarcinoom is belangrijk omdat dit kan helpen bij het beslissen of een bepaalde patiënt een resectie moet ondergaan of niet. Als een resectie uitgevoerd is kan met behulp van prognostische factoren een schatting gemaakt worden hoelang een patiënt ongeveer kan overleven.

Echter, wanneer een arts een patiënt met een pancreaskop- of periampullair carcinoom behandelt, is het meest belangrijk dat de handelswijze verandert van een fatalistische benadering in een reële en optimistische benadering. Langdurige overleving en, bij bepaalde patiënten genezing, komt voor.

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