SURGICAL AND ADJUVANT TREATMENT OF PANCREATIC CANCER

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General introduction

General introduction

Pancreatic cancer, including ampullary, distal bile duct and pancreatic head cancer, is one of the most lethal human cancers and still is a major unsolved health problem at the start of the 21st century. It has been estimated that this disease causes 30.000 deaths per year in the USA with an incidence of 9-10 cases per 100.000 and slightly increased male: female and black: white ratios.[1,2] The incidence of pancreatic cancer in the Netherlands is approximately 8.4 per 100.000 patients.[3] This number has been quite steady over the past ten years. Pancreatic cancer currently ranks as the fifth most common cause of cancer related deaths in the western countries. Over the past 20 years the disease continuous to have an appalling prognosis with less than 1% of patients surviving more than 5 years from diagnosis, so that mortality rates and annual incidence are virtually identical.[4-7]

In numerous studies, risk factors associated with pancreatic cancer have been explored (Table 1). Tobacco smoking, diabetes mellitus and age factors are frequently studied. In diabetic patients K-ras mutation pathway has been described to be related to a higher risk for pancreatic carcinoma.[8]

The risk factors consistently referred to, are age and cigarette smoking.[9] Age specific incidence rates show that the disease is uncommon before the age of 45-years but incidence rates increase steadily thereafter so that more than 80% of cases occur in the 60-to 80-year-old age group.[9] Cigarette smoking has been reported to account for 20-30% of pancreatic cancer incidence, with reported odds rations ranging from 1.6 to 5.4.[10] Another risk factor which has been reported frequently in international literature is family history.[11,12] There are several genetic syndromes associated with an increased risk of pancreatic cancer, including hereditary pancreatitis. Patients with hereditary pancreatitis harbour a mutation in trypsinogen gene PRSS1. Auto activation of trypsin results in repeated attacks of pancreatitis and so mitogenic stimulant can lead to higher risk of getting carcinoma.[13,14] Germline mutation in DNA mismatch repair genes might provide micro satellite instability and hereditary non-polyposis colorectal cancer which is also related to increased risks for pancreatic carcinoma. Further BRCA2 germline mutations (breast cancer) the Peutz-Jeghers syndrome, familial breast cancer and familial atypical multiple-mole melanoma have been associated with increased risks for getting pancreatic cancer.[11] In the USA, in the Johns Hopkins Hospital a National Familial Registry for Pancreas Tumours has been established and encounters the largest collection of familial cases of pancreatic cancer. Early detection of patients with increased risks might benefit from early treatment.

Table 1 **Risk factors for pancreatic cancer**

Demographic factors
Old age (most reliable and important factor)
Sex (more common in males than in females)
Ethnic origin (mortality highest in black populations)
Genetic factors and medical conditions
Family history
Herediatry pancreatitis
Heriditary non-polyposis colorectal cancer
Peutz-Jeghers syndrome
Familial breast cancer
Chronic pancreatitis
Diabetes Mellitus
Gastrectomy
Deficiency in carcinogen metabolism and DNA repair
Environmental and lifestyle factors
Cigarette smoking
Occupational exposures
Low dietary intake of fruits and vegetables
Food preparation and cooking methods (grilling or charring confers the highest risk)

In some epidemiological studies of pancreatic cancer, a protective role has been noted for diets high in fruits and vegetables.[15,16] This effect might be related to dietary intake.[17] Exposure to carcinogens has long been suspected as a causal factor for pancreatic cancer, but evidence is insufficient.[18-20] The primary causal factors for pancreatic cancer are yet poorly understood. Worldwide research efforts aimed at exploring and quantifying risk factors are critical to the eventual prevention of the disease.

Molecular Biology and Genomics

In the past decades, there has been a significant increase in our knowledge of the biology and pathofysiology of pancreatic cancer although a great deal of mechanisms is yet to be explored. Many malignant diseases, including pancreatic ductal carcinoma results from the accumulation of acquired mutations. The multigenic nature of most pancreatic ductal cancers is reflected in the abnormalities of three broad classifications of genes i.e., oncogenes, tumour-suppressor genes, and genomic maintenance genes. [21,22]

The accumulated mutations in such genes are believed to occur in a predictable time course. Hruban et al. showed that pancreatic cancer follows a stepwise development from non-invasive intraepithelial precursor lesions to invasive cancer (figure 1).[23]

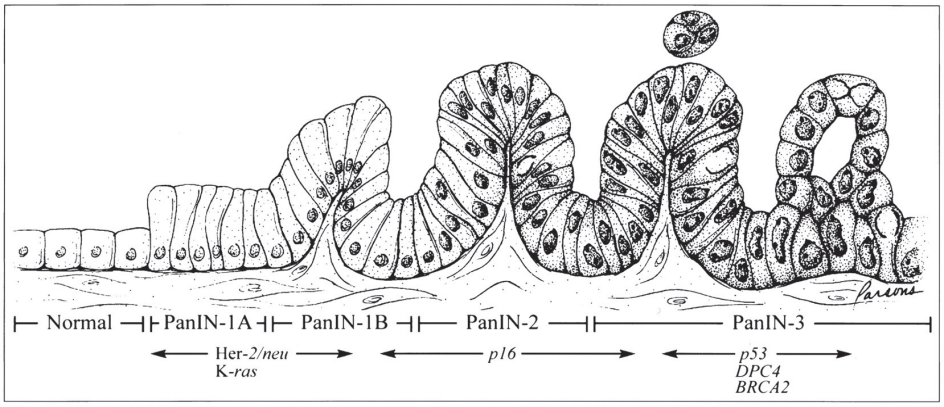
Normal duct epithelium progresses to infiltrating cancer through a series of histological defined precursors (PanINs) e.g. the histological progression from PanIn 1A to papillary duct lesion (PanIN-1B) to atypical papillary duct lesion (Pan IN-2) to severely atypical duct lesion/carcinoma in situ (PANIN-3) is associated with accumulation of specific genetic alterations.

In 1988, Perucho et al. showed that many human pancreatic carcinomas contain a mutant K-ras gene.[24] Since then there has been an explosion in our understanding of pancreatic cancer genetics. More than 85% of pancreatic ductal cancers have an activating point mutation in the K-*ras* gene at a very early stage of pancreatic-cancer development.[24] K-ras plays a pivotal role in cell proliferation and differentiation.

In the late 90's K-*ras* mutations have been detected in the duodenal juice, pancreatic juice, and stool of patients with pancreatic cancer. These findings might be helpful in the near future in order to develop an early detection strategy.[25,26]

The second most frequently inactivated tumour-suppressor gene is *TP53*, a well-characterised tumour-suppressor gene located on chromosome 17p. P53 plays an important role inducing cell apoptosis when cell damage occurs. Mutations will lead to loss of inhibitory cell-cycle regulatory mechanisms. Inactivation of this gene is a late event in tumour genesis. The *p16* tumour-suppressor gene is inactivated in around 95% of pancreatic cancers[27,28] and typically occurs later in pancreatic carcinogenesis. P16 is an inhibitor of CDK4-6 which in his turn phosphorylate the

FIGURE 1 **Progression model for pancreatic cancer. Normal duct epithelium progresses to infiltrating cancer (*left* to *right*) through a series of histological defined precursors (PanINs). The overexpression of HER-2/*neu* and point mutations in the K-*ras* gene occurs early, inactivation of the *p16* gene at an intermediate stage, and the inactivation of *p53, DPC4,* and *BRCA2* occur relatively late. (With permission from dr. Hruban)**



retinoblastoma protein. It also is involved in inhibition of the transforming growth factor (TGF-B)[29] The *MADH4* gene (*DPC4* or *SMAD4*) is inactivated in 55% of pancreatic adenocarcinomas and plays a role in the TGF-B inhibitory pathway.[30] Like *TP53*, *MADH4* inactivation is a late event in pancreatic tumour genesis.

Depending on the target population and assessment of molecular techniques, the individual mutational frequencies of tumour-suppressor genes *p16*, *TP53*, *MADH4*, and *BRCA2* were 82%, 76%, 53%, and 10%, respectively. [31]

In normal cells, cell growth, cell differentiation, and cell death are controlled and regulated through various signals that are well coordinated to ensure the maintenance of cell homeostasis. In malignant cells such as pancreatic cancer increased dysregulation of signalling pathways has been observed and many such neoplastic cells need neither mitogenic signalling to develop and further proliferate, nor do they react to inhibitory signals. The biology of pancreatic cancer is thought to be related to mutation and inactivation of these oncogenes and tumour suppressor genes, as well as abnormalities in growth factors and their receptors, which affect the downstream signal transduction pathways involved in the control of growth and differentiation and longevity genes that control apoptosis.[32]

These perturbations confer a tremendous survival and growth advantage to pancreatic cancer cells, as manifested by development of invasive and metastatic phenotypes that are resistant to all conventional treatments.

Hanahan and Weinberg have described the typical characteristics of tumour cell growth. (Table 2) Pancreatic cancer has been known to over express many growth factors and their receptors. The epidermal growth factor family are transmembrane proteins that bind to various growth actors resulting in signal transduction, which results in effects on cell differentiation. EGFR-1 is one of the most frequently described factors in pancreatic cancer and is known to be significantly over expressed.[33,34] Vascular endothelial growth factors are the main signalling molecules responsible for binding to endothelial cells of pre-existing blood vessels and activates them in the process

TABLE 2 **Characteristic of tumours cells and behaviour of growth factors and their receptors. (After Hanahan and Weinberg, Cell 2000)**

Characteristics of malignant growth	***Pancreatic cancer***
Autonomous growth control	Increased expression of: EGF, FGE, PDGF, IGF and their receptors
Resistance to growth control inhibition	Increased expression of TGF-B and its receptors; Smad4 mutation Smad 6/7 overexpression
Resistance to apoptosis	Increased expression of EGF, IGF and their receptors
Angiogenesis	Increased expression of VEGF, FGF-2 and their receptors
Invasiveness and metastasis	Increased expression of TGF-B,HGF and their receptors

of angiogenesis[35,36] Other molecules are the fibroblast growth factor,[37] and many cytokines, such as transforming growth factor,[38] interleukin 1,[39] interleukin 6,[40] tumour necrosis factor,[41] and interleukin 8,[42] these factors play a role in cell division, cell death, migration and tissue repair. The abundance of growth-promoting factors and the disturbance of growth inhibitory factors lead to evasion of programmed cell death, self-sufficiency in growth signals, angiogenesis, and metastasis.

An important focus of current pancreatic-cancer research seeks to understand the upstream molecular mechanisms leading to constitutive activation of these transcription factors. Aberrant expression of multiple-metastases-related proteins, such as interleukin 8 and vascular endothelial growth factor, might result from the alterations of several transcription-factor activities.

In general it is believed that K-ras mutation is the first step in pancreatic cancer genesis. This is followed by inactivation of tumour suppressor gene p53 and p16 so that the main mechanisms in cell-cycle regulation are disrupted. Further the transforming growth factor (TGF) inhibitory pathway is disturbed. The acquisition of aberrations in the aforementioned genes leads to profound and irreversible changes in cell regulation; this is believed to be the early stage of pancreatic cancer growth. In the late stage of pancreatic cancer development, however, important stress factors, such as hypoxia and acidosis, which are frequently encountered in the tumour microenvironment, further upregulate those metastases related proteins through activation of many transcription factors. Recent data indicate that tumour hypoxia plays a crucial role in tumour progression and tumour aggressiveness. Graeber et al. showed that hypoxia resulted in increased growth of p53 mutated cells, whereas normal cells under the same condition went into apoptosis.[43,44] Therefore, at advanced stages, uncontrolled tumour growth and the consequent development of a stress environment might increase tumour angiogenesis, growth, and development of metastases. Understanding the expression and regulation of these molecules might unravel the pathophysiology of pancreatic cancer, and suggest new targets for preventive and treatment approaches to pancreatic cancer.

Tumour types

Almost 80-90% of all pancreas tumours are adenocarcinomas with a ductal phenotype. Neuroendocrine tumours and acinar cell carcinomas represent about 2-5% of all pancreatic tumors.[45,46] Pancreatic ductal adenocarcinomas are characterized histological by atypical glands embedded in a dense fibrotic stroma. Although histological very similar, adenocarcinomas of the distal bile ducts and the ampulla of Vater should be considered separately because they usually have a better prognosis owing to a higher rate of resectability due to an earlier detection of symptoms

(jaundice) and less invasion in large vessels. Trede et al[47] showed that even small periampullary tumours tend to infiltrate in peripancreatic tissue. Pancreatic tumours (< 2cm) showed 75% infiltration in blood vessels and 60% in perineural tissue, ampullary cancer (< 2 cm) showed only 33% blood vessel invasion and 25% perineural infiltration, whereas bile duct tumours (< 2 cm) showed similar percentages ingrowth as pancreatic head cancer.

Pathology reports from large series from high volume centres in Europe (Trede et al)[47] and USA[48-50] showed that 80 percent of ductal carcinomas were located in the head (periampullary region), 16% in the body and 2.5% in the tail of the gland. Of the tumours in the periampullary region 80% is located in the head, 15 % in the ampulla and 15% in the distal common bile duct. The diameter of the tumours depends generally on their location in the pancreas. Carcinomas of the ampulla are smaller than tumours in the head, bile duct and body. Tumours in the tail are usually larger than 4 cm.

Nowadays there is evidence that periampullary tumours do differ according to histological characteristics. Pathological details from the largest series known to date[49] showed a median tumour diameter of 3 cm in patients with pancreatic ductal adenocarcinoma. The majority of these cancers were poorly or moderate differentiated. There was a 29% incidence of margin positivity, and 70% of patients had node positive resections. In contrast to those with pancreatic head cancer, patients undergoing resection for ampullary or distal bile duct adenocarcinoma had a significantly lower incidence of positive resection margins (range 3-9%) and a lower incidence of node positive resections (range 42%-62%). Tumour diameters are also smaller with a median diameter of 2 cm for both ampullary and bile duct cancer. After multivariate analysis four factors were found to adversely effect survival: 1. Tumour diameter > 3 cm; 2. Positive resection margins; 3. Positive lymph nodes and 4. The presence of a poorly differentiated tumour.[49]

These findings suggest ductal adenocarcinoma of the pancreatic head is a biological different tumour compared to bile duct and ampullary adenocarcinoma. Most tumour types other than pancreatic ductal adenocarcinomas tend to be more amenable to therapeutic interventions such as resection, chemotherapy, or irradiation.[46]

Clinical features

The general features of a periampullary tumour are mainly the consequence of tumour extension; carcinomas of the head and more particularly those of the distal common bile duct or ampulla of Vater will cause progressive jaundice in an early onset.[51] In patients with small tumours, painless jaundice might be the only sign. Many patients however, experience an antecedent period of fatty diarrhoea, weight

loss, abdominal back pain followed by obstructive jaundice. Back pain is probably caused by invasion of the tumour into the splanchnic plexus and retroperitoneum. Nausea and vomiting can be caused by jaundice, or in a progressed stadium by duodenal obstruction the latter is a late manifestation of the disease. New onset of diabetes is observed in 15% of cases and about 3% of pancreatic cancer patients present with acute pancreatitis.[46]

Diagnostics

The overall 5-year survival rate for patients with pancreatic carcinoma is approximately less than 5%.[7] At the time of diagnosis the majority of patients have distant metastasis or/and locally advanced pancreatic carcinoma. The goal of CT-scanning is to detect those patients who might undergo a potential curative resection. With modern scanning techniques it is possible to detect liver lesion smaller than 1cm, peritoneal metastasis, suspect lymphnodes as well as vascular encasement.

If patients present with painless jaundice, the work-up in the Erasmus MC is first to perform a CT scan. Thereafter it is mandatory to drain the obstructed biliary tract using endoscopic retrograde cholangiopancreatography (ERCP).[52]

In the past high mortality rates of up to 30% made surgeons cautious to perform a Whipple procedure without a definitive tissue diagnosis. Today however with mortality rates lower than 5% the need for a percutaneous taken tissue sample is not recommended; moreover there is a risk of peritoneal seeding using this technique. Therefore in the Erasmus MC biopsy of a suspected pancreatic mass are taken using endoscopic ultrasound guided biopsy. This technique has the advantage of extra imaging the tumour in relation with the large vessels, and offers the possibility of a tissue diagnosis without the risk of seeding out of the resection field. The technique can also be considered for patients with locally advanced disease in whom neoadjuvant therapy is being considered or if palliation with chemoradiotherapy is necessary.[53-55] With the use of this technique, pancreatic biopsy samples obtained during laparotomy are rarely required and should be discouraged. For patients presenting with liver metastases and an obvious pancreatic mass, liver biopsy is an appropriate alternative, and if positive for adenocarcinoma, is acceptable as evidence of metastatic pancreatic cancer.

In sum, thin cut (2mm) dynamic multiphase helical CT scan of the abdomen is the most important preoperative imaging study.[56]

Laparoscopy with or without utrasonography is a surgical tool which is frequently recommended to rule out the presence of small superficial livermetatases or peritoneal metastases for patients who seem to have resectable disease or locally advanced disease on the basis of preoperative imaging studies.[57] For patients with

locally advanced disease detection of metastases with laparoscopy prevents the non-effective chemoradiation and for patients with resectable disease an unnecessary explorative laparotomy.

Resectable disease is defined, based on preoperative work up, as a pancreatic tumour without evidence of involvement of the superior mesenteric artery or celiac axis, a patent superior mesenteric portal venous confluence and no evidence of distant metastases. Around 10-20% of patients admitted to the hospital are suitable to undergo a resection. Most patients have locally advanced disease or distant metastases at time of diagnosis. Resectable tumours are generally located in the pancreatic head. Consequently, a standard pancreaticoduodenectomy (Whipple's operation) or a modified procedure of this approach (Pylorus preserving technique) is performed.

Pancreaticoduodenectomy

The surgical history of the treatment of periampullary tumours encompasses the past 100 years. Alessandro Codivilla, an Italian surgeon was the first surgeon to try, in 1898 to perform an en bloc resection of the head of the pancreas and duodenum for periampullary carcinoma, but the patient did not survive the postoperative period.[58] In Germany, in 1912 Walter Kausch, described the first successful pancreaticoduodenctomy in two stages.[59] In 1914, Hirschel reported a successful one-stage pancreaticoduodenectomy.

In 1935 Allan Oldfather Whipple reported three patient with ampullary cancer treated by a two stage pancreaticidoudenectomy.[60] In 1937 Brunschwig reported extending the indication for pancreaticoduodenctomy to include cancer of the head of the pancreas.[61] During the 1940s and 1950s pancreaticduodenectomy was accomplished routinely as one stage procedure, applied to patients with periampullary neoplasms and was performed with increased frequency. During the 1960s and 1970s, pancreaticoduodenectomy was a formidable operation, which carried a hospital mortality that approaches 25% in some series and led some authors to suggest that its use should be abandoned.[62,63] There were however exceptions to this high mortality rate, notably a report by Howard in 1968 describing 41 consecutive patients treated by pancreaticoduodenctomy without hospital mortality.[64] In recent years improved hospital mortality and survival after pancreaticoduodenectomy have been reported.[65-68] Trede et al.[69] reviewed 118 consecutive resections without an operative death in 1990, whereas a report from the Johns Hopkins in 1993 described 145 consecutive pancreaticoduodenectomies without mortality.[48] Overall, although pancreaticoduodenectomy remains a formidable operation, many centres now have reported hospital mortality rates of < 4%, with the mortality rate approaching 1% in

selected series. At present leakage of the pancreaticojejunostomy is the most feared complication and accounts for the remainder of postoperative mortality. [70]

To date the standard resection resection still bares Whipple's name. Since the introduction of this technique several modifications have been reported, including the pylorus-preserving pancreaticoduodenectomy (PPPD) described by Watson in 1944.[71] Later on this technique was re-introduced by Traverso and Longmire in the late 1970s for chronic pancreatitis. [72] The classic Whipple operation consists of an en bloc removal of the pancreatic head, the duodenum, the common bile duct, the gall bladder, and the distal portion of the stomach together with the adjacent lymphnodes. This operation can lead to specific complications such as early and late dumping, postoperative weight loss and postoperative reflux. Leaving the functioning pylorus at the gastric outlet, the PPPD represents a surgical alternative that is being performed by an increasing number of surgeons. Preservation of the pylorus in pancreaticoduodenectomy has been shown to lead to a long-term improvement in gastrointestinal function, improved postoperative weight gain and less dumping. The pylorus preserving procedure is a less extensive operation, and should lead to decrease in operative time and less intra-operative blood loss.[73] [74] On the other hand prolonged hospital stay due to delayed gastric emptying has been reported.[75,76] Another criticism especially in malignant disease is radicality of the pylorus preserving pancreaticoduodenectomy. In some patients, especially the ones with large tumours of the pancreatic head, the PPPD has been doubted to be curable.[50,77] In our centre the standard Whipple operation is performed for tumours invading the post pyloric duodenum or tumours with suspected infiltration in the antrum and suspected lymphnodes around the pylorus. Today the best technique to treat periampullary cancer is still under debate. In the literature only a few trials had been performed. Seiler et al.[78] randomised 139 patients for either a standard Whipple procedure or a PPPD. The Whipple group had a significant shorter operation time, and no difference was found in mortality and morbidity. The incidence of delayed gastric emptying was identical in both groups. For long-term follow-up, a total of 76 patients with histological proven pancreatic or periampullary carcinoma were analyzed. There was no difference in tumour recurrence and in long-term survival after a median follow-up of 1.5 years (0.1-3.5). They concluded both procedures were equal radical. Lin et al.[79] included 36 patient and reported equal intraoperative results for both procedures. Delayed gastric emptying was observed more frequently after PPPD (six of 16 patients) than after the Whipple procedure (one of 15 patients), with marginal significance (P = 0.08, two-sided Fisher's exact test). Unfortunately no information about radical resection was given in this paper.

In conclusion literature leaves us inconclusive results. Results from a retrospective study in the Erasmus MC showed favourable outcome for the PPPD.[73] Based on these results we conducted a multicentre randomised clinical trial to establish

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whether the PPPD is a safe and radical procedure in patients with malignant disease of the periampullary region compared to the standard Whipple's procedure.

Survival and recurrence

As a result of better surgical technique, mean operating time, morbidity, and mortality as well the need for perioperative transfusions, reinterventions have been greatly reduced over the past few decades. Decreased hospital mortality, from 25% (1960-70s) to below 5% in present time, certainly has helped improve survival. The most stunning example of these better surgical skills is presented in the series of the John Hopkins. In this series of 1000 consecutive pancreaticoduodenectomies a mortality rate of 1 % was reached.[49] The median operative time decreased from 8.8 hour in the 1970s to 5.5 hours during the 2000s. Postoperative length of stay dropped from a median of 17 days in the 1980s to 9 days in the 2000s. Overall survival for patients with pancreatic head adenocarcinomas was 18%; for the lymphnode negative patient, it was 32%; and for node negative, margin negative patients, it was 41%. Among the other periampullary tumours, 5-year survival for distal common bile duct carcinoma was 22%, for ampullary adenocarcinoma 5-year survival was 39% and for duodenal cancer five-year survival was 52%. Other high volume institutions report similar survival rates around 20% after resection for pancreatic head cancer.[49,69,80] Compared with survival rates from the past (rates of less than 5%) todays reported rates truly increased.

Thus, operating time, hospital stay and mortality have been greatly reduced due to better surgical technique. Important to keep in mind is the facts that at about 80-90% of patients do have nonresectable disease and if resectable, survival is still disappointing compared with other solid tumours. As is shown in the aforementioned paragraphs resectable disease is mainly located in the pancreatic head. When there is no lymph node or vascular invasion, 5-year survival rate is at about 20%. Prognostic factors include nodal status, negative resection margins and tumour size. To improve the therapeutic outcomes in patients with pancreatic cancer several strategies haven been pursued: extended pancreaticduodenctomy; total pancreatectomy; superradical resections procedures and preoperative and intraoperative radiotherapy. Comparison of these different procedures did not reveal any benefit for extensive procedures. In a recently published metaanalysis of standard and extended lympadenectomy by Michalski et al.[81] who found similar survival rates and mortality and morbidity rate.

Irrespective of the therapy used local recurrence in the retroperitoneal resection area, followed by liver metastases and peritoneal dissemination are common and thereby determine survival. Even after a macroscopically radical resection, distant

micro metastases may already exist and tumour cells are often observed at one or more edges of the resected specimen (R-1) in 20 to 51% of cases.[82,83] [51,84-87] An explanation for this early seeding and early local recurrence can be found in tumour behaviour and tumour characteristics and has been described in several studies. Relevant prognostic variables reported are tumour size, positive lymph nodes and histological differentiation.[82,83,88,89] These factors strongly limit survival after resection and together with the metastatic intend of this type of tumour suggest that pancreatic cancer is a systemic disease. In this manner surgery as sole treatment is not enough to gain long term survival. Patients treated with surgery alone, develop local recurrence in up to 50%-80% peritoneal recurrence in 25%, and liver metastases in 50%. [51]

Adjuvant treatment

As is shown above comparison of the various surgical approaches does not provide significant difference in terms of overall survival, moreover reveals higher mortality and morbidity with the more radical procedures.[82]

However a comparison of patients with negative and positive resections margins showed 5-year survival rates of 22% and 0%, respectively.[83] Further we know that positive lymph nodes significantly decrease survival. These results have prompted several studies of surgery in combination with radiotherapy and/or chemotherapy. In order to study the benefit of these so called adjuvant treatment much effort has been put in trials comparing adjuvant chemoradiotherapy and chemotherapy to surgery alone. The results were contradicting among different trails.[84,86,90-92]

Adjuvant systemic chemotherapy

There are not many studies published on adjuvant chemotherapy alone in pancreatic cancer. In 1980 Splinter et al. started a pilot study to investigate the feasibility of five courses of adjuvant 5-fluorouracil, Adriamycin and mitomycin C (FAM) after a curative resection of pancreatic or periampullary cancer. The survival of this group of patients was compared with that of 36 patients who underwent a curative resection alone between 1977 and 1984. Four patients received less than 20%, 4 patients 50%-60% and 7 patients greater than or equal to 80% of the calculated dose of adjuvant chemotherapy. The chemotherapy was badly tolerated. Only 1 patient resumed some of his normal activity during chemotherapy. The 3-year actuarial survival after curative resection with and without FAM was similar, i.e. 24% and 28% respectively. These data suggest that adjuvant FAM after a Whipple's oper-

ation or total pancreatectomy was not feasible because of additive postoperative and chemotherapy-induced morbidity.[93]

In 1994 Baumel et al.[82] reported retrospectively a large cohort of 787 patients who had undergone pancreas resection, 43 of whom received adjuvant chemotherapy. No difference in survival was demonstrated. The first randomised controlled trial was performed by Bakkevold et al[91] in 1993. In this study 47 patients with resected pancreatic ductal cancer were randomised to either postoperative combination chemotherapy of 5-FU, doxorubicin, and mytomycin C every 3 weeks or surgery only. A significant improvement was seen in median survival from11 months to 23 months with chemotherapy, however no improvement in long-term survival (3 and 5 year) was seen. Unfortunately it is difficult to draw conclusions on this study in relation to pancreatic head cancer because 14 patients with ampullary cancer were included. Lately, The European Study Group for Pancreatic Cancer (ESPAC) randomised more than 500 patients to adjuvant chemotherapy, chemoradiotherapy, and surgery alone.[86] The chemotherapy consisted of an intravenous bolus 5-FU (425 mg/m^2) and folonic acid (20 mg/m^2) and was given on 5 days out of 28 days for six cycles. The median survival for patients treated with chemotherapy was 21.6 months for chemotherapy versus 14.8 months for patients with surgery alone. The same survival benefits for chemotherapy were observed irrespective of the extent of resection or the development of postoperative surgical complications. The ESPAC-1 study showed a reduction in the hazard ratio (HR) of 36% in favour of adjuvant chemotherapy. (HR 0.64, confidence interval (CI) 0.52-0.78). Despite its size, the ESPAC-1 trial is itself controversial because of the use of different randomisation options based on doctors preferences. Further patients in this trial were allowed to receive additional treatment options, this raises additional questions about the effect of primary treatment and if additionl treatment has affected the primary outcomes.

One of the latest randomised adjuvant trials is from Japan.[94] It consisted of 5-FU and mitomycin C in resected pancreaticobiliary carcinomas. In total, 508 patients were randomised, of whom 173 patients had ductal adenocarcinomas. There were 89 patients included to receive chemotherapy and 84 to the control arm, of whom 45 and 47 respectively underwent curative resections. The chemotherapy group received rapid infusion mitomycin C on the day of surgery, slow infusion 5-FU for 5 days in week 1 and 3, followed by oral 5-FU. The median survival was approximately 12 months in both the chemotherapy and the control group, with no significant difference in 5-year survival (11.5% and 18% respectively).

The main chemotherapy regimen in this study was 5-FU which was administered orally. The surprisingly low survival rates in both groups might be explained by the unpredictable absorption of 5-FU.

Recently Oettle et al. finished a large multicentre trial.[95] The objective was to test the hypothesis that adjuvant chemotherapy with gemcitabine administered after complete resection of pancreatic cancer improves disease-free survival by 6 months or more. Patients received adjuvant chemotherapy with 6 cycles of gemcitabine on days 1, 8, and 15 every 4 weeks (n=179), or observation ([control] n=175).

Median disease-free survival was 13.4 months in the gemcitabine group (95% confidence interval, 11.4-15.3) and 6.9 months in the control group (95% confidence interval, 6.1-7.8; P<. 001, log-rank). Remarkable is the very low survival rate in the control group in most other series survival after surgery and best supportive care ranges between 10 and 12 months. Estimated disease-free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group, and 7.5% and 5.5% in the control group, respectively. Subgroup analyses showed that the effect of gemcitabine on disease-free survival was significant in patients with either R0 or R1 resection. There was no difference in overall survival between the gemcitabine group (median, 22.1 months; 95% confidence interval, 18.4-25.8; estimated survival, 34% at 3 years and 22.5% at 5 years) and the control group (median, 20.2 months; 95% confidence interval, 17-23.4; estimated survival, 20.5% at 3 years and 11.5% at 5 years; P=.06, log-rank).

Adjuvant regional chemotherapy

In a surge for high dose chemoradiation without the risks of systemic toxicity a new treatment module was designed years ago. This technique uses intra-arterial catheters to deliver high dose local chemotherapy.

The published studies so far have produced encouraging results. Different therapeutic regimens have been tried using selective arterial and/or venous delivery. Link and Beger et al.[96,97] reported several studies using adjuvant chemotherapy consisting of mitoxantrone, folonic acid, cisplatin and, 5-FU. Initially 20 patients (18 with pancreatic head adenocarcinoma, 2 cystadenoma) underwent the regimen infused via the celiac axis. A median survival of 21 months was achieved compared with 9.3 months for historical controls. An update of this study, with 24 patients, showed a median survival of 23 months and a 4-year survival of 54%.

Ishikawa et al[98] delivered postoperative hepatic infusion of 5-FU, via catheters placed in both the hepatic artery and portal vein, in 27 patients. This perfusion was undertaken for 28-35 days. There were no treatment related complications in the 20 patients who survived surgery. A 3-year survival rate of 54% was achieved, with mortality from hepatic metastases at a mere 8%. This was compared to historical controls and found to be significantly better.

These results were the reason for starting a prospective randomised controlled trial in the Erasmus MC to determine the effect of chemotherapy via the celiac trunk and radiotherapy for the tumour bed in order to gain significant survival benefit. The trial has been closed now and results are soon going to be published.

Adjuvant chemoradiotherapy

Adjuvant (postoperative) therapy has been studied in a few trials but the role of adjuvant therapy in resectable pancreatic cancer is still uncertain, and no recommended standard protocol exists.

The Gastrointestinal Tumour study group (GITSG) was the first to report from adjuvant chemoradiation in a randomised clinical trial.[92] The protocol used contained 40 Gy radiotherapy combined with fluorouracil and then weekly fluorouracil for two years. Median survival was significantly longer in the adjuvant treatment group compared to the surgery group (20 months versus 11 months), with respectively 18 percent and 8 percent survival at five years.[92] Further larger randomised studies however did not confirm a benefit of adjuvant treatment.[84,91,94] Moreover, it is unclear whether the survival advantage in the GITSG trial was due to the combination of chemoradiation and maintenance chemotherapy or to only one of these treatments. Therefore ErasmusMC Rotterdam conducted a randomised phase III multicentre trial in cooperation with the EORTC Gastro-intestinal group. This trial was initiated in 1987 (EORTC 40891) and used the same amount of radiotherapy however unlike the GITSG no maintenance 5-FU was given. Based on 218 patients, this trial results at a median follow-up of 7.3 years did not show a benefit for adjuvant chemoradiation although they suggested a trend in favour of chemoradiation (p=0.09) in the patients with ductal pancreatic adenocarcinoma. [84]

p=0.09
Geen Kapitaal?
+ Cursief?

Later on The European Study Group for Pancreatic Cancer (ESPAC) undertook a multicentre factorial phase III trial to investigate the possible benefits of adjuvant chemoradiation and maintenance chemotherapy in patients with pancreatic cancer. In this study a deleterious effect of adjuvant chemoradiation on survival was shown, with a median survival of 15.5 months in the 175 patients who received chemoradiation compared with 16.7 months in the 180 patients who did not. Also there was no survival benefit conferred by adjuvant chemoradiation in patients with microscopically positive resection margins (R-1) whereas chemotherapy significantly improved survival in patients with resected pancreatic cancer.[85,86,99]

Of interest is the cohort study of Metha et al.[100] from Stanford. In this study 52 patients were treated with chemoradiation. The tumour bed and regional lymph nodes were irradiated with a dose of 45 Gy in 1.8-Gy fractions followed by a boost to the tumour bed in 355 of patients with a positive resection margin (total dose 54 Gy).

Concomitant portal venous infusion of 5-FU (200-250 mg/m^2 per day, 7 days per week) was given during the entire radiotherapy course. A remarkable median survival of 32 months was achieved. Certainly these results are far superior to other studies that have used concomitant bolus 5-FU or even continuous-infusion 5-FU, however the results are non-randomised.

Klinkenbijl et al.[84] found a trend towards prolonged survival in patients treated with chemoradiation whereas Neoptolemos et al.[86] found a deleterious effect for chemoradiotherapy and a positive effect of chemotherapy. Long-term follow-up gives an opportunity to show actual survival curves instead of actuarial survival and thereby might reveal a define conclusion whether chemoradiotherapy is effective or not.[7]

Locally advanced disease and therapies

Locally advanced pancreatic cancer is defined as a tumour that encases a vascular structure, such as the superior mesenteric artery, celiac axis, or superior mesenteric vein-portal confluence with absence of distant metastases. Tumours associated with bulky peripancreatic lymph adenopathy are also deemed unresectable.

Since 1982 Erasmus MC has offered treatment to patients with locally advanced non-resectable adenocarcinoma without presence of distant metastases and with a Karnofsky performance score of 80 or more. Radiotherapy consisted of 50 Gy external upper abdomen radiation in two courses, concomitant with intravenous 5-FU 375 mg/m2 given as a bolus injection 4-6h before radiation on the first 4 days of each treatment course. The treatment protocol was completed in 18 patients without complications. The median survival time was 10 months, which compares favourably with a 3-5 months median survival time when treatment is withheld. [101] This intervention provides a survival advantage and offers a palliative benefit.

In the early and mid 1980s the GITSG did a three-treatment group randomised trial in patients with locally advanced pancreatic cancer.[102,103] Patients received radiation alone to a dose of 60 Gy, 5-FU plus intermediate dose radiation to 40 Gy or fluorouracil plus radiation to 60 Gy. Those receiving chemoradiation had a median survival of 42-44 weeks; those undergoing radiation alone had a median survival of 23 weeks. Thus the combination therapy doubled survival compared with radiation alone. Several other trials have shown an improvement in objective response rates, overall survival and a statistically significant clinical benefit when compared to the best supportive care.[104,105] Despite the fact that the achieved objective response rate is encouraging there are controversial results concerning overall survival: with 1-year survival rates from 22% (Gemcitabine-irinotecan) and 34,8% (Gemcitabine-capecitabine).[106-108]

In an attempt to increase survival Moore et al.[109] added an EGFR targeted agent to gemcitabine and compared the treatment to gemcitabine alone. In this randomised phase III clinical trial a total of 569 patients were randomly assigned to gemcitabine plus erlotinib (100 or 150 mg/d orally) or gemcitabine plus placebo. Median survival was 6.24 versus 5.91 months in the gemcitabine alone group (p=0.038).

The rationale for chemoradiation for locally advanced pancreatic cancer without metastases has been very recently discussed in a meta-analyses by Sultana et al.[110] This analysis included 794 patients in eleven studies up till 2006. Length of survival with chemoradiation was increased with a 31% reduction in risk of death following chemoradiotherapy, compared to radiation alone (HR 0.69; CI 0.51–0.94) but chemoradiation followed by chemotherapy did not lead to a survival advantage over chemotherapy alone (HR 0.79; CI 0.32–1.95) caution is necessary interpret ting this conclusion because important clinical differences could not be ruled out due to the wide C.I. Unfortunately meta-analyses could not be performed for the comparison therapy versus best supportive care for there where no qualified randomised trials.

Neoadjuvant treatment

Chemoradiation for locally advanced pancreatic cancer has also been studied in neo adjuvant setting. More over neo-adjuvant treatment has not been studied specifically for primarily resectable pancreatic cancer but largely in suspected locally advanced pancreatic cancer. Neo-adjuvant therapy has several theoretical advantages. For eventually resectable patients who initially deemed non resectable in pre operative work up it reduces the time interval between diagnosis and systemic treatment. Many patients cannot be treated directly after surgery due to wound healing and postoperative complications. Approximately 20%-45% of resected patients never undergo adjuvant therapy because of postoperative problems.[84]

Further neoadjuvant therapy may also be given in the hope to downstage locally advanced cancer and achieve an enhanced resection site. In patients with rapidly progressive disease a major surgical procedure might be avoided.

There have been only a few (non randomised) studies on the use of neoadjuvant therapy. Snady et al[111] reported median survival of 32 months in 20 patients who had a resection from an original group of 68 patients treated first with simultaneous split course EBRT plus 5-FU, streptozin and cisplatin. The median survival of the whole group was 23.6 months and 32 months in the 20 patients who also had a resection. During the same period another group of 91 patients with respectable disease initially underwent resection (5% mortality < 30 days), of which 63 (69%) received chemotherapy with or without EBRT. The median survival in this latter

group was 14.0 months (p=0.006) compared with RT-FSP-group). Median survival in patients who had resection and adjuvant treatment was 16 months compared with 11 months in those who did not have adjuvant therapy (p=0.025). In contrast the M.D. Anderson Group in their (non randomised) studies have not shown a significant difference in survival between those patients who underwent neoadjuvant compared with adjuvant treatment.[112] Mehta et al have recently reported a median survival of 30 months with neoadjuvant therapy but only in nine selected patients.[113]

All aforementioned studies on neoadjuvant therapy suffer more or less from confounding factors, however the results and the rationale for introducing neoadjuvant treatment are sound but yet non –proven due to lack on qualified randomised trials.

There is still place for studies analyzing the effect of chemoradiotherapy for patients with locally advanced disease. The goal is downstaging the tumour that might eventually result in making tumours resectable and even curable.

Interferon

Interferon-based adjuvant chemoradiation therapy has been introduced as a novel treatment option after pancreaticoduodenectomy for pancreatic adenocarcinoma. In a study by Traverso et al. 43 patients with adenocarcinomas in the pancreatic head underwent PD and were treated adjuvantly. Pathologic findings were stage I (2%), II (12%), III (72%), and IVa (14%) while 84% had positive lymph nodes. Tumour extended through the capsule of the surgical specimen in 70%. These patients then received our investigational protocol consisting of external-beam irradiation at a dose of 4,500 to 5,400 Gy (25 fractions over 5 weeks) and three-drug chemotherapy: continuous infusion 5-FU (200 mg/m(2) daily, days 1 to 35), weekly intravenous bolus cisplatin (30 mg/m(2) daily, days 1,8,15,22,29), and subcutaneous alpha, interferon (3 x 10(6) units, days 1 to 35). This chemoradiation was followed by continuous infusion 5-FU (200 mg/m(2) daily, weeks 9 to 14 and 17 to 22). Chemoradiation was generally initiated between 6 and 8 weeks after surgery.

Actuarial overall survival for the 1-, 2-, and 5-year periods was 95% (confidence interval [CI] = 91% to 98%), 64% (CI = 56% to 72%), and 55% (CI = 46% to 65%), respectively.

This follow-up report further suggests overall survival may be improved for patients with adenocarcinoma in the pancreatic head using an adjuvant interferon-based chemoradiation protocol. These results are obtained despite a high incidence of node involvement and advanced tumour stage. From this limited patient series, the actuarial 2-year and 5-year overall survival rates suggest a potential for improved long-term survival. Results of a multi-institutional study are underway.

Summary

Surgery today is the only change of cure for patients with pancreatic cancer.

Adjuvant chemotherapy may positively affect survival although reported survival benefits are marginal. Chemoradiotherapy, despite the widely acceptance in the USA should not be given routinely because nowadays there is no evidence that shows favourable effect compared to surgery alone.

In the future choice of therapy might be based both on molecular and histopathological assessment of the tumour. Knowledge of the molecular basis of pancreatic cancer has led to various discoveries concerning its character and type. Well-known examples of genetic mutations in adenocarcinoma of the pancreas are k-ras, p53, p16, DPC4. Use of molecular diagnostics and markers in the assessment of tumour biology, may in future reveal important subtypes of this type of tumour and may possibly, predict the response to adjuvant therapy. Defining the subtypes of pancreatic cancer will hopefully lead to target specific, less toxic and finally more effective therapies eventually resulting in long-term survival or even complete cure.

The main challenge is to improve survival rates over the coming years. Therefore both evaluation of current surgical and adjuvant therapies, and initiating novel studies on biological behaviour are of pivotal importance.

AIM of this thesis

The aim of the thesis is to evaluate modern surgical techniques, and to determine clinical, histological and molecular factors that may predict long-term survival. In the final part of the thesis the effect and benefit of adjuvant treatment after curative resection and neoadjuvant therapy for locally advance disease is studied.

Outline of this thesis

A general introduction is given in chapter 1.

In chapter 2 an overview of the results of surgical and adjuvant strategies is discussed.

A randomised controlled trial comparing the standard Whipple procedure with the pylorus preserving pancreaticoduodenectomy (PPPD) is described in chapter 3.

Losse alinea's zo houden?

The aim of this study was to find out which of the most used surgical resections to date gives the best chance for cure and the least morbidity. This is emphasized in a clinical multicentre randomised trial.

In chapter 4 clinical, pathological and molecular prognostic factors after R-0 resection are described. In this study a search was made for factors, which could foresee long-term survival and might give a lead for more specific adjuvant treatment

Chapter 5 describes the effect of chemoradiation after curative resection for pancreatic cancer. This is studied in a prospective randomised multicentre trial with an actual follow up exceeding more than ten years.

In chapter 6 we discuss the need for radiotherapy after irradical resections this is followed by a retrospective analysis of our experience with chemoradiation for patients with locally advanced adenocarcinoma of the pancreas (chapter 7).

The summary and conclusions are described in chapter 8.

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Chapter 2

Survival after surgical management of pancreatic adenocarcinoma

Does curative and radical surgery truly exist?

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Abstract

Surgery for pancreatic cancer offers a low success rate, but it provides the only likelihood of cure. Modern series show that, in experienced hands, the standard Whipple procedure is associated with a five-year survival of 10 to 20% with a perioperative mortality rate of less than 5%. Most patients, however, will develop recurrent disease within two years after curative treatment. This occurs usually either at the site of resection or in the liver. This suggests the presence of micrometastases at the time of operation. Negative lymphnodes are the strongest predictor for long-term survival. Other predictors for a favourable outcome are tumour size, radical surgery and a histopathologically well-differentiated tumour. Adjuvant therapy has so far only shown modest results, with 5-FU chemotherapy to date the only proven agent able to increase survival. Nowadays the choice of therapy should be based on histopathological assessment of the tumour. Knowledge of the molecular basis of pancreatic cancer has led to various discoveries concerning its character and type. Well known examples of genetic mutations in adenocarcinoma of the pancreas are k-ras, p53, p16, DPC4. Use of molecular diagnostics and markers in the assessment of tumour biology, may in future reveal important subtypes of this type of tumour and may possibly, predict the response to adjuvant therapy. Defining the subtypes of pancreatic cancer will hopefully lead to target specific, less toxic and finally more effective therapies.

Long term survival is observed in only a very small group of patients contradicting the published actuarial survival rates of 10-45%. Assessment of clinical benefit from surgery and adjuvant therapy should therefore not only be based on actuarial survival but also on progression-free survival, actual survival, median survival and quality of life (QOL) indicators. Survival in surgical series is usually calculated by actuarial methods. Without information on the total number of patients, the number of actual survivors and a clear definition of the subset of patients, actuarial survival curves can prove to be misleading. Proper assessment of QOL after surgery and adjuvant therapy is of the utmost importance, as improvements in survival rates have so far proved disappointing.

Introduction

Adenocarcinoma of the pancreas remains a formidable therapeutic challenge. For the majority of patients this is a systemic disease. Surgical resection offers a low success rate, but provides the only chance of cure. Allessandro Codivilla and later Walter Kausch first described the technique of pancreaticoduodenectomy in 1898 respectively 1912. Allen Old Father Whipple later popularised the procedure that

today bears his name.[1,2] Since Whipple's time significant advances have been made in the surgical management of pancreatic cancer. In early series published in the late 1960s postoperative morbidity rates exceeding 60% and mortality rates approaching 25% were reported. Most recent series from institutions that specialise in treating pancreatic cancer report mortality rates less than 5%, with morbidity remaining high at 30 to 60%. The majority of perioperative complications are not life threatening, though they are responsible for increased length of hospital stay and cost, readmission for care, and delays in adjuvant therapy. Limited progress has been made at improving the survival of patients with this disease despite the advances made in surgical technique and perioperative care. The 5-year survival rate is the lowest of all known types of cancer. Low rates of resectable tumours and early recurrence are the main problems facing a surgeon treating pancreatic cancer. The resectability rate for a total of 16,942 patients in the USA was only 13,3% and 5-year survival 4%.[3]

The incidence of adenocarcinoma of the pancreas has been increasing worldwide in recent years and it is currently the fourth leading cause of cancer related mortality in North America.[4] In the Netherlands and in Germany the incidence ranges between 9 and 19 patients per 100,000 inhabitants, making it the fourth leading cause of cancer related death. At the time of diagnosis, more than 85% of tumours have extended beyond the organ's margins, and invasion of the perineural spaces within and beyond the pancreas is present.[5,6,7,8,9]

Definitive curative resection is possible in no more than approximately 10% of all cases. The likelihood of a curative resection depends on both location and stage of the tumour. Localisation of the tumour near the papilla is correlated to early detection due to the presence of obstructive jaundice.

The main challenge is to improve survival rates over the coming years. Since the beginning of the 20th century not much improvement of survival has been achieved despite extensive trials into adjuvant and neoadjuvant therapy regimes. Improvement of survival has mostly been reached by better surgical skills and improvements in peri- and postoperative care. As has been stated earlier, mortality of less than 5% should be achievable in high volume centres.

An urgent need exists for better insight into both genetics and natural behaviour of pancreatic cancer. Molecular biology studies and molecular diagnostics might lead to more sensitive and specific treatment programs and will hopefully improve survival for patients who are diagnosed with pancreatic cancer.

Hope exists that in the new millennium, a multidisciplinary and integrated approach to pancreatic adenocarcinoma will unravel the mystery of this malignancy, making it more amenable to early screening and therapy.

Surgical treatment

The ultimate goal of surgical management of pancreatic neoplasm is total curation. Preferably surgical treatment should remove all visible tumour with low mortality and morbidity and short hospitalisation. Surgery ideally includes a radical (R0) resection and reestablishment of gastrointestinal continuity. Although surgical management of pancreatic cancer has so far enjoyed low success rates, it still provides the only hope of curation. Since the introduction of pancreaticoduodenectomy by Walter Kausch in 1912, significant advances have been made. Postoperative morbidity and mortality rates vary in various publications over the decades. Modern series show that in experienced hands, the standard Whipple procedure is associated with a five-year survival of 10 to 30% in completely resected patients with a perioperative mortality rate of less than 5%.[10,11,12,13,14,15,16,17,18,19] This relatively low perioperative mortality rate represents a decline from over 15% in the 1970s, thus making the Whipple operation a much more attractive option. The most important factor in these falling mortality rates appears to be concentration of cases in so called high volume institutions. From the Medicare database, a fourfold increase in mortality is found when pancreaticoduodenectomy procedures are performed in hospitals with less than one case per year compared to operations performed in hospitals handling more than 16 cases per year. A similar improvement in long term outcome was noted.[20,21]

The prognosis for pancreatic cancer remains poor even with surgically negative margins in appropriately selected patients. The most important prognostic factor in radical resections has been shown to be nodal status. Five-year survival after pancreaticoduodenectomy is only about 10 percent for node-positive disease, while it can be 25 up to 30% percent for node negative disease. Other predictors of a favourable outcome include a tumour size less than 3cm, negative margins (R0 resections), well differentiated tumours, and intraoperative blood loss of less than 750 ml.[13,22,14,18]

Contraindications for curative resections are the presence of distant metastases, peritoneal seeding, tumour infiltration into mesenteric and portal vessels, and extension of tumour tissue into the small bowel mesentery.

Modifications of the standard Whipple procedure have been developed in an attempt to improve outcome or minimise the morbidity associated with the operation. Extensive experience has been gained, especially by japanese centres with ultra radical surgery. This type of resection includes excision of the portal vein, total or regional pancreatectomy, and extensive retroperitoneal lymphadenectomy. However, for this type of resection, several reports failed to demonstrate improved survival. A further problem associated with total pancreatectomy is the development of brittle diabetes.[23] Some groups in Japan routinely complement the Whipple operation with an extensive lymph node dissection (extended lymphadenectomy). The reason for

this being that since periampullary malignancies frequently metastasise to lymph nodes that are beyond the confines of the standard pancreaticoduodenectomy.[7] A single prospective trial comparing conventional pancreaticoduodenectomy versus a more extended lymphadenectomy was conducted in 81 patients with a potentially curable adenocarcinoma of the pancreatic head.[24] While overall survival was found to be identical for both treatment groups, subgroup analysis indicated better survival in patients with positive nodes undergoing extensive lymphadenectomy.

Yeo et al. demonstrated in their study[25] that radical pancreaticoduodectomy, i.e. addition of a distal gastrectomy and extended retroperitoneal lymphadenectomy to a standard pancreaticoduodenectomy, can be performed with similar morbidity and mortality as compared to the standard pancreaticoduodenectomy. This however could not be shown to benefit survival rates.

Pylorus-preserving pancreaticoduodenectomy (PPPD), a relatively less aggressive operation that preserves the pylorus was studied in the 1980s. Shorter operation time, less blood loss and shorter hospital stay were found to be advantages as compared to the standard pancreaticoduodenectomy.[26] The PPPD is increasingly being performed in the United States.[27] Three randomised trials have directly compared a pylorus preserving operation to standard pancreaticoduodenectomy.[28,29] The study from Seiler et al.[29] showed no differences in either tumour recurrence or survival after short follow up. From the small and under-powered study of Lin et al.[28] no difference was noted in type of recurrence or long term survival between the two groups.

Unpublished data from our own multi-centres randomised study,[30] which compared PPPD versus standard Whipple procedure in 170 consecutive patients, showed a similar incidence of delayed gastric emptying. No significant differences in bloodloss, duration of operation, hospital stay and postoperative weight loss could be found either. Long term survival and disease free survival was also comparable. Thus both procedures must be considered equally effective in the surgical management of pancreatic cancer. The best predictors of survival after surgery are stage of disease, tumour grade, and resection margins. Nonetheless, even in those with potentially resectable disease, five-year survival following pancreaticoduodenectomy is only about 25 to 30 percent for node-negative and 10 percent for node-positive tumours.[13,31,32]

Standardised surgical technique for suturing pancreaticojejunostomies has led to a decrease in pancreatic fistulas, thus minimising local septic complications. The avoidance of the pancreaticojejunostomy does not lead to less complications.[33]

More than 95% of the patients undergoing surgical resection are in an advanced stage of cancer. In one third of the patients undergoing a R0 resection, liver metastasis is the most frequent site of recurrent disease. Most patients who undergo a curative resection eventually develop recurrence, this usually occurs at the site of primary resection or in the liver. However, little is known about the precise pattern

of recurrence of pancreatic carcinoma. From recently published series,[34,35,36,37,38] it is known that the majority of patients who underwent a macroscopically radical resection develops a tumour recurrence within two years of operation. The most common sites of recurrence were the locoregional areas, the liver and peritoneal cavity. The recurrence occurs even more frequently in those with a microscopically irradical resection (R1).

More recent data suggests that outcomes may be improving over time. This is possibly related to the combined effect of an increase in the proportion of patients undergoing surgery at teaching hospitals, lower procedure-related mortality rates, a better selection of surgical candidates, and/or greater use of adjuvant chemotherapy and radiotherapy.

Nevertheless, these patients still have a relatively poor prognosis, and systemic chemotherapy, radiation or a combination of chemotherapy and radiation have all been used either prior to resection (neoadjuvant therapy) or following surgical resection (adjuvant therapy) in an effort to improve the cure rate achieved with surgery alone.

The eventual outcome of surgical treatment appears to be limited by the dissemination pattern of pancreatic cancer. All international classification systems of pancreatic cancer (UICC, International Union Against Cancer; AJCC, American Joint Cancer Committee; JPS, Japanese Pancreatic Society) rely on tumour size, lymph nodes status, stage of infiltration and present of distant metastasis. Achieving a R0 resection is the prime goal of surgery; macroscopically free resection margins are associated with an increased chance of survival. Birk et al.[5] found that patients without lymphnodes metastasis and a tumour size smaller than 2 cm without distant metastasis, have a significant survival benefit after an R0 resection. (Table 1)[39]

TABLE 1 **Survival after radical resection (R0) of adenocarcinoma of the pancreas**

Author	*R0 (n)*	*1 yr (%)*	*2 yr (%)*	*3 yr (%)*	*5 yr (%)*	*7 yr (%)*	*Median (months)*
Richter et al.[39] 2003 n=194	122	-	-	-	25,4	12,3	-
Yeo et al.[89] 2002 n= 140	81 (pancr) 34 (ampul)	77 85	10 56	-	-	-	21 NYR
Sohn et al.[17] 2000 n=526	423	69	-	-	23	-	19
Klinkenbijl et al.[44] 1999 n=108	108 control arm	-	41	-	22	-	19
Yeo et al.[43] 1997 n=443	443	73	-	37	-	-	21
Trede et al.[18] 1989 n=118	44	-	-	25	-	-	-

NYR = not yet reached; Pancr = pancreatic; Ampul = (peri)ampullary

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Table 2 **Survival rates according to the JPS and UICC stage classification**

Kobari 1998; [40] ***N=1689* JPS**	***Stadium***	***3 year (%)***	***5 year (%)***
	I	66,2	48,1
	II	37,2	27,7
	III	25,4	22,3
	IV	12,7	8,8
***N=1521* UICC**	I	44,3	32,5
	II	22,5	11,5
	III	16,3	12
	IV	9,6	6,6

JPS = Japanese Pancreatic Society; UICC = International Union Against Cancer

Preoperative staging remains unable to reliably predict the presence of lymphnodes involvement and the precise extent of this. Kayahara et al[36] has shown that even in cancer stage I and II there is extensive cancer cell infiltration in the surrounding tissue of the resected pancreas specimen. (Table 2)[40] Molecular biological methods like reverse transcriptase polymerase chain reaction and immunostaining have given us deeper understanding of micrometastases. A better understanding of the underlying cancer cell dissemination pattern may explain the observed frequency of recurrence rates of patients undergoing a curative surgical resection.

This paper will seek to provide a review of adjuvant and neoadjuvant therapies for pancreatic exocrine cancer. Separately discussed issues are the surgical management of localised disease, treatment of locally advanced disease, and chemotherapy for advanced disease.

Adjuvant therapy

Survival after curative resection is limited for most patients due to the development of local or metastatic tumour recurrence. Several adjuvant regimens, designed to reduce these recurrences, have been evaluated in prospectively randomised trials.

In 1985 the Gastro Intestinal Tumour Study Group (GITSG)[41] studied the efficacy of combined external beam radiation (EBRT) and 5-fluorouracil (5FU). After surgery patients were randomised to receive either 5FU-EBRT or no further treatment in the control group. Survival in the treatment arm of the study was significantly higher than in the control arm (20 vs. 11 months, p=0,03). The trial was terminated prior to reaching the original accrual goal and only 43 patients entered the trial over a period

of 8 years. Both the Norwegian Pancreatic Cancer Trial (NPCT)[42] and a report by Johns Hopkins[43] supported the GITSG results. The only two large multi-centres randomised trials, the EORTC[44] and ESPAC-1,[32] however, also failed to show the survival benefit suggested by the smaller GITSG study.

In the EORTC study we were also not able to show significant survival benefit for 5FU-EBRT (24.5 vs. 19 months, p=0.208). After exclusion of periampullary tumours, median survival for pancreatic head cancer demonstrate a trend towards better survival after treatment (12.6 vs. 17.1, p=0.099). The ESPAC-1 study showed a moderate, but nonetheless significant survival benefit for chemotherapy alone (19.7 vs. 14 months p=0.0005) and no benefit for the combination of 5FU and EBRT (15.5 vs. 16.1 months, p=0.24). This provided confirmation for our finding that 5FU-EBRT does not significantly improve survival.

Treatment failure is found either as local or distant recurrence. In the EORTC study recurrence patterns for the treatment and control group were very similar. Half of all primary recurrences were local; the other fifty percent of patients exhibited distant recurrences in addition to the local recurrence. Fifty percent of all progressions developed liver metastases secondary. Beger and Link et al.[45,46] and Lygidakis et al.[47] have published results of prospective trials assessing the effect of intra-arterial chemotherapy on local recurrence and liver metastases. Intra-arterial chemotherapy has theoretical advantages, since it may increase the drug concentration both in the primary tumour and in the liver. It is believed that overall drug effectiveness is determined by the amount of lymphatic drainage and the absolute drug concentration. Lygidakis et al.[47] showed in his study an improved survival for combined regional, SMA infusion, and chemo-immunotherapy (Gemcitabine, Carboplatin, Mitomycin, 5FU, Leucovorin, Interleukin-2). (mean survival: 31.07, *SD=17.315* vs. 18.83 months, *SD=11.745*)

Link et al.[46] achieved a median survival of 21 months, 10 months more than in his retrospective control group (p=0.0003). At the present time a prospective randomised trial (ESPAC-2) is being conducted, to further investigate this promising treatment modality.

Neo-adjuvant treatment has not been studied for primarily resectable but largely for non-resectable, locally advanced pancreatic cancer. Neo-adjuvant therapy has several theoretical advantages. For resectable patients it reduces the time interval between diagnosis and systemic treatment. The reason for this being that patients cannot be treated directly after surgery due to wound healing and postoperative complications. Approximately 20% of resected patients never undergo adjuvant therapy because of postoperative problems.[44] Down staging might be able to turn unresectable tumours into resectable ones and make resection feasible in primarily unresectable cases. In patients with rapidly progressive disease a major surgical procedure might be avoided. Preoperative treatment may help to sterilise the tumour

field, theoretically reducing the risk of tumour seeding during surgery. Devascularisation of the surgical field, thus minimising tissue-oxygenation is avoided and this might improve efficacy of chemo- and radiotherapy. Several retrospective studies on this subject have been conducted, reporting a benefit in resectability and survival for those patients qualifying for resection.[48,49,50,51,52] This indicates that neoadjuvant therapy might be beneficial in selected primarily unresectable patients. This finding has not yet been confirmed in large phase III trials.

Current adjuvant therapy is relatively safe, although treatment related deaths have been reported in several studies. Current chemotherapeutic treatment cannot prevent, but might delay disease progression. The only adjuvant therapy that can be recommended on the bases of high level evidence, is 5FU chemotherapy.[44,32]

The adjuvant-therapy studies mentioned earlier are all, except for Lygidakis et al.,[47] 5FU based. Several palliative studies comparing Gemcitabine (GEM) versus 5FU show better results for GEM[53], achieving similar survival and comparable tolerability but higher response rates and progression-free survival. Combinations of GEM (or 5FU)[54] with cisplatin(CIS) seem to be even more effective.[55,56] Use of GEM-CIS combinations in a (neo-) adjuvant setting deserves further investigation.[57]

Current choice of therapy is based on histopathological assessment of the tumour. The molecular basis of pancreatic adenocarcinoma has been studied over recent years and has uncovered various tumour subtypes. Several genetic mutations have been found in adenocarcinoma of the pancreas (K-ras, p53, p16, DPC4) and several hereditary patterns have been uncovered constituting approximately 5-10% of all cases[58,59] (PRSS1, FAMM[60], STK11/LKB1, BRCA-2, HNPCC, Li-Fraumeni{p53}).[61] Use of molecular diagnostics and markers in the assessment of tumour biology, might be able to differentiate subtypes of this tumour in future. There is evidence that specific K-ras mutations (75-90% are K-ras positive) influence survival.[61,60] Response to chemoradiation might be influenced by p53 expression. Patients with p53 positive tumours exhibit shorter survival after chemoradiation than those with p53 negative tumours.[62] Defining the subtypes of pancreatic cancer in terms of tumour biology and response to treatment will make the choice of therapy more specific.[63,62]

Knowledge of the molecular basis of (pancreatic) cancer has also presented new targets for therapy. Current developments in specific anti tumour agents are promising.

Imatinib mesylate (Gleevec®, Novartis), a specific Bcr-Abl tyrosine kinase inhibitor (TKI), has yielded great results in CML and as a c-kit tyrosine kinase inhibitor in gastrointestinal stromal tumours (GIST). Although not thought to be effective in pancreatic cancer,[64] it shows great potential for target-specific therapy. An example of the consequences of these exciting developments for treatment of gastrointestinal tumours are the specific agents targeting the EGF-receptor,[65] (tyrosine kinase inhibitors: erlotinib (Tarceva®, Genentech/OSI/Roch) gefitinib (Iressa®, AstraZeneca),

monoclonal antibodies (cetuximab(Erbitux® ImClone). These agents are currently under investigation in late-phase trials, hopefully leading to future use in pancreatic cancer treatments.

Recent discoveries have also been made concerning cyclo-oxygenases (COX). These are key enzymes that mediate the production of prostaglandines from arachidonic acid. Two isoforms of these important enzymes, COX-1 and COX-2 have been described. Data from animal and human studies suggest an important role for COX-2 in gastrointestinal carcinogenesis.[66] Up-regulation of Cyclooxygenase-2 (COX-2) has been observed in pancreatic adenocarcinoma.[67] This process is initiated by a number of growth factors and tumour promoters and has been implicated in cancer progression.[68] Furthermore COX-2 also appears to have a role in the development of resistance to conventional cancer therapy. Increased resistance to apoptosis appear to be an especially important factor in this regard.[69,70] Enhanced growth-inhibition of pancreatic carcinoma cells by COX-2 inhibitors in combination with chemotherapy has also been described.[71] Selective COX-2 inhibitors, such as celecoxib (Celebrex®, Pfizer), have recently been approved for the treatment of patients with rheumatoid arthritis and osteoarthritis and these drugs can be used with minimal side effects. Currently we are conducting a phase II trial to assess the role of these agents in pancreatic cancer.

In the field of immunotherapy other examples of tumour specific approaches can be found. Current clinical trials[72] are investigating the induction of anti tumour response by the bodies own immune system by the use of cytokines and vaccines. Mechanistic approaches using targeted therapies, such as the examples mentioned earlier, may help to find a more effective and less toxic therapy for pancreatic cancer.[73] Unfortunately such a revolution has so far not been witnessed in the treatment of pancreatic cancer.

Survival statistics and definition of endpoints in pancreatic cancer surgery

One must be cautious to draw direct conclusions based on the survival figures presented in most studies when reviewing the results of surgery and/or adjuvant therapy. It is important to be aware of the fact that selected patients for surgery and adjuvant therapy only represent a fraction of all pancreatic cancer cases. They can therefore not be considered to be representative for the survival of the total patients group after first diagnosis for pancreatic cancer. Further long-term survival is observed in only a very small group of pancreatic cancer patients. This finding contradicts the published actuarial 5-year survival rates of 20-45% among resected patients. Gudjonsson did find, after correction for repetition, no more than 300-350 survivors after 65 years of resections.[74] He stated that the statistical method used is responsi-

TABLE 3 **Randomised Prospective Trials Adjuvant Therapy for Pancreatic Cancer**

Year	*Author*		*Methods*	*Stage(UICC)*	*N*	*Groups*		*Ro*	*R1*	*Ro/R1+o*	*N+*	*Median*	*Periam-pullary*
1985	Kalser[41]	GITSG	5FU-RT	Resectable	43	21	treatment	21		100%	29%	20	
						22	control	22		100%	27%	11	
1993	Bakkevold[42]	NPCT	AMF	I(22)II(1)III(7)	61	30	treatment	30		100%		23	14/61
				I(19)II(1)III(10)		31	control	31		100%		11	
1999	Klinkenbijl[44]	EORTC	5FU-RT	T1-2,No-1a, Mo &	218	110	treatment	84	20	81%	47%/40%*	24,5	93/114
				T1-3,No-1a,Mo (periampullary)		108	control	76	25	75%	54%/39%*	19	
2001	Neoptolemos[32]	ESPAC-1	5FU-RT	Resectable	541	175	5FU-RT	145	30	83%	56%	15,5	
						178	control	146	32	82%	55%	16,1	
						238	5FU	193	45	81%	51%	19,7	
						235	control	193	42	82%	55%	14.0	
2002	Lygidakis[47]		IART	uicc III	128	40	Control	39	1	98%	100%	18.83	
						45	CHEM	43	2	96%	100%	25.02	
						43	CHEM-Immuno	42	1	98%	100%	31.07	

* Periampullary

AMF: 5FU, doxorubicin, mitomycin; IART: Intraarterial chemotherapy; CHEM: GEM ,Carboplatin, Mitomycin, 5FU; Immuno: CHEM+interleukin-2

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ble for misleading survival results. In surgical science, survival is most commonly calculated using the Kaplan-Meier statistical method, instead of the actual method. The difference being that the actual method uses only proven survivors without lost data and therefore is unlikely to exaggerate results. There is however another approach to actuarial methods. This is to take the number of patients alive at the start of a particular period, minus the known deaths over that period. This figure is then divided by the number of patients alive and this figure is then multiplied for each period or after each death. As long as there is no loss to follow-up, no difference between the actual and actuarial method will be found. In daily practise however, clinical trials will always have more or less losses to follow-up. Loss of data is completely ignored by the Kaplan-Meier method, the most frequently used method to calculate survival in surgical studies. Loss of data, in other words censored cases, might influence survival dramatically using the actuarial Kaplan-Meir method; this has also been shown clearly by Gudjunsson, (Table 3). Therefore publication of only actuarial survival figures should be considered scientifically unacceptable without information on the total number of patients in the study group, the number of observed (actual) survivors, and a clear definition of the precise subset of patients followed after resection.

Besides actual survival as an endpoint evaluation, the observed median survival and progression free survival have been introduced in surgical series as appropriate primary endpoints from which to measure treatment benefits. Indicators of response in terms of clinical benefit have been introduced in recent trials as an additional endpoint to evaluate the effect of chemotherapeutic agents. A combination of improvements in pain perception, performance status, and weight gain is used to objectify clinical benefit. Clinical benefit response, however, can underestimate the effects of chemotherapy because it does not include the assessment of other symptoms. Further more it can overestimate the results of chemotherapy, the reason for this being that it does not properly assess the side effects.[75,76] Therefore QOL studies have been introduced in the latest adjuvant clinical trials.

Quality of Life (QOL)

PPPD is gaining acceptance as an appropriate procedure for various malignant and benign diseases of the pancreas and periampullary region.[77,78,79,24,80,81,82,25] As experience with pancreaticoduodenectomy grows, there is an increasing number of survivors who have recovered from the procedure and who live with the resulting altered upper gastrointestinal anatomy. These survivors have only been marginally studied in terms of their post procedure quality of live (QOL) and as determined by parameters such as pain, stool habits, activity levels, among other parameters.[83,84,85,86,87,88]

Additional prospective studies incorporating both preoperative and serial postoperative QOL assessment are needed to further investigate the QOL after resection.

The rapidly progressive nature of pancreatic cancer causes deterioration of QOL over time, which leads to reduce of psychological, physical and social functioning. Thus "increased survival" might in reality mean more survival months of ever decreasing quality of live. This makes QOL a very important tool to measure the clinical benefit of the adjuvant and neoadjuvant treatment protocols.

In advanced pancreatic cancer QOL was found significantly to be higher in patients receiving chemotherapy compared to those receiving best supportive care. QOL after resection of pancreatic cancer is mainly determined by the presence or absence of recurrent disease.

QOL assessment in pancreatic disease is currently still in the early stages of data retrieval and evaluation. Additional studies incorporating both preoperative and serial postoperative QOL assessment are needed. Study results are also needed to evaluate the QOL for the various nonsurgical management strategies. In pancreatic cancer treatment trials, especially in series with multimodality treatment, clinical response as well as QOL measurements are of utmost importance to evaluate the effect of the treatment given. The primary end points of trials should be actual survival, median survival and progression-free survival.

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Chapter 3

Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure

A prospective, randomised, multi-center analysis of 170 patients with pancreatic and periampullary tumors

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Abstract

In a prospective randomised multi-center study the pylorus preserving pancreaticoduodenectomy was compared to the classic Whipple operation in respect to operation time, blood loss, hospital stay, delayed gastric emptying and survival. No significant difference was noted in duration of operation, blood loss, hospital stay, mortality, morbidity and delayed gastric emptying. Long-term follow up showed no significant difference in survival between both groups.

Both surgical procedures are equally effective for the treatment or pancreatic and periampullary carcinoma.

Objective
A prospective randomised multi-center study was performed to assess whether the results of PPPD equalize those of the standard Whipple (SW) operation, especially with respect to duration of surgery, blood loss, hospital stay, delayed gastric emptying (DGE) and survival.

Summary Background Data
Pylorus-preserving pancreaticoduodenectomy (PPPD) has been associated with a higher incidence of delayed gastric emptying, resulting in a prolonged period of post-operative nasogastric suctioning. Another criticism of the pylorus-preserving pancreaticoduodenectomy for patients with a malignancy is the radicalness of the resection. On the other hand PPPD might be associated with a shorter operation time and less blood loss.

Methods
A prospective randomised multi-center study was performed in a non-selected series of 170 consecutive patients. All patients with suspicion of pancreatic or periampullary tumor were included and randomised for a SW or a PPPD resection. Data concerning patients' demographics, intraoperative and histological findings as well as postoperative mortality, morbidity and follow-up up to 115 months after discharge were analyzed.

Results
There were no significant differences noted in age, sex distribution, tumor localization and staging. There were no differences in median blood loss and duration of operation between the two techniques. DGE was observed equally in the two groups. There was only a marginal difference in postoperative weight loss in favor of the standard Whipple procedure. Overall operative mortality was 5.3%. Tumor positive resection margins were found for 12 patients of the SW group and 19 patients of the

PPPD group (P < .23). Long-term follow-up showed no significant statistical differences in survival between the two groups (P < .90).

Conclusions
The SW and PPPD operations were associated with comparable operation time, blood loss, hospital stay, mortality, morbidity and incidence of DGE. The overall long-term and disease free survival were comparable in both groups. Both surgical procedures are equally effective for the treatment of pancreatic and periampullary carcinoma.

Introduction

Pancreatic cancer is one of the most fatal malignant diseases today and ranks fifth in cancer mortality worldwide. Survival after surgery is still disappointing with 5-year survival rates ranging from 10% to29%.[1-6]

The introduction of partial pancreaticoduodenectomy is credited to Godivilla, an Italian surgeon and Kausch[7], a German surgeon from Berlin. Later on this technique was refined by Whipple et al.[8]

Several modifications have been reported, including the pylorus-preserving pancreaticoduodenectomy (PPPD) described by Watson in 1944.[9]

This technique was re-introduced by Traverso and Longmire [10] in the late 1970s for chronic pancreatitis. Preservation of the pylorus in pancreaticoduodenectomy has been shown in retrospective studies to lead to a long-term improvement in gastrointestinal function, as indicated by more postoperative weight gain, fewer peptic ulcers and less dumping. Furthermore, the pylorus preserving procedure simplifies the operation, thus leading to shorter operations and less intra-operative blood loss.[11] Initial studies reported a high incidence of complications, including delayed gastric emptying, ulcerative lesions of the anastomosis[12,13] and great concern about resection margins.[5,14] Nevertheless, similar survival rates have been described for both techniques.[2,15-18]

Only two relatively small studies have been performed to study PPPD prospectively. In a prospective randomised study of 31 patients by Lin et al.[17] no differences in operation time, blood loss, and blood transfusion were observed. Delayed gastric emptying was observed more frequently after PPPD than after the Whipple procedure, with marginal statistical significance. (P = .08) Seiler et al.[19] found shorter operation time, less blood loss and fewer blood transfusions in the PPPD-group of their series of 77 patients. No difference in operative mortality was found but the SW group exhibited a higher morbidity rate.

In a large randomised trial in which the extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma was compared with a standard resection

to preserve the pylorus,[20,21] similar mortality and some increased morbidity in the extended resection group were reported.

We conducted a prospective randomised multi-center study to evaluate whether PPPD has an advantage over the standard Whipple procedure.

Methods

Study design

The study protocol was approved by the Ethics Committee of each center. Informed consent was obtained according to the local rules prevailing at each participating institution.

The following hospitals in the Netherlands participated: Erasmus Medical Center Rotterdam; University Hospital Maastricht; Leiden University Medical Center; Ignatius Hospital, Breda; Reinier de Graaf Gasthuis, Delft; De Weezenlanden Hospital, Zwolle and Medical Center Leeuwarden.

The design of this prospective multi-center trial consisted of a pre-treatment evaluation and a randomised treatment with either a standard Whipple (SW) or a pylorus-preserving pancreaticoduodenectomy (PPPD). The postoperative morbidity and mortality data were evaluated every 3 months up to 115 months of follow-up.

Preoperative Evaluation

Preoperative work-up was standardized in all centers. A CT scan of the upper abdomen and a chest X-ray were requested. In most cases an ERCP also was performed. PTC (percutaneous transhepatic cholangiography), angiography, CT-angiography and MRI were optional.

Inclusion Criteria

We included 170 consecutive patients between January 1992 and December 2000 with suspected pancreatic or periampullary cancer that was assumed to be resectable according to preoperative diagnostic imaging (CT and/or MRI). Patients with a previous gastric resection were excluded.

Exclusion Criteria

Patients with distant metastasis or local unresectable tumors as indicated by preoperative work-up and intra-operative findings, were excluded. Patients with direct invasion of the pylorus or stomach as well as patients with positive peri-pyloric lymph nodes were excluded; all of the remaining patients were included in the analysis for efficacy. However, for analysis of survival, patients with lesions other than pancreatic or periampullary adenocarcinoma were excluded.

Blinding and randomization

An equal number of blind envelopes with protocols for the SW and the PPPD resection was prepared. The envelopes were used sequentially as patients were enrolled in the study. Therefore there was strict randomization in both arms. Randomization was carried out in the operation room: a sealed envelope was opened only after it was ascertained that both operation techniques were feasible in the patient concerned. Eighty-seven patients were randomised for PPPD (50 male: 37 female) with a median age of 64 years. 83 patients were randomised for a Whipple resection (58 male: 25 female) with a median age of 62 years. Two patients in the PPPD group were converted to the SW resection during operation as the surgeon expected duodenal involvement; these two patients remained for analysis in the PPPD group.

Surgery

All patients were placed on a regimen of prophylactic antibiotics consisting of 2-gram cefazolin (Cefacidal®, Bristol-Meyers Squibb, Woerden, Holland) and 500 mg metronidazol (Flagyl®), Aventis Pharma, Hoevelaken, Holland). In addition, octreotide (Sandostatin®, Novartis Pharma, Arnhem, Holland) was administered to all patients preoperatively and continued postoperatively for 7 days at a dosage of 100µg given subcutaneously three times a day.[22]

Surgical Procedure

The standard, pylorus-preserving resection involved division of the duodenum 2 cm distal to the pylorus with resection of all of the duodenum distal to the transection site, removal of the gallbladder and common bile duct (proximal to the level of the cystic duct junction), resection of the head, neck, and uncinate process of the pancreas (underneath the superior mesenteric vein, lateral from the mesenteric-portal vein axis, flush with the superior mesenteric artery) and removal of the periampullary tumor. For the standard resection, a distal gastrectomy varying from 20 to 40% was performed. Frozen section was performed routinely at the transection site of the pancreatic remnant in all patients. In case of macroscopically suspected other margins a frozen section of this margins was also performed. An end-to-side invaginated pancreaticojejunostomy was performed. Further downstream an end-to-side hepaticojejunostomy and side-to-side gastroenterostomy or an end-to-side pylorus-jejunostomy was made.

Postoperative Management

All patients were managed according to a standard postoperative pathway. All patients received histamine H2-receptor antagonists as prophylaxis against stress ulceration and octreotide treatment was continued for seven days. At the end of the operation a drain was left in the area of the pancreaticojejunostomy and the hepaticojejunos-

tomy. The drain was removed if the amylase concentration was less than 300 U/L (less than twice the serum concentration) and production was less than 50ml per day or after postoperative day 10. Pancreatic fistula was defined as drainage of more than 50ml amylase-rich fluid per day through the surgically placed drains on or after postoperative day 10, or pancreatic anastomotic disruption demonstrated radiographically.

A biliary fistula was diagnosed if there was persistent secretion of bilirubin-rich drainage fluid of more 50ml per day or after the tenth post-operative day.

Postoperative bleeding was defined as the need for more than 2 units of red blood cells more than 24 hours after surgery or relaparotomy for bleeding.

The nasogastric tube was removed when the production has decreased to less than 200 ml per 24 hours.

Delayed gastric emptying was defined as gastric stasis requiring nasogastric intubation for ten days or more or the inability to tolerate a regular diet on the 14th postoperative day.[23]

Nineteen (10 SW and 9 PPPD) patients received postoperative chemoradiotherapy according to the EORTC study in which the Erasmus Medical Center Rotterdam paticipated.[24]

Pathological review

All pathology specimens were reviewed to determine the primary pathological diagnosis and the extent of the disease. Tumor stage was determined according to the UICC classification sytem and the TNM system.[25] Resection margins of the specimen were stained and were considered positive if the neoplasm was present at the pancreatic neck, uncinate processus, common bile duct, duodenum/gastric resection area, mesenteric artery and portal vein and the circumferential margin which is defined as the dorsal resection margin (peripancreatic fat and fascia of Trietz) or beyond the anterior pancreatic parenchyma anteriorly (peripancreatic fat, mesenteric base of the transverse colon or posterior peritoneum of the lesser sac). A periampullary tumor was defined as a tumor of the ampulla of Vater or periampullary duodenum and distal common bile duct.

Follow-up

Patient follow-up, obtained via office records from the outpatient clinic, was completed up to May 2002. Patient demographics, intraoperative factors, pathological findings and postoperative course were evaluated. Parameters such as blood loss, duration of operation, delayed gastric emptying, intra operative and postoperative complications, hospital stay, hospital mortality and weight loss were recorded at discharge. Follow-up evaluations were conducted every three months following dis-

charge. When signs of recurrent disease occurred during the interval, a CT scan or MRI was performed.

Statistical analysis

Data were expressed as median and range. The primary endpoints in this study were blood loss, operation time and hospital stay. The secondary endpoints were delayed gastric emptying and survival. A power-analysis for these endpoints, based on data from a former study, had shown that at least 65 patients with pancreatic and periampullary adenocarcinomas had to be included in each group.[15] With this number of patients it should be possible to demonstrate (α=0.05; β=0.05) that blood loss and operation time will be less with pylorus preserving pancreaticoduodenectomy as compared to the standard Whipple's resection. This number of patients is also sufficient to achieve a reduction of hospital stay. Survival was calculated from the date of surgery using the Kaplan-Meier method and compared with the log-rank test. Data were compared using the Mann-Whitney test. Percentages between groups were compared using Fisher's exact test and the Chi-square test. The level of significance was set at $P < .05$.

Results

Demographics and preoperative characteristics of this study are listed in Table 1.

TABLE 1 **Patient characteristics**

Patient characteristics	***SW**** **(n=83)**	***PPPD**** **(n=87)**	**P-*Value***
Age (y)*	62 (27-78)	64 (43-78)	.269
Gender (male/female)*	50/37	58/25	.112
Weight pre-op (kg)*	70.6 (46-102)	70.0 (43-110)	.717

* SW, standard Whipple; PPPD, pylorus-preserving pancreaticoduodenectomy;
Data given are number of patients or median (range)

Follow-up results

Based on the final histological diagnosis, 29 patients with benign lesions (14 in the SW group and 15 in the PPPD group) and 7 with endocrine tumors (3 in the SW group and 4 in the PPPD group) were excluded from the survival analysis. For long-term follow-up a total of 134 patients with histological proven pancreatic and periampullary adenocarcinoma were included and analyzed. Median follow-up was 18.5 months (range 1-115 months). The median intraoperative blood loss was 2.0 L, (0.3-9.5 L) in the SW resection group and 2.0 L (0.4-21.0 L) in the PPPD group with a *P*-value of

.70. The median operative time was 300 minutes (range 160-480 min.) in the SW group and 300 min (range 130-600 min.) in the PPPD group (P=.10).

Number of units packed red blood cells given during operation was equal in both groups, with a median of 2 in each group (P=.70).

During the postoperative course there were no differences in specific procedure-related or general complications. 16 patients in the SW group underwent a relaparotomy versus 13 patients in the PPPD group (P=.40)(Table 2).

Days of nasogastric intubation were similar in both groups, with a median of 5 days (range 1-48) in the SW group and 6 days (range 1-57) in the PPPD group (P = .80). There were also no significant differences in days until regular diet was tolerated.

Spaties rond = teken zo houden?

The incidence of delayed gastric emptying was comparable in both groups, 18 patients in the SW group and 19 patients in the PPPD group (P = .80). We did find a

TABLE 2 **Postoperative complications, relaparotomy, and mortality**

Complications	***SW**** **(n=83)**	***PDDD**** **(n=87)**	**P-*Value***
Pancreatic fistula	12 (14%)	11 (13%)	
GE leakage	2 (1%)	0	
Bile leakage	0	2 (2%)	.528
Post-operative bleeding	6 (7%)	6 (7%)	.933
Intra-abdominal abscess	8 (10%)	9 (10%)	.878
Other complications	23 (28%)	19 (22%)	.375
Relaparotomy	16 (19%)	13 (15%)	.479
Mortality#	6 (7%)	3 (3%)	.270

* SW, standard Whipple; PPPD, pylorus-preserving pancreaticoduodenectomy; # Operative mortality within 30 days.

TABLE 3 **Postoperative days of nasogastric intubation, Days until normal diet, Incidence of Delayed Gastric Emptying, Postoperative hospital stay in days, and lapse in bodyweight**

Outcome	***SW****	***PPPD****	**P-*Value***
Days of nasogastric intubation	5 (1-48) [83]	6 (1-57) [87]	.835
Days until regular diet tolerated orally	10 (0-54) [83]	10 (0-58) [87]	.574
Delayed gastric emptying*	18 (23%) [80]	19 (22%) [85]	.800
Hospital stay, days	20 (11-138) [67]	18 (4-175) [74]	.488
Body weight on discharge (kg)	67 (44-92) [67]	65 (41-98) [74]	.789
Pre-illness body weight (kg)	75 (53-92) [75]	79 (50-120) [76]	.571
Pre-operative body weight (kg)	71 (46-102) [77]	70 (46-102) [81]	.764

* Delayed gastric emptying is defined as nasogastric suction for ten days or more, or diet on or before the 14th post-operative day. Data given are median (range) or number of patients. Data given in brackets indicate number of patients concerned, i.e. excluding patients not analyzed

significant correlation between DGE and intra-abdominal complication. (Postoperative bleeding, abscess and intra-abdominal leakage) ($P < .05$)

The median hospital stay was in both groups equal (19 days) ($P = .50$). Postoperative weight loss was observed in both groups with a median of 8 kg in the SW resection group and 13,5 kg in the PPPD group. ($P = .70$) (Table 3) These differences equalize during follow-up. (Figure 1)

Pancreatic adenocarcinoma was found in 43 patients in the SW group and in 47 patients in the PPPD group (Table 4). Twenty-three patients in the SW group and 21 patients in the PPPD group were diagnosed with a periampullary carcinoma.

TABLE 4 **Pathology**

Characteristics	***SW** (n=83)***	***PDDD** (n=87)***	
Malignant			
Pancreatic adenocarcinoma	43 (52%)	47 (54%)	
periampullary adenocarcinoma	23 (27%)	21 (24%)	
Other malignancy	3 (4%)	4 (5%)	
Total	69 (83%)	72 (83%)	
Benign			
Chronic pancreatitis	10 (12%)	9 (10%)	
Benign villous adenoma with dysplasia	4 (5%)	6 (7%)	
Total	14 (17%)	15 (17%)	
Lymph nodes	***SW* (n=69)#**	***PDDD* (n=72)#**	
Hepatoduodenal ligament	5 (7%)	4 (6%)	
Peripancreatic	26 (38%)	25 (35%)	
Mesenteric artery/vein	7 (10%)	6 (8%)	
Perigastric/Pyloric	0	2 (2%)	
Tumor negative lymph nodes	31 (45%)	35 (49%)	
Margins positive resection	***SW** (n=69)***	***PPPD** (n=72)***	**P-*Value***
Duodenum/gastric	0	1 (1%)	
Pancreatic remnant	1 (1%)	1 (1%)	
V.porta/V.mesenterica	2 (3%)	2 (3%)	
Mesenteric artery	3 (4%)	4 (6%)	
Circumferential	5 (7%)	10 (14%)	
Inferior Cava vein	1 (1%)	1 (1%)	
Total	12/69 (17%)	19/72 (26%)	.230

* SW, standard Whipple; PPPD; pylorus-preserving pancreaticoduodenectomy. Data given are number of patients. Peripancreatic: anterior and posterior pancreatoduodenal nodes. Circumferential margin: posterior resection margin and the margin beyond the pancreatic parenchyma anteriorly.

Benign; géén kopjes met SW, steekproef?

FIGURE 1 **Body-weight versus time of follow-up**

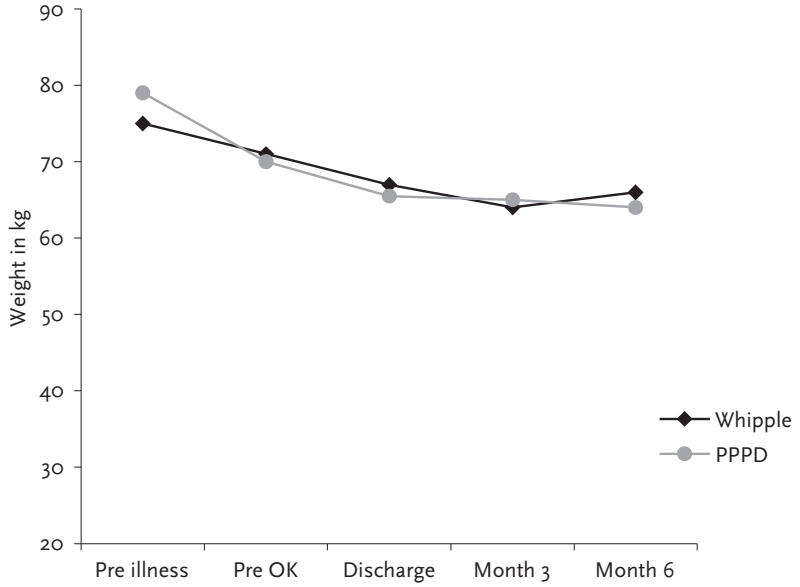


FIGURE 2 **Overall survival rates for patients with adenocarcinoma**

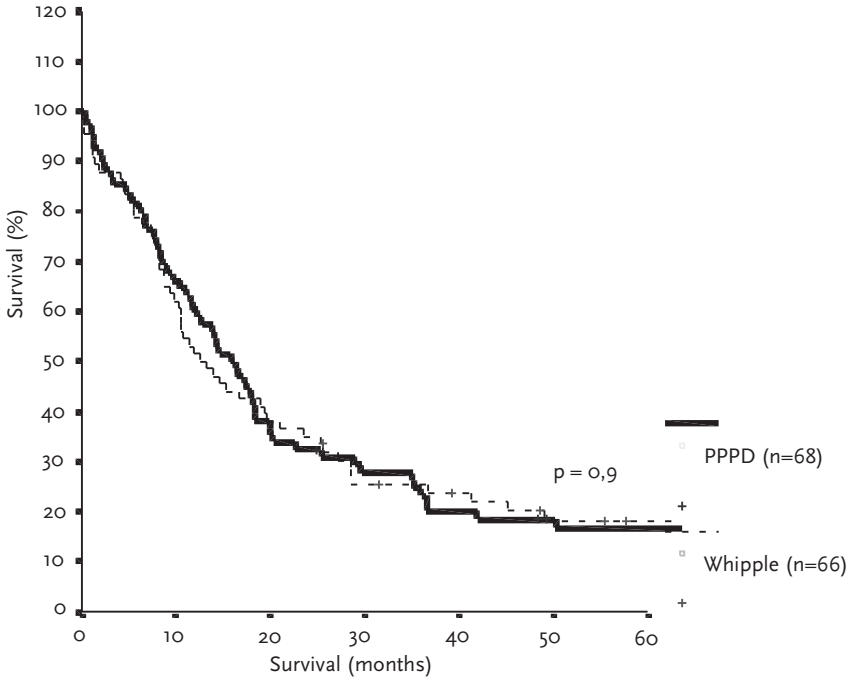


FIGURE 3 **Periampullary adenocarcinomas (DBD, ampullary and duodenal carcinomas)**

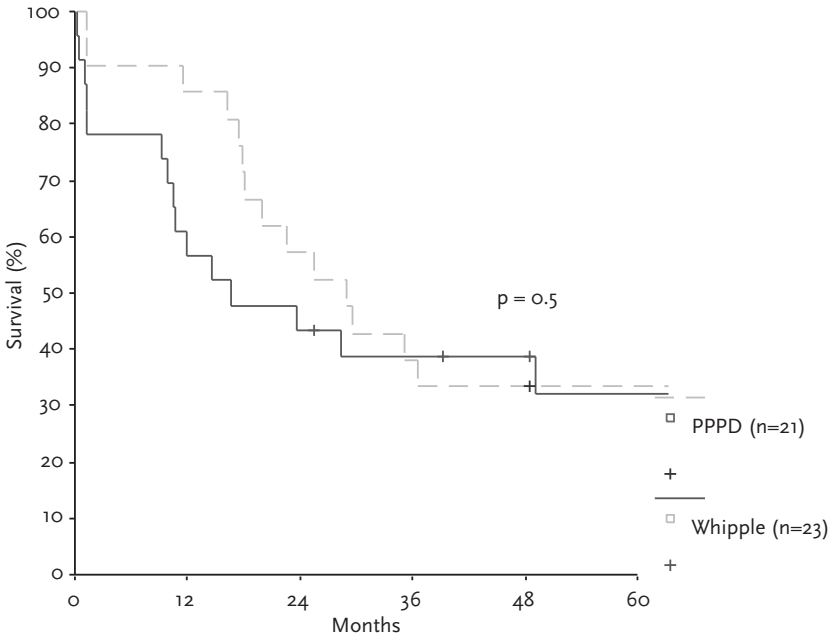
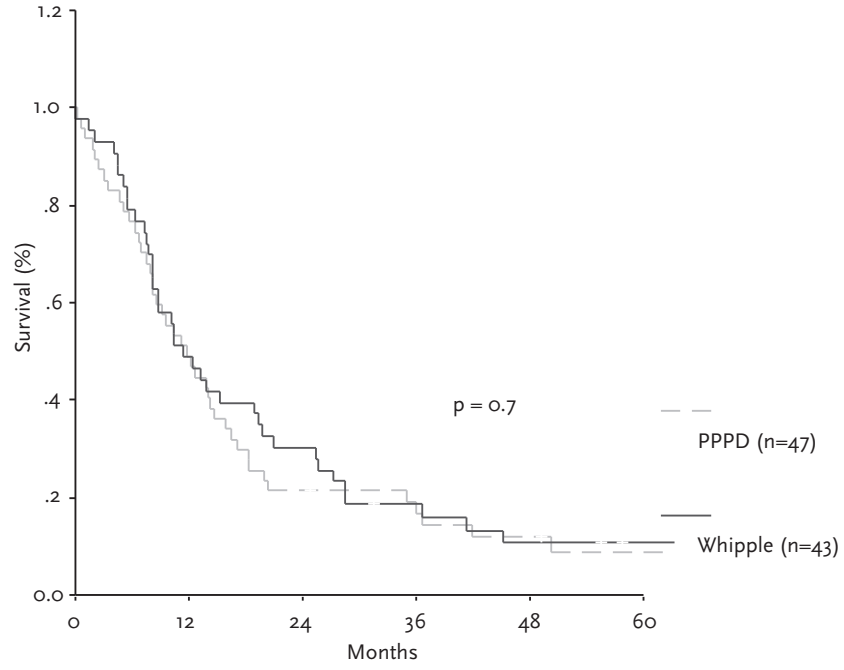


FIGURE 4 **Pancreatic adenocarcinomas**



Tumor positive lymph nodes were found in 38 patients in the Whipple group versus 37 patients in the PPPD group ($P = .70$). Loco-regional tumor positive lymph nodes were equally spread in both groups ($P = .60$).

Overall operative mortality rate was 5.3 %, 6 patients in the SW group and 3 patients in the PPPD group died within 30 days.

The overall median disease free survival was 14 months in the SW-group and 15 months in the PPPD group ($P = .80$). The overall disease free survival was similar in both groups ($P = .90$). There was no difference in median overall survival rates between the two groups ($P = .90$) (Figure 2).

Periampullary cancer was diagnosed in 44 patients. Of whom 21 patients underwent a PPPD and 23 patients a SW resection. The median disease free survival was 49 months in the SW group and 23 months in the PPPD group ($P = .60$). Median survival in the SW group was 17 months versus 29 months in the PPPD-group which is not statistically significant ($P = .50$)

Ninety patients had pancreatic cancer of which 47 patients underwent a PPPD and 43 patients a SW. The median disease free survival was 7 months in the SW group and 6 months in the PPPD group ($P = .90$) The median survival was 11 months in the SW group and 12 months in the PPPD group ($P = .70$).

Combining both carcinoma groups there was no difference in median overall long-term survival rates between the two randomised groups as shown in figure 3. ($P = .90$)

Tumor positive resection margins were noted in 12 (17%) patients in the SW group and 19 (26%) patients in the PPPD group ($P = .23$). Most of these positive margins were located at and around the pancreatic resection area, which was defined as circumferential (Table 4) and not on the pancreatic remnant.

Discussion

We hypothesized that pylorus-preserving pancreaticoduodenectomy is associated with a reduced operation time, less blood loss, shorter hospital stay and a more physiological food passage. Two smaller randomised studies reported a shorter operation time and less blood loss, fewer transfusions and a lower morbidity for the PPPD. However the power of both studies might be considered low.[17,18]

In this study the duration of the operation was equal for the two procedures. The median blood loss also did not differ between the two groups (2.0 L) (Table 1). Compared to reports from some large centers,[20,26] blood loss in the present series was two times higher, however, in comparison to other multi-center studies[18,27] there are only small differences.

When the results of this study are analyzed, one must take into consideration the fact that we performed a multi-center analysis of both large volume and small volume centers which is a realistic situation in most countries.

The overall operative mortality in this study was 5.3 %. Multi-center studies are often associated with a higher mortality rate, ranging from 5 % in Italy[27] to 10% in France[28] and 17.2 % in the United States.[29]

PPPD has been associated with delayed gastric emptying, an increase in morbidity and prolonged hospital stay. Warshaw and Torchiana first reported this phenomenon after their initial study of 8 patients in 1978.[30] According to the literature, the incidence of delayed gastric emptying is estimated to range between 25-70%[12,15,23,30-36] which is sufficient reason for some to abstain from the PPPD procedure. The incidence of delayed gastric emptying in this study was equal in the two groups, 18 in the Whipple group versus 19 in the PPPD group.

Several factors are thought to play a role in the pathophysiology of delayed gastric emptying. In the present series we found a correlation between delayed gastric emptying and intra-abdominal complications($P < .05$). This relationship was reported previously.[23,37,38] Gastric dysrhythmias, disruption of gastroduodenal neural connections, ischemia of the pylorus muscle and ligation of the right gastric artery all have been related to delayed gastric emptying.[32,39-42]Resection of the duodenum, the primary production site of most gastrointestinal hormones, might also play a role in the pathogenesis of this complication. Yeo et al.[36] reported in a randomised trial that administration of erythromycin, a motulin agonist, decreased the incidence of DGE by 37%. Since this difference, was not statistically significant, we did not include erythromycin as standard therapy.

In the present study hospital stay, 20 days for the SW group and 18 days for the PPPD group, was not significantly different ($P = .50$). These results are comparable to other randomised studies.[18,27]

An argument in favor of pylorus preservation may be that patients subsequently have a better nutritional status compared to patients after a gastrectomy.[23,33] Postoperative weight loss was observed in both groups with a median of 8 kg for the Whipple resection group versus 13.5 kg for the PPPD group. This is not statistical significant ($P = .70$). An argument against the use of PPPD for the resection of pancreatic tumors is the potential risk of positive duodenal resection margins,[5,14] resulting in lower survival rates. In this study one patient in the PPPD group had a positive resection margin at the duodenal site. There were no significant differences in tumor positive resection margins; subsequently we did not detect any significant differences in survival.

According to other randomised studies which compared the PPPD versus SW[18] and SW versus the extended pancreaticoduodenectomy,[27] our survival outcomes are highly comparable. It is important to note that we included the in-hospital mortality

in our survival rate calculation in contrast to some other studies.[21] Furthermore it should be noted that adjuvant therapy was not routinely provided in contrast to other trials.[21,43,44] We did not recommend adjuvant chemotherapy and radiotherapy for our patients since the outcome of the published trials comparing the effects of adjuvant chemoradiotherapy to surgery alone.[24,45] did not show a statistically significant difference in survival in favor of the adjuvant therapy.

In conclusion, the incidence of delayed gastric emptying in this study of 170 consecutive patients was similar after PPPD and Whipple resection. Postoperative nasogastric drainage period was comparable in both groups. As far as the duration of operation, blood loss, hospital stay and postoperative weight loss are concerned, there were also no significant differences. The PPPD appears to be just as radical compared to the standard Whipple procedure. Long-term survival and disease free survival did not exhibit significant differences. Thus, both procedures are equally effective for treatment of pancreatic cancer.

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Chapter 4

Long-term survival after R-0 resection for pancreatic and periampullary cancer

A pivotal role for the EGF-R

Dig Surg. 2007;24(1):38-45

Klopt deze aanduiding?

Abstract

Background/ aims

Pancreatic cancer has a dismal prognosis. Ampullary cancer (defined as: cancer of the ampulla of Vater or the distal common bile duct), has a better prognosis and is thought to be a biologically different tumor. Aim of this study was to find factors that could predict survival after radical (R-0) resection for pancreatic and ampullary cancer.

Methods

We analyzed clinical and pathological data from 93 patients who underwent a true R-0 resection for pancreatic or ampullary cancer. Furthermore we performed a Tissue Micro-Array protein expression analysis for several growth factor receptors and oncogenes: HER-2, EGF-R, ER, PR, C-myc, P53, P16, RB-1 and Chromogranin A as a neuroendocrine differentiation marker.

Results

Median survival (14 vs 42 months) and time to recurrence (16 vs 42 months) were significantly longer for ampullary than for pancreatic cancers. Pre-operative pain, perineural invasion, lymph node metastasis and tumor differentiation grade are indicators of poor survival. No differences in protein expression were found between groups except for EGF-R expression, which was expressed more in pancreatic cancers (p=0.026).

Conclusion

Outcomes for ampullary- are better than for pancreatic cancers. This different biological behaviour can possibly be explained by differences in EGF-R expression.

llary-

Introduction

Of all gastrointestinal malignancies, pancreatic cancer has the poorest prognosis, with a 5-year survival of less than 5%.[1,2] Men are more frequently affected by this disease than women (relative risk 1.5).[2] Ampullary cancers, however, carry a better prognosis.[3] This evident difference may be due to earlier clinical presentation or different biological behaviour. Curative resection offers the only chance of cure, but is possible in only 10% of patients.[4] Adjuvant chemo- or chemo-radiotherapy after curative resection are of limited value.[5] Even after a macroscopically radical resection (R-0), distant micrometastases probably already exist[6] and tumor cells are often observed at one or more edges of the resected specimen (R-1).[7,8] Reported rele-

vant prognostic variables for survival after resection are: tumor size, lymph node metastasis, histological differentiation and resection (R) status.[9-12] Most studies include radical (R-0) as well as non-radical (R-1/R-2) resections. To eliminate the apparent effect of R-1 status on (local) recurrence and survival it would be interesting to evaluate true R-0 resections only.

The aim of this study was to determine clinical, histological and molecular factors that could predict recurrence and survival after R-0. Special focus is on the differences between ampullary (defined as: cancer of the ampulla of Vater or distal common bile duct) and pancreatic cancers. Additionally a Tissue Micro Array (TMA) analysis of resected tumors (R-0) was added in order to search for relevant molecular factors.[13,14] For immunohistochemical staining we selected common antibodies raised against proteins that are frequently expressed in (pancreatic and ampullary) cancers such as: Retinoblastoma (RB-1)[15,16], p16[17], C-myc[18], p53[17]. Potential targets for therapy: HER-2[19], Epithelial Growth Factor Receptor (EGF-R).[20] Potential markers for a male/female difference: Oestrogen- (ER) and Progesterone Receptor (PR).[21] Chromogranin-A was used as a neuroendocrine differentiation marker.

Methods

From a consecutive series of 176 resections for pancreatic and ampullary adenocarcinoma, specimens were revised. For the purpose of this study we defined ampullary cancer as: cancer of the ampulla of Vater and the distal common bile duct. Duodenal tumors were not included. Pancreatic cancers adjacent or close to the ampulla were classified as pancreatic cancer. R-0 was defined as absence of macroscopic and microscopic residual tumor at 1 mm from the margin of the resection specimen. Even if there were lymph node metastases restricted to the resected area, the resection was considered R-0. 70 patients had an R-1 and 6 patients an R-2 resection. In 7 cases the pathologist was not able to define whether a true R-0 resection was performed. Therefore 93 patients were evaluated in this study.

One pathologist reviewed all specimens of R-0 resected tumors. Histological differentiation, tumor size (T), location and extent as well as vaso-invasive growth (small blood vessels), perineural invasive growth and lymph node metastasis (N) were assessed. Staging was performed according to the UICC-classification, 2002.[22]

Pre-operative data, including age, gender, weight loss, pain (back-pain and pain in the epigastric region), jaundice and diabetes mellitus, were obtained from clinical records.

Pre-operative staging and Surgical Techniques

All patients underwent conventional ultrasonography and/ or computed tomographic scanning. Most patients (76%) underwent endoscopic retrograde cholangiopancreatography (ERCP) and subsequent preoperative biliary drainage using endoprotheses. After excluding extra regional and distant metastases, an estimation of the resectability was made by judging the involvement of the common hepatic artery, superior mesenteric and portal vein (SMV/PV). The dissection of the pancreas was to the left of the SMV/PV. Histological examination of the frozen section of the remaining pancreatic surface was performed. In case of a standard Whipple resection (SW), 1/3 of the stomach was also resected. Only tumors without macroscopically infiltration of the post pyloric duodenum and in absence of positive lymph nodes along the pylorus were treated by a pylorus-preserving pancreaticoduodenectomy (PPPD). Lymph nodes were dissected on the right hand side of the SMV/SMA up to the celiac trunk and in the hepatoduodenal ligament along the common hepatic artery. Per-operative data included the type of operation performed (PPPD or SW), BLOOD loss (ml) and transfusions (units). Post-operative data included complications, hospital stay and adjuvant therapy (5-FU and radiotherapy).

Kop of subkop? Zie ook volgende pag..

Tissue Micro Array (TMA)

We identified 75 patients for which paraffin blocks were available. In all other cases paraffin blocks were either lost or insufficient. The TMA was constructed as described by Kononen et al..[13] For each carcinoma, we prepared three tissue cores of 0.6 mm in diameter from the paraffin tissue block to ensure adequate representation of the neoplastic cells. The tissue cores from each carcinoma were then mounted in linear arrays in a paraffin TMA block. Tissue cores from various organs (pancreas, duodenum, and gallbladder) were used as controls, for orientation purposes and to estimate background labelling for each of the immunohistochemical markers. Immunohistochemistry labelling was performed according to standard protocols. In brief, 4-µm sections for each TMA were transferred to starfrost™ slides (Starfrost, Berlin, Germany) and immunostaining was performed using the Ultravision Large Volume Detection System Anti-Polyvalent, HRP (Labvision, Fremont, CA) after deparaffinization microwave (700W) pre-treatment was performed for 15 minutes using citrate buffer (100mM citric monohydrate pH6.0). Antibodies (clone) (Manufacturer) used for immunostaining were: ER-a (1D5), PR (PgR636), P16 (E6H4), p53 (DO-7), RB-1 (RB-1), EGF-R (H11), HER2 (C-erB-2) (DAKO A/S, Denmark), Chromogranin A (LK2H10) (Biogenex Inc., USA) and C-myc (9E10) (Santa Cruz Inc., USA).

TMA Scoring Strategy

One pathologist and one experienced analyst examined the TMA slides for each immunohistochemical marker with a multi-observer microscope. Both observers were blinded for the type of cancer and its location on the slide. Only moderate or strong labelling was scored as positive. Weak or "blush" labelling was ignored. A 2-tiered scheme (positive or negative) was used scoring the TMA. A percentage exceeding 1% of positive cells was regarded as protein over-expression. A score of negative or positive for each carcinoma was determined after examining the 3 tissue cores. Focal and diffuse positive scores were combined for the sake of statistical analysis.

Statistics

Survival analysis consisted of overall survival and time to recurrence. Curves were calculated by the Kaplan-Meier method, followed by log-rank tests. Factors, which showed to be significant in the univariate analysis, were entered into a multivariate Cox proportional hazards model to evaluate their independent prognostic value by backward elimination. To determine whether factors differed between patients with ampullary versus pancreatic carcinoma, appropriate interaction terms were used. P values (two-sided) of less than 0.05 were considered significant. All calculations were performed using SPSS 13.0 statistical software (SPSS Inc., USA).

Results

Survival

Follow-up was more than 10 years (median 12 years). Median survival and time to recurrence were significantly longer for ampullary than for pancreatic cancers (14 and 42, p=0.001, 16 and 34 months, p=0.024, respectively, table 1). Survival curves are shown in figure 1. There were no differences between groups in site of recurrence (p=0.497).

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Pre-operative factors

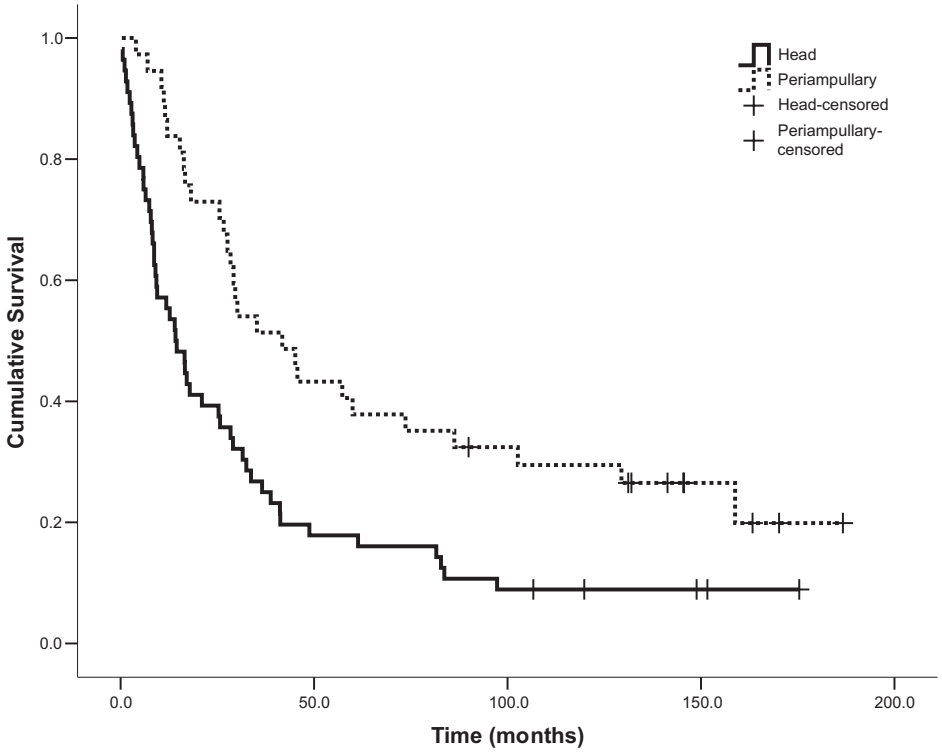
No differences in pre-operative factors were observed between both groups. Survival was better for women than for men in the pancreatic cancer – but not in the ampullary group. Preoperative abdominal – and back pain influenced survival and time to recurrence significantly for both groups. Jaundice was a predictor of survival and time to recurrence in ampullary cancers. Weight loss and diabetes mellitus did not influence survival (Table 1 and 2).

Table 1 **Group Comparison**

	Factor Positive (%)	*Head* (N=56)	*Ampullary* (N=37)	*Total* (N=93)	*P* (Fisher Exact)
Pre-operative Factors	Male	37(66)	19(51)	37(39)	0.191
	Age (years)	63	63	63	0.993
	Pain	31(55)	20(56)	51(55)	1
	Jaundice	49(88)	30(83)	79(86)	0.76
	Pruritus	13(23)	15(44)	28(31)	0.059
	Weight loss	45(80)	28(78)	73(79)	0.796
	>5kg	23(51)	18(64)	41(56)	0.335
	Obstruction	5(9)	5(14)	10(11)	0.505
	Diabetes	10(18)	8(22)	18(20)	0.603
	Endoprothesis	44(79)	27(71)	71(78)	1
Peri-operative Factors	PPPD	28(50)	18(49)	46(50)	1
	PV resection	1(2)	0	1(1)	1
	AMS-Resection	0	1(3)	1(1)	0.398
	Blood loss (ml)	2700	1950	2400	**0.028#**
	Blood loss 1liter	5(9)	6(18)	11(13)	0.324
	Transfusion (U)	2.4	1.5	1.2	**0.038#**
	Transfused patients	22(41)	7(21)	29(33)	0.064
	Complications	24(44)	20(54)	44(48)	0.396
	Leakage pancreaticojejunostomy			5(5)	
	Pancreatic Fistula			(6(6)	
	Leakage biliary anastomosis			1(1)	
	Abdominal Abcess			11(12)	
	Minor Complications			17(18)	
	Mortality			2(2)	
	Hospitalisation (m)	28	21		0.048#
	Radiation / 5-Fu	19(34)	9(24)	28(30)	0.363
Pathological Factors	T1	7(12)	8(22)		n.t.
	T2	15(27)	16(43)		n.t.
	T3	34(61)	13(35)		n.t.
	Diameter CM	23(41)	28(76)	51(55)	**0.001**
	N	29(52)	26(70)	55(59.1)	0.088
	M	0	0	0	
	G1	6(11)	7(19)		0.509$
	G2	43(79)	25(68)		
	G3	7(12)	5(13)		
	R-0	56(100)	37(100)		
	Perineural Invasion	31(55)	7(19)	38(41)	**0.001**
	Vasoinvasive	11(20)	5(14)	16(17)	0.579
Survival	Recurrences	41(73)	26(70)	67(72)	0.816
	Local	7(18)	6(26)		0.497$
	Distant	18(46)	8(35)		
	Both	12(31)	9(39)		
	Deaths	51(91)	28(76)	79(85)	0.073
	Median Survival (m)	14	42		**0.001***
	Median Time to Recurrence (m)	16	34		**0.024***
	Factor (%)	***Head*** (N=47)	***Ampullary*** (N=28)	***Total*** (N=75)	***P*** (Fisher Exact)
Tissue Micro Array	ER-a	0(0)	1(3.7)	1(1)	0.365
	PR	5(11)	1(3.7)	6(80)	0.406
	P16	10(21)	9(33)	19(25)	0.28
	P53	9(20)	5(19)	14(19)	1
	RB-1	28(62)	20(77)	48(64)	0.293
	C-Myc	19(41)	16(59)	35(47)	0.154
	Chromogranin A	10(22)	6(22)	16(21)	1
	EGF-R	11(24)	1(3.7)	12(16)	**0.026**
	HER-2	4(9)	3(11)	7(9)	1

PPPD: pylorus preserving pancreaticoduodenectomy, N: positive lymphnodes, G: differentiation grade, m: months, AMS: superior mesenteric artery, PV: portal vein, *log-rank test, # T-test, $Chi-square for 3x2 table, n.t.: not tested.

FIGURE 1 **Kaplan-Meier *survival curves* for ampullary and pancreatic cancers (p=0.001, log-rank test)**



No at risk	*Months:*	*12*	*24*	*36*	*48*	*60*	*72*	*84*	*120*
Head	N=56	31	22	15	11	10	10	5	3
Ampullary	N=37	32	27	19	16	14	13	13	10

Peri-operative findings

The surgical technique used (PPPD vs. SW) DID not correlate with survival (p=1.000). Per-operative blood loss and peri-operative blood transfusions (units) were higher in the pancreatic cancer group (p=0.028 and 0.038). Hospitalization was longer for pancreatic cancers (p=0.048). However these factors did not influence survival (Table 1 and 2).

Mortality and Morbidity

Two patients (2%) died postoperatively because of aspiration pneumonia and sepsis. These patients remained in our analysis because of the intention to treat principle. Postoperative complications occurred in forty-four (48%) cases. In 5 patients (5%) leakage of the pancreaticojejunostomy was seen, defined as presence of amylase (3x serum concentration) in drainage or abdominal fluid. Six patients developed a

TABLE 2 **Univariate analysis**

Univariate Analysis		***Relation to Survival***			***Time to Recurrence***		
Factor Positive (%)	*Direction of Effect*	*Head* (N=56)	*Ampullary* (N=37)	*Pooled** (N=93)	*Head* (N=56)	*Ampullary* (N=37)	*Pooled** (N=93)
Male	-	**0.028**	0.688	**0.046**	0.072	0.614	0.086
Pain	-	**0.018**	**0.001**	**0.000**	**0.006**	**0.000**	**0.000**
Jaundice	+	0.364	**0.029**	**0.044**	0.773	**0.017**	0.097
N	-	0.064	**0.013**	**0.004**	**0.016**	**0.006**	**0.000**
G	-	**0.034**	0.624	**0.012**	**0.046**	0.384	**0.012**
Perineural Invasion	-	0.273	**0.001**	**0.025**	0.053	**0.000**	**0.001**
C-Myc	+	**0.034**	0.968	0.078	**0.015**	0.858	**0.038**
EGF-R	-	0.084	N.T.	0.080	**0.037**	N.T.	**0.042**

N: positive lymphnodes, G: differentiation grade, pain: pre-operative back and abdominal pain. * test for trend, N.T.: not tested.

pancreaticocutaneous fistula. Leakage of the biliary anastomosis occurred in one patient. Eleven patients (12%) had an intra-abdominal abscess. Minor complications were found in 17 patients (18%). Complications did not influence survival or time to recurrence (Table 1 and 2).

Adjuvant therapy

Adjuvant therapy (5-FU chemotherapy and radiotherapy) was given to 28 patients distributed evenly between both groups (p=0.363) (Table 1). Survival data is omitted here because of bias. These patients participated in a trial in which we compared the effect of chemo-radiation with surgery alone.[3]

Pathological Factors

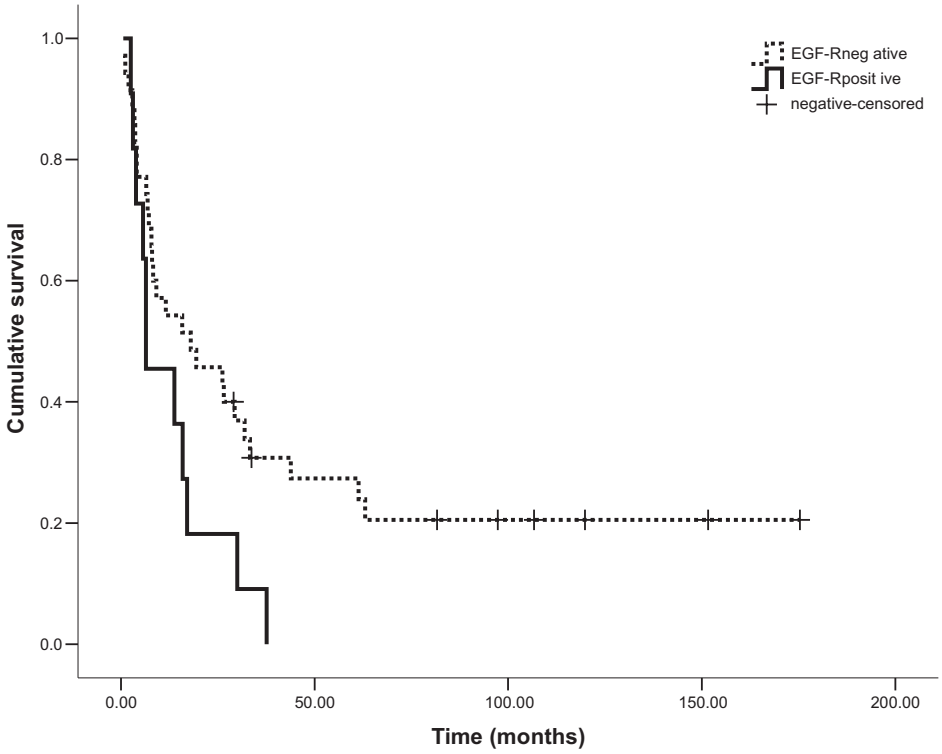
Pancreatic head tumors were larger (p=0.001) than ampullary. Perineural invasion was also observed significantly more in this group (p=0.001).

The strongest negative histological factor for survival and time to recurrence was lymph node involvement in the resected specimen. Tumor diameter as well as extent of the tumor (T) did not influence survival. Histological grading was correlated with survival and time to recurrence for pancreatic head cancers. Invasive growth into intrapancreatic perineural tissue significantly influenced survival (p=0.001) and time to recurrence (p=0.000) in ampullary cancers. Tumor invasion of small surrounding blood vessels was not correlated with survival (Table 1 and 2).

Tissue Micro Array

The overall failure rate secondary to lack of interpretable neoplastic tissue was 3%. In all other cases in which cores were without malignant glands, interpretation of

FIGURE 2 **Kaplan-Meier curves for EGF-R expression in pancreatic head cancers, *time to recurrence* (p=0.037, log-rank test)**

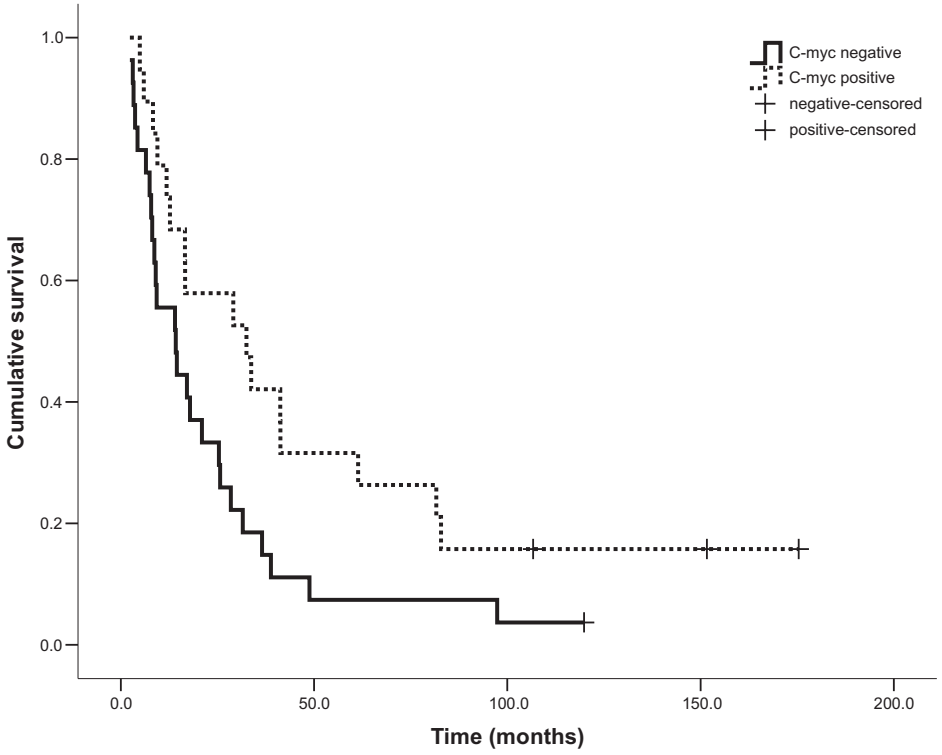


No at risk	*Months:*	*12*	*24*	*36*	*48*	*60*	*72*	*84*	*120*
Positive	N=11	5	2	1	0				
Negative	N=35	19	16	9	8	8	6	4	2

the labeling pattern was possible with the remaining tissue cores from that same carcinoma. Although histologically very similar, adenocarcinomas of the ampullary region are thought to be biologically different compared to pancreatic ductal adenocarcinomas. However for most tested proteins the labeling was not significantly different between both groups. Interestingly, EGF-R is expressed more frequently in pancreatic than in ampullary cancers (p=0.026). For pancreatic cancers, EGF-R over-expression is an indicator for shorter time to recurrence (p=0.037) (Figure 2). A trend was observed towards poor survival (median survival: 14 vs 25 months, p=0.084). Furthermore, no long-term survivors were observed in the EGF-R positive group. C-myc over-expression is correlated with improved survival (p=0.034) and longer time to recurrence (p=0.015). It is clear that these last two factors are of significance for pancreatic head cancers but not for ampullary cancers (table 1 and 2).

Ik vond géén verwijzing in de tekst naar Figure 3.

FIGURE 3 **Kaplan-Meier *survival curves* for C-myc expression in pancreatic head cancers (p=0.034, log-rank test)**



No at risk	*Months:*	*12*	*24*	*36*	*48*	*60*	*72*	*84*	*120*
Positive	N=19	14	10	7	5	5	4	2	2
Negative	N=27	15	9	5	3	2	2	2	0

Multivariate Analysis

All factors that were significant in the univariate analysis were entered in a cox-regression model. Independent prognostic factors for survival for the pancreatic head group were: pre-operative back and abdominal pain (B(exp):0.548 / p=0.05) and differentiation grade (2.004/0.016). No independent prognostic factors were found for ampullary cancers.

For time to recurrence independent prognostic factors for the pancreatic head group were: pre-operative back and abdominal pain (0.446/0.015), positive lymph nodes (0.491/0.033), EGF-R over expression (0.448/0.034). Independent prognostic factors for ampullary cancers are pre-operative back and abdominal pain (0.224/0.007) and perineural invasion (0.199/0.031).

Discussion

Median survival and time to recurrence after radical resection were significantly longer for ampullary than for pancreatic cancers. This evident difference may be due to earlier clinical presentation or different biological behavior. We found no differences in pre-operative factors between both groups.

Pre-operative back and abdominal pain was found in 51(55%) patients. It was also an independent negative prognostic factor for time to recurrence for both groups and for survival in univariate analysis. We further found that intra-pancreatic perineural invasion was a negative prognostic factor for survival (not for pancreatic cancers, p=0.273) and time to recurrence in the univariate analysis (both groups). Pre-operative pain as a negative prognostic factor has been reported earlier by Ridder et al.[23] and Okusaka et al.[24] Forty-one % of patients with preoperative pain had intra-pancreatic perineural growth and 55% of perineural growth had preoperative pain. These findings suggest that pain is not always caused by intra-pancreatic perineural growth and vice versa. Indeed pain is usually interpreted as resulting from tumor infiltration into extra-pancreatic (retro-pancreatic) splanchnic nerves and thus may indicate advanced tumor growth beyond the borders of the pancreas.

In the present study 72% of all patients had recurrence of their cancer and almost half of all recurrences were local (table 1). This is similar to previously reported rates in two large trials on adjuvant therapy by Klinkenbijl[3] and Neoptolemos et al.[25] Although both studies included only 18-22% R-1 resections, the reported rate of recurrence was approximately 70 % and 37-52% of these recurrences were local.

Possibly our definition of R-0 may have included some "irradical" resections. Verbeke et al. suggested that R-1 can be underestimated when pathological examination is not completely standardized.[26] They compared pathological examinations in two consecutive periods with and without a highly standardized protocol. The number of R-0 resections for pancreatic cancer in the standardized period was lower than in the non-standardized period (p=0.009). Interestingly, long-term survival for pancreatic cancer was not predicted by R status in either cohort. A similar observation was made by Neoptolemos et al. in a sub-analysis of their trial on adjuvant therapy. They found that R status was not an independent prognostic factor for survival. Only after omission of nodal status and differentiation grade, R status became significant.[12,25]

It is intuitive that R-1 is a predictor of poor survival, and indeed long-term survivors are sparse after R-1. Therefore R-0 is often considered to be the most important factor predicting favorable outcome after resection. Consequently, extended resec-

tions, including extensive clearing of retroperitoneal soft- and lymphatic tissue, have been advocated. Several randomized controlled trials[27-29] were performed but failed to show a survival benefit for extended surgery. In a recent study by Hishinuma et al. 27 patients who had undergone extended resection were studied by autopsy. Most resections were R-0 (25/27), 3 patients died postoperatively, the majority died of metastatic disease and only 4 patients died due to local recurrence. Evidence of local recurrence was found in 18 of 24 (75%).[30] This study clearly shows that even after extended surgery local recurrences are still frequent. Possibly R-0 and R-1 are both accompanied by (occult) metastatic disease. Indeed, in an overview of advanced molecular detection techniques[6], it was shown that tumor cells can be found pre- and peri-operatively in peritoneal lavage fluids, the liver, blood, "tumor negative" lymphnodes and bone marrow of patients without "conventional" evidence of metastatic disease. As a result, R-0 offers an opportunity for long-term survival for a limited number of patients. However, in the majority of cases resection cannot provide curation and recurrence remains imminent. This further emphasizes the importance of additional prognostic parameters to predict outcomes after "R-0" ("R") resection and to select patients in need of (aggressive) systemic adjuvant therapy.

The Tissue Micro Array technique proved to be a simple, efficient and relatively inexpensive method to explore protein expression in large groups of patients. Our failure rate of 3% is acceptable and did not cause statistical problems. Expression of p53 and p16 proteins is well known in pancreatic cancer.[17] Nevertheless their prognostic value remains unclear. We found similar expression of p16 (21-33%) (table 1) compared to previously reported studies (13-59%).[17] Expression of p53 in our study (19-20%) was lower than previously reported (35-69%).[17] This may be due to our techniques or a selection bias in our group (R-0). RB-1 protein expression has been reported previously in tissue and cell-lines, the exact prevalence however was unclear.[31,32] We found RB-1 to be positive in 62-77% of cases. C-myc, a proto-oncogene, expression has been previously reported.[18] We found improved survival for patients with over-expression of this protein. This is counterintuitive since, as a known proto-oncogene, it is thought to promote oncogenesis and tumor growth. Alternatively C-myc expression is thought to be an early step[18] in the rapid oncogenesis of pancreatic cancer[33] and may be an indicator of relatively early point in tumor progression. Hypothetically this implicates an early stage disease and thus a less aggressive nature. Nevertheless, the exact role of C-myc remains unclear. We found 22% of cancers to be positive for Chromogranin A, a neuroendocrine differentiation marker. This is similar compared to a previous report of neuroendocrine differentiation by Tezel et al..[34] However, they did not find any Chromogranin A positive tumors in their specimens, in contrast to 18-36% expression of other neuroendocrine markers (NCAM, NSE, Synaptophysin, CD57). This may be due to differences in antigen retrieval,

immunohistochemical techniques and/or antibody clones used. HER-2 was positive in only 9-11% of cases and did not show correlation with survival. This is comparable with previously published results 8-58%.[17]

EGF-R, a well-known growth factor receptor, was positive in ampullary (4%) but significantly more often in pancreatic cancers (24%, p=0.026). This is in accordance to expression rates previously reported (28-68%).[17] The difference in EGF-R expression between pancreatic and ampullary cancers was previously suggested by Friess et al..[35] Although their study did not provide matched clinical and survival data, they suggested a role for the EGF-R in the less favorable outcome for pancreatic cancers. In our study, EGF-R over-expression is a negative prognostic factor for time to recurrence (p=0.037) and possibly survival (p=0.084) in pancreatic cancer. This effect on survival has been described previously in several studies, while others found no effect.[17,36] For head and neck cancer EGF-R expression was shown to be correlated to survival and relapse.[37] In breast- and colorectal cancer, however, no correlation was evident.[38,39]

So in conclusion, the difference in biological behavior between pancreatic and ampullary cancers could be confirmed in this study. The poor prognosis of patients with pancreatic cancer can possibly be related to the increased EGF-R expression of these tumors compared to ampullary cancers. Our data support the rationale to use drugs that have recently been designed to target the EGF-R selectively (Tarceva, Iressa, Erbitux)[40] in adjuvant targeted therapy regimens.

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Chapter 5

Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation

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Summary

Background

The role of adjuvant chemoradiation in pancreatic cancer remains unclear. This report presents the long-term follow-up results of EORTC trial 40891, which assessed the role of chemoradiation in resectable pancreatic and periampullary cancer.

Methods

218 patients were randomized after resection of the primary tumor. Eligible patients had T1-2 N0-N1a M0 pancreatic cancer or T1-3 N0-N1a M0 periampullary cancers, all histological proven.

Patients in the treatment group (n=110) underwent post-operative chemoradiation (40 Gy plus 5-FU). Patients in the control group (n=108) had no further adjuvant treatment.

Findings

After a median follow-up of 11.7 years, 173 deaths (79%) have been reported. The overall survival did not differ between the two treatment groups (Chemoradiation treatment versus Controls: death rate ratio 0.91, 95% CI: 0.68-1.23, p-value 0.54). The 10-year overall survival was 18% in the whole population of patients (8% in the pancreatic head cancer group and 29% in the periampullary cancer group).

Interpretation

These results confirm the previous short-term analysis, indicating no benefit of adjuvant chemoradiation over observation in patients with resected pancreatic cancer or periampullary cancer. Patients with pancreatic cancer may survive over 10 years. Recurrence occurred up to seven years, one even after 7 years.

Introduction

Pancreatic cancer has a poor prognosis with an overall survival rate ranging from 0.4 to 4 percent, and is one of the top five causes of death from cancer in the western world[1,2]. Surgical resection improves the outcome, but only about 10 percent of patients are eligible for the procedure. Most treatment failures are due to local recurrence, hepatic metastases or both, and occur within one to two years after surgery.[3,4]

Adjuvant therapy has been studied in a few trials but its routine use is not universal because earlier trials reported contradictory results.[5-11,13]

The Gastrointestinal Tumor study group (GITSG) randomly assigned 43 patients to surgery alone or chemoradiation followed by maintenance chemotherapy.[5-7] The

median survival was significantly longer in the adjuvant treatment group compared to the surgery group (20 months versus 11 months), with respectively 18 percent and 8 percent survival at five years.[5,7,28,29] Further larger randomized studies however did not confirm a benefit of adjuvant treatment.[12-14] Moreover, it is unclear whether the survival advantage in the GITSG trial was due to the combination of chemoradiation and maintenance chemotherapy or to only one of these treatments.[9] The first large multicenter trial in pancreatic cancer was a randomized phase III conducted by the EORTC Gastro-intestinal group, initiated in 1987 (EORTC 40891). Based on 218 patients, this trial did not show a benefit for adjuvant chemoradiation although they suggested a trend in favor of chemoradiation (p=0.09) in the patients with ductal pancreatic adenocarcinoma .[13]

In 1994, the European Study Group for Pancreatic Cancer (ESPAC) undertook a multicenter factorial phase III trial to investigate the possible benefits of adjuvant chemoradiation and maintenance chemotherapy in patients with pancreatic cancer. In this trial, a deleterious effect of adjuvant chemoradiation on survival was shown whereas chemotherapy significantly improved survival in patients with resected pancreatic cancer.[15-17]

The goal of this trial was to evaluate the effect of adjuvant treatment with post-operative radiotherapy and 5-FU after potentially curative resection in patients with cancer of the pancreatic head and periampullary region. We here report the long-term results (with 11.7 years follow-up) of the EORTC 40891 trial. Together with the results of the ESPAC-1 trial, these results might allow for more definitive conclusions about the value of adjuvant chemoradiation. It is the first time actual survival rates of more than ten years are presented for resectable pancreatic cancer.

Methods

The trial design has been reported extensively before.[13] Therefore we shall summarize only the main aspects. It was designed as a multicenter trial with a central pathology review. Eligible patients were patients with T1-2 N0-1a M0 pancreatic head cancer or T1-3 N0-1a M0 periampullary cancer. TNM staging (according to the UICC's 1987 guidelines) was modified for N stage. N1a-stage positive lymph nodes were located within the resection specimen, and N1b-stage positive lymph nodes were located outside the resection area for instance, retroperitoneally along the aorta. Cancer of the periampullary region was defined as tumor in the distal common bile duct, papilla of Vater or duodenum. Patients with stage T3 pancreatic head cancer and stage T4 periampullary cancer were excluded because of ingrowth into surrounding organs, with a limited prognosis.

After tumor resection, whenever the pathology report was available and the patient had recovered from surgery, (but within 8 weeks of surgery), patients were randomized between chemoradiation and observation by minimization, with stratification for institution and tumor localization (pancreatic head vs. periampullary).[18] A Whipple procedure or pylorus-preserving pancreatoduodenectomy was accepted as standard resection. An extended lymph node resection was not performed.

The chemoradiation regimen differed from that used in the GITSG study. 5-FU was given concomitantly with radiotherapy, and as a continuous infusion instead of a bolus injection. Radiotherapy was started 2 to 8 weeks after surgery and given using megavoltage equipment (min 6MV) using a 3 or 4 field technique. Radiotherapy was delivered over a period of 6 weeks, with a 2-week break. A total of 40 Gy was delivered in two courses of 20 Gy (2 Gy/d, 5d/wk at weeks 1-2 and 5-6). During each course, chemotherapy was started before radiotherapy and consisted of 5-FU (25 mg/kg/day), with a maximal daily dose of 1500 mg. Depending on toxicity, the second course consisted of zero (if grade 3-4 toxicity), three (if grade 1-2 toxicity), or five days of 5-FU (if no toxicity). Toxicity was scored according to the World Health Organization (WHO) guidelines.

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The primary end-point was survival, secondary end-point was recurrence of disease.

The trial was designed to detect an absolute increase of 20% in 2-year overall survival (from 30% to 50%, 110 events needed) with 80% power and a two-sided 0.05 significance level. The sample size was 218.

All efficacy analyses were performed according to intention-to-treat (i.e. as randomized) and with a 5% significance level. Toxicity reports are on all patients who started their treatment. Event-free rates were estimated by Kaplan-Meier method and compared by log-rank test. The Cox proportional hazards regression was used for prognostic factor modeling and to adjust the treatment comparison for most important prognostic factors. A backward variable selection was applied, with a 0.05 significance level. Factors evaluated were gender, age (<60 years (median) vs ≥60 years), T-category (tumor ≤2 cm vs >2 cm), microscopic invasiveness of the resection margin (yes vs no), lymph node involvement (yes vs no), degree of differentiation of the tumor (1 vs 2 vs 3-4), vasoinvasive growth (yes vs no) and WHO performance status (0 vs 1-2). Ordinal categories were defined for histopathological grading. Adjacent levels of discrete variables with small numbers were pooled together. Internal model validation was performed by the bootstrap resampling technique (1000 replicates).

Results

Between September 1987 and April 1995, 218 patients were randomized to the EORTC trial 40891, 108 patients in the observation arm (Obs) and 110 patients in the treatment arm (Trt). Patients were recruited from 29 centers in Europe, but 4 centers entered 70% of all patients. At the time of this analysis, the median follow-up was 11.7 years and the patients still alive had been followed for a median of 9.8 years (min=3.5 months, max=14.3 years).

Eleven patients were ineligible (5 on Obs and 6 on Trt): N1b: 5 patients, T3 tumors: 5 patients and 1 patient had concurrent disease. The patient's baseline characteristics were reported earlier and were comparable between the two study groups (Table 1).

Treatment Data

Ten of the 104 eligible patients in the Trt group refused to start treatment, and another 11 patients developed contraindications to adjuvant treatment after randomization (the most noticeable were long-lasting septic shock developed as a result of leakage of the pancreaticojejunostomy in one patient; rapid progression in four patients; one patient had only one functional kidney, located within the radiation field). In two more patients, revision of pathology reports showed that a T3 tumor was included. As a result, in the treatment arm a total of 81 eligible patients could be evaluated for treatment toxicity.

Chemoradiation

As reported previously, 75 of the 81 eligible treated patients received 40 Gy radiation therapy[13]. The median dose of 5-FU 197 mg/kg (range: 99 to 275 mg/kg) corresponding to a median dose intensity of 89% (range: 50% to 122%).

Toxicity

As reported earlier, thirty-five patients (44%) received only 3 days of 5-FU infusion during the second course of radiotherapy because of grade 1 or 2 acute toxicity. No leucopenia or thrombopenia worse than WHO grade 2 was observed, and the daily dose of 5-FU was never reduced. Minor non-hematological toxicity was observed in a few patients, with a maximal WHO grade 3 toxicity, especially nausea/vomiting (7 [8%] patients), diarrhea (1 [1%] patient) and constipation (1 [1%] patient). The only instance of major toxicity was observed in one patient who developed duodenal ulcer after the first treatment course. It was treated with anti-acids and beta-blockers but did not heal after 6 weeks, therefore the second course was not given.

TABLE 1 **Baseline Characteristics (all patients). TNM data according to 1987 UICC criteria**

		***Observation* (n=108)**	***Treatment* (n=110)**
Median age (years) [range]		61 [39-79]	58 [23-78]
Median time from surgery to randomization (days) [range]		17 [1-57]	17 [6-57]
Sex; number (%)	Male	58 (54)	68 (62)
	Female	50 (46)	42 (38)
WHO performance status	0	55 (51)	63 (57)
	1	44 (41)	44 (40)
	2	9 (8)	3 (3)
Weight loss relative to normal weight (%) (range)	8 (-28 – 37)	7 (- 15-30)	
Jaundice	Yes	64 (59)	71 (64)
	No	42 (39)	39 (36)
	Unknown	2 (2)	0 (0)
Resection Margins	Negative	80 (74)	87 (79)
	Negative after re-resection	2 (2)	1 (1)
	Positive	24 (22)	22 (20)
	Unknown / Missing	2 (2)	0 (0)
Vasoinvasion	Yes	36 (33)	35 (32)
	No	70 (65)	73 (66)
Histopathological grading	Well differentiated	42 (39)	35 (32)
	Moderately differentiated	45 (42)	44 (40)
	Poorly differentiated	20 (19)	30 (27)
	Unknown	0 (0)	1 (1)
Pathology data	Pancreatic duct	57 (53)	63 (57)
	Papillary	39 (36)	33 (30)
	Duodenal	1 (1)	1 (1)
	Bile Duct	10 (9)	13 (12)
	Unknown	2 (2)	0 (0)
T category (pancreatic head)	T1	6 (11)	16 (25)
	T2	48 (84)	39 (62)
	T3	2 (3)	6 (10)
	Unknown / Missing	1 (2)	2 (3)
T category (periampullary region)	T1	5 (10)	5 (11)
	T2	23 (46)	16 (34)
	T3	19 (38)	25 (53)
	T4	1 (2)	1 (2)
	Unknown / Missing	2 (4)	0 (0)
N category (pancreatic head)	N0	26 (46)	28 (44)
	N1a	21 (37)	23 (37)
	N1b	2 (4)	0 (0)
	Unknown / Missing	8 (14)	12 (19)
N category (periampullay region)	N0	24 (48)	25 (53)
	N1a	21 (42)	18 (38)
	N1b	2 (4)	1 (2)
	Unknown / Missing	3 (6)	3 (6)

Overall Survival

After 11.7 years of follow-up, 173 patients have died. The cause of death was malignant disease in 143 (83%) patients (75 [86%] Obs, 68 [79%] Trt), in-hospital death in 4 (2%) patients (0 Obs, 4 [5%] Trt), nonmalignant/nontoxic death in 13 (8%) patients (4 [5%] Obs, 9 [11 %] Trt), and unknown in 13 patients (8 [9%] Obs, 5 [6%] Trt). There was no evidence that survival was influenced by treatment (HR=0.91 [95% CI: 0.68-1.23], p=0.540, Figure 1), with a median survival of 1.6 years [95% CI: 1.2-2.3 years] and 1.8 years [95% CI: 1.5-2.4 years] in the Obs and Trt group, respectively. The 5-year survival rates were 22% [95% CI, 14-31%] in the Obs group and 25% [95% CI, 16-34%] in the Trt group, and the 10-year survival rates were 18% [95% CI, 11-26%] in the Obs group and 17% [95% CI, 9- 25%] in the Trt group.

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No difference was seen when analyzing the two tumor locations separately (HR=0.76 [95% CI: 0.52-1.12] for pancreatic head cancer and HR=1.03 [95% CI: 0.63-1.68] for periampullary cancer), but these analyses lack statistical power (Figures 2 and 3).

In both treatment arms, the median survival for the pancreatic head cancers was only about 1 year (1.0 year [95% CI: 0.8-1.4 years] in Obs and 1.3 year [95% CI: 1.1-1.8 years] in Trt).

Progression-free survival

Of the 218 patients, 76 (70%) in the Obs group and 75 (68%) in the Trt group had a documented progression of disease. The site of first progression and the site of distant progression are shown in Table 2.

FIGURE 1 **Survival**

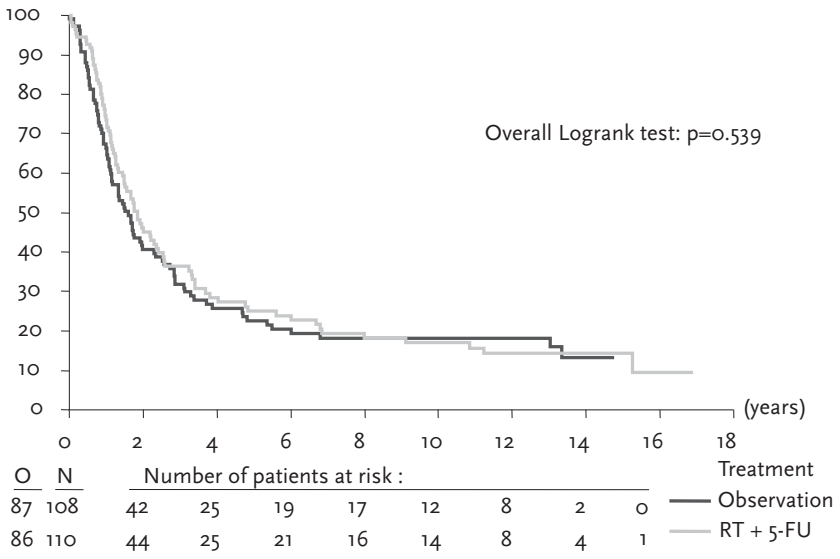


FIGURE 2 **Survival, Pancreatic head cancer**

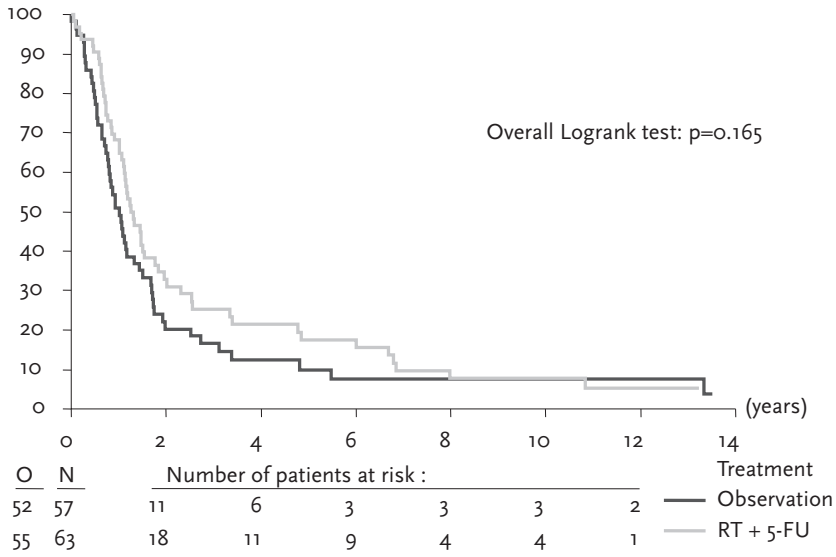
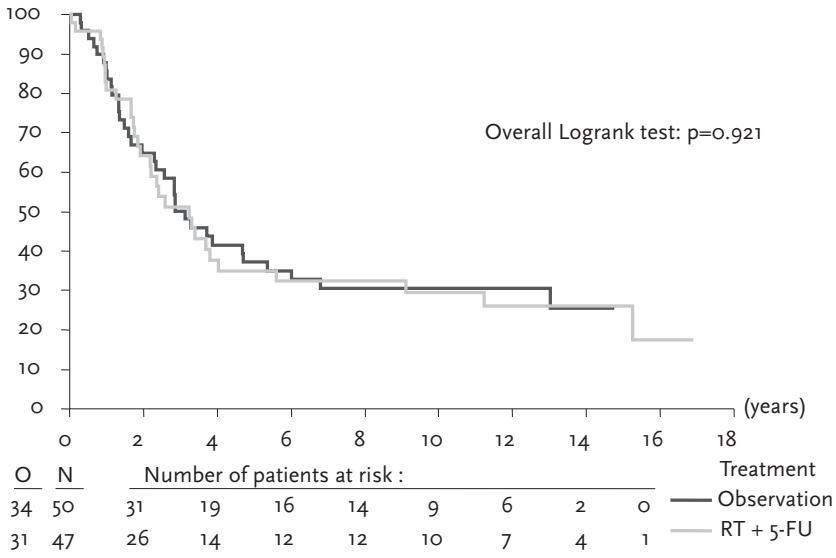


FIGURE 3 **Survival, Periampullary cancer**



No advantage of adjuvant treatment in progression-free survival was shown, neither on all patients (HR=0.94, 95% CI: 0.70-1.26, p=0.663), nor in the 2 tumor locations separately (HR 0.81, 95% CI: 0.55-1.17, p=0.259 pancreatic head and HR 1.0 95% CI: 0.63-1.65, p=0.930 periampullary) For all patients in the Obs group, the median progression-free survival was 1.2 years [95% CI: 0.9-1.7 years] and it was 1.5 years

Table 2 **Progression Status (all patients)**

	Observation* (N=108) *Number (%)	***Treatment* (N=110) *Number (%)***
No documented progression	32 (30)	35 (32)
Documented progression	76 (70)	75 (68)
Site of first progression		
Local	16 (21)	15 (20)
Distant	35 (46)	36 (48)
Both	23 (30)	22 (29)
Second malignancy	1 (1)	1 (1)
Unknown/Missing	1 (1)	1 (1)
Site of distant progression		
Liver	37 (49)	38 (51)
Lung	8 (11)	5 (7)
Other	28 (37)	23 (31)
Pancreatic head	N=57	N=63
Progression	45 (79)	47 (75)
No progression	12 (21)	16 (25)
Periampullary	N=50	N=47
Progression	30 (60)	28 (60)
No progression	20 (40)	19 (40)

[95% CI: 1.0-1.8 years] in the Trt group. The 5-year progression-free survival rates were 20% [95% CI, 12-27%] and 21% [95% CI, 13-29%], respectively, and the 10-year rates were 17% [95% CI, 9-23%] and 16% [95% CI, 9- 24%].

The results regarding overall survival and progression-free survival were similar when the analyses were repeated in the per protocol subgroup of eligible cases who followed the assigned treatment policy. There were 75 patients in the treatment group and 102 in the observation group. Median overall survival was 1.9 years [95% CI: 1.4-2.5 years] in the treatment group and 1.6 years [95% :0.8-1.5 years] in the obs group.

The median progression- free survival was 1.6 years [95% CI: 1.2-1.9 years] in the treatment group and 1.33 years [95% CI: 1.0- 1.8 years] in the obs group.

Influence of Prognostic Factors

Prognostic factors for overall survival were evaluated separately for patients with cancer in the pancreatic head and for patients with a periampullary tumor. Due to small numbers in the T1 and R1 categories, T category and invasiveness of the resection margin could not be studied in the periampullary cancer patient group. For the pancreatic head tumor, a larger tumor (p=0.004), a worse histopathological grade

(p=0.042), the presence of vasoinvasive growth (p=0.041) and a deteriorated WHO performance status (p=0.021) were associated with a shorter survival by univariate analysis. A marginal non-statistically significant impact of positive lymph nodes was also observed (p=0.090). The final multivariate model retained only T-category, grade and WHO performance status as independent prognostic factors. The bootstrap internal validation showed good model stability and internal validity as the three variables were the most frequently retained (in 79.2%, 45.0% and 58.5% of the models, respectively, against <31.0 % for all other variables).

When adjusting for the three independent prognostic factors, the conclusions remained unchanged as regards the absence of treatment effect (Table 3).

Univariate analysis in the periampullary group showed that positive lymph nodes (p=0.030), vasoinvasive growth (p=0.006) and a worse degree of differentiation of the tumor (p<0.001) were associated with a shorter survival. At the end of the multivariate selection process, 3 variables were retained as independent prognostic factors: vasoinvasive growth, presence of positive lymph nodes and age >60 years. The validation showed that these variables were selected in 72.2%, 56.2% and 53.5% of the models, respectively (against =35.0% for all other variables). The multivariate model with these three variables was also the most frequently selected model (19.5%).

When adjusting for age, N category and vasoinvasive growth, the conclusions regarding the treatment effect in the periampullary cancer patients remained unchanged (Table 3).

TABLE 3 **Cox proportional hazards models for overall survival separately for pancreatic head- and periampullary cancers, adjusting for the baseline covariates with the strongest prognostic value**

Variable	*Death rate Hazard ratio (95% confidence interval)*	*p-value*
Pancreatic head cancer		
Treatment (radiochemotherapy vs no adjuvant therapy)	0.74 (0.49-1.10)	0.137
T-category (T2-4 vs T1)	2.38 (1.38-4.10)	0.002
Histopathological grade	1.41# (1.10-1.79)	0.006
Performance status (WHO 1-2 vs 0)	1.62 (1.08-2.43)	0.019
Periampullary cancer		
Treatment (radiochemotherapy vs no adjuvant therapy	1.09 (0.65-1.84)	0.750
Age (≥60 vs <60 yrs)	1.87 (1.10-3.19)	0.021
Nodes (Positive vs neg.)	1.86 (1.09-3.18)	0.023
Vasoinvasive growth (Present vs Absent)	2.70 (1.53-4.76)	<0.001

trend: grade 2 (moderate) vs grade 1 (well) and grade 3 (poor) vs grade 2

Discussion

To our knowledge this is the first randomized trial of pancreatic cancer with a follow up exceeding 10 years. This trial shows no difference between adjuvant chemoradiotherapy and observation, neither for survival nor for progression-free survival. This study also shows that long-term survival after curative resection is possible in 12% of all patients (26/218 patients are still alive by year 10). In addition, only 1 cases of 31 recurred after 7 years . This means that future trials in pancreatic cancer should manage to provide a follow-up of 7 years or longer.

Overall prognosis of pancreatic cancer is still dismal. The incidence of locoregional recurrence is high (up to 80%), and occurs in most cases together with distant metastases. Patients with periampullary carcinoma have a more favorable outcome, with a 5-year survival rate of 40% to 70%.[19-26] To improve survival, several therapeutic modalities have been tested (intraoperative radiotherapy, chemotherapy, and combinations of both) in patients with unresectable and resectable disease, with varying success.[12,27-37] The GITSG trial, with 43 patients, was the first study to show a benefit of adjuvant treatment in pancreatic cancer.[7, 5,28,29] Because of the long accrual time and the small number of patients entered in the GITSG study, we decided to assess the possible value of radiotherapy and 5-FU as an adjuvant to surgery in a larger group of patients. The current trial was initiated in 1987 and accrued 218 patients with resected pancreatic head and periampullary cancer. The adjuvant treatment was the same as in the GITSG trial except that the 5-FU treatment was only during the first week of each radiation course. Radiotherapy and 5-FU treatment did not induce major toxicity (the worst observed toxicity was WHO grade 3); all patients but the one with severe toxicity completed the treatment. However, despite the success of this treatment in the only other randomized study[7], the present trial demonstrated no advantage for adjuvant chemoradiation, neither for progression-free, nor for overall survival . The first analysis of this trial, at a median follow-up of 7.3 years and based on 144 events, suggested a trend towards advantage of adjuvant chemoradiation in patients with pancreatic head cancer (median overall survival was 12.6 months in the Obs group and 17.1 months in the Trt group (HR=0.7, 95% CI: 0.5-1.1, p=0.099)). The present long-term follow-up analysis, with a median follow-up of 11.7 years and 173 events, confirmed the absence of a difference in survival, overall and in the different disease groups.

This trial has been criticized[15,17] for being powered for a too optimistic difference (20% benefit at 2 years, HR=0.58). At present, with 173 events, the study has 80% power to detect a somewhat smaller benefit (15.7%) in 2-year survival (HR=0.65). The study still lacks power to detect smaller differences and differences within subgroups, in particular for the analyses by tumor type that are based on a smaller number of events. We think that this trial together with the ESPAC-1 results provide a

strong evidence for concluding that adjuvant treatment using chemoradiation is not effective. Chemotherapy alone may be effective according to the ESPAC study, the five-year survival rate was 21 percent for patients who did receive chemotherapy and 8 percent among patients who did not receive chemotherapy. The effect of chemotherapy was encouraging although 18 percent of the patients had positive resection margins.

Radiotherapy with chemotherapy has been applied as neoadjuvant treatment with some success, but the value of this treatment is not yet proven.[30,38-44]

For the time being, surgery alone is considered inadequate and adjuvant chemotherapy should be considered. The question remains as to what kind of adjuvant chemotherapy should be proposed. New chemotherapeutic agents such as docetaxel, gemcitabine, and topotecan have been studied, with response rates of 10% to 25%.[45] Link et al described a technique of intra-arterial infusion chemotherapy using the celiac axis after resection; they found promising results with respect to median survival, but only in 18 patients after curative resection.[46-48]

As discussed above the trial missed power to detect small differences between subgroups. Beforehand it would have been better to include only pancreatic cancer and not periampullary cancer which nowadays is known to have a better prognosis and a different tumor behaviour. Further this trial would have benefit from prestudy entry CT-scanning, more precise: not only a CT-scan before surgery but also a CT-scan before starting radiotherapy.

We have learned lessons from this trial design. For future trials on pancreatic cancer there is a need for quality control of pathology assessment. Every specimen needs to be examined and described following a complete and strict protocol.

In this trial's protocol the pathologist needed to describe the location of the tumor, the size of the tumor, the extent of tumor in resection margins and the frozen sections. Further the number and location of lymphnodes involved with tumor, vasoinvasive growth of tumor, histopathological grading and finally the TNM classification had to be given. There was no standardized protocol for the pathologist how to determine and describe the presence or absence of tumor at the surgical margins. As a consequence, some patients with R-2 tumors might have been included in this trial. In our opinion a standardized pathology protocol how to assess specimens tumor margins is likely to minimize the risk of including R-2 resections. Both this and the fact that we included R-1 tumors (according to our inclusion criteria) implicate that the median survival is rather low, approximately one year.

In conclusion our results show no beneficial effect for combined radiotherapy with 5-FU chemotherapy as standard adjuvant treatment after curative resection for either pancreatic or periampullary cancer.

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Chapter 6

Adjuvant 5-FU based chemoradiotherapy for patients undergoing R1/R2 resections for pancreatic cancer

Dig Surg. 2005;22(5):321-8

Abstract

Background
Pancreatic cancer is the fifth leading cause of cancer related death worldwide. Among patients treated with surgery alone, liver metastasis occurs in up to 50%, peritoneal recurrence in 25%, and local recurrence occurs in 50-80% of all patients who underwent resection. Even after a macroscopically curative resection, tumour cells might be observed by microscopy at one or more edges of the resected specimen in 20% to 51% (R-1) which might account for the high local recurrence.

Aim of the study
In this study an analysis was performed in 54 patients who underwent an irradical resection (R-1 and R-2) for pancreatic cancer. Thirty-three patients were treated with chemoradiotherapy. To evaluate the effect of therapy on survival and recurrence, this group was retrospectively compared to a group of 21 patients that did not receive chemoradiotherapy.

Methods
Radiotherapy consisted of 50 GY external upper abdomen radiation in two courses of 3 weeks, concomitant with intravenous 5-FU 25-mg/kg/24 hours continuously on the first 4 days of each treatment course. Follow-up was performed mainly by CT-scanning and occasionally by US and was completed for all but one patient.

Results
The treatment protocol was completed in all patients without complications. Local recurrence was found in 6 (18%) patients in the group of patients who received adjuvant therapy versus 16 (48%) patients in the group that did not receive adjuvant therapy (p=0.001). The median survival time for the treated group was 12.8 months versus 13.7 months in the group that did not receive chemoradiotherapy (p=0.9). Three (9%) patients are still alive 140, 88 and 70 months after receiving surgery and adjuvant treatment.

Conclusion
Adjuvant chemoradiotherapy clearly gives asignificant better local control. However, treatment with 5-FU and radiotherapy does not improve survival due to distant metastases. In only a few patients this therapy probably prolongs survival. More effective treatment methods have to be designed to prevent metastatic disease and improve survival.

Introduction

In 2002, adenocarcinoma of the exocrine pancreas will account for approximately 28,900 deaths in the U.S.-the fifth leading cause of cancer related death for both men and women this year (following lung, colon, breast, and prostate cancer.[1] Exocrine pancreatic cancer characteristically spreads by infiltration of lymphatics, perineural tissues and bloodvessels resulting in lymphatic, peritoneal and distant spread. Sub clinical metastases are present in most patients at the time of diagnosis, even when imaging studies are normal. Therefore, disease recurrence following potentially curative pancreaticoduodenctomy remains common, and long-term survival is realized in only 10%-20% of patients who undergo potentially curative surgery.[2] Even after a macroscopically curative resection, tumour cells might be observed by microscopy at one or more edges of the resected specimen in 20% to 51% (R-1).[2-7] Among patients treated with surgery alone, local recurrence occurs in up to 50%-80% peritoneal recurrence in 25%, and liver metastases in 50%.[2] Therefore, a treatment approach combining local and systemic adjuvant treatment in pancreas and periampullary cancer seems interesting. One small prospective study and some retrospective data suggested that the combination of pancreaticoduodenectomy with postoperative adjuvant 5-fluorouracil (5-FU) and external-beam radiation therapy (EBRT) improved survival in curative resected patients compared to surgery alone.[8,9] From European trials evidence now exists that adjuvant radiotherapy and 5-FU is not effective for curative resected patients with adenocarcinoma of the pancreas. The recently published large randomised trials by The European Organization for Research and Treatment of Cancer (EORTC) and European Study Group of Pancreatic Cancer (ESPAC)-1 showed no survival benefit for patients treated with chemoradiotherapy.[3,4,6,8] ESPAC-1 only showed survival benefit for patients who were treated with chemotherapy; patients who underwent curative resections and treated with chemoradiotherapy did not prove to live longer than patients who were treated with surgery alone. The EORTC-study showed a 5.5 months increase in median survival but this difference was not statistically significant. In these studies local recurrence rate was not positively affected by chemoradiotherapy in patients who underwent curative resections. In both studies not only patients with R-0 resections were included but also patients with R-1 resections.

Where no doubt remains about the lack of beneficial effects adjuvant chemoradiotherapy has for curative resected patients, radiation therapy with or without chemotherapy has been showed to prolong survival in loco regional advanced disease, especially the combination of external radiotherapy combined with 5-fluorouracil (5-FU).[11-18] However, interpreting these results it has to be mentioned that no prospective randomised multicenter trials have been performed to confirm the suggestion that chemoradiotherapy might be beneficial for these patients. The

results obtained in patients with irresectable disease leads us to the concept that radiotherapy with the radiosensitizer 5-FU may have an effect on tumour growth of pancreatic cancer and might give a better local control and prognosis in patients with irradical resected or locally advanced pancreatic cancer.

Until now data of survival rates, patterns of recurrence and local tumour control of patients who received chemoradiotherapy after macroscopically and microscopically irradical resections are rare. Most studies report on mixed radical and irradical resected groups. Willet et al. did not find survival benefit for patients with tumor present at the resection margin, the UKPACA and later on the ESPAC-1 however, showed that patients with R-1 resections appeared to benefit from adjuvant chemotherapy but not from chemoradiotherapy in means of survival.[4,6,19,20]

In this study we performed an evaluation of the effects of treatment on local and distant recurrence in patients who showed to have undergone macroscopically (R-2) as well as microscopically (R-1) irradical resections.

Materials and methods

We reviewed all hospital charts from 1990 to 2000 of patients who underwent pancreatic resections for suspected malignancies of the pancreatic head. None of the patients had evidence of metastatic disease by physical exam, chest radiograph, computed tomography (CT) scan of the abdomen, or by explorative laparotomy before resection. Either a standard Whipple procedure or a pylorus preserving pancreaticoduodenctomy (PPPD) was performed. Diagnosis of pancreatic adenocarcinoma was established by definitive histological examination of the resection specimen and, included type (origin) of carcinoma, tumour size, grade of differentiation and, lymph node involvement. Special attention was paid to the resection margin(s). During operation standard frozen sections were performed of the hepatic and pancreatic resection area. Post-operatively perineural invasion and vaso-invasive ingrowth was also scored.

All of the histopathology specimen were revised by a single pathologist. Only patients with macro-and microscopically tumour positive resection margins (R-2/R-1) for invasive pancreatic ductal adenocarcinoma were included in this analysis and patients with ampullary, duodenal, and distal bile duct tumors or patients with pancreatic islet cell or cystadenomas were excluded for were included. The resection margins were defined into the ventral or dorsal part of the pancreatic head, uncinate process (base of the mesenteric artery, resection margin around the portal or mesenteric vein) and pancreas transsection line, bile duct transection line and duodenum/stomach.

Radiotherapy

Adjuvant treatment schedule

After post-operative recovery a new helical CT-scan was performed two weeks before the start of radiotherapy (RT) in order to again exclude metastatic disease and to plan the RT-field. On an intention to treat basis the decision was made for no additional therapy, or for radiotherapy with concomitant 5- fluorouracil (5-FU).

Postoperative radiotherapy and 5-FU was started when the clinical condition of the patient allowed for it but within 2 months after the operation. Radiotherapy and 5-FU treatment were performed in the Dr Daniël den Hoed Cancer Centre, Rotterdam.

Radiotherapy was given according to our protocol consisting of 50 Gy EBRT combined with intravenous 5-FU in two courses, with a split-course of 2-3 weeks. 5-FU was given as a continuous infusion with a dose of 25 mg/kg/24 hours, with a maximum of 1500 mg, the first 4 days of both radiation courses.

The first course consisted of 13 times 2 Gy, followed after the split, by 12 times 2 Gy, 5 days per week. Radiation technique involved multiple-field treatment planning using computed tomography (CT). Megavolt energy of 25 MV was preferred, although occasionally 4, 6 or 8 MV was used. Three-field plans using wedges were more common.

The target volume comprised the tumour and first lymph nodes stations as seen on the planning CT, adding 10 mm for the planning target volume.

The main concern was protection of the kidneys (a renography was always performed) and spinal cord. Technical details of the radiotherapy protocol have been previously published.[21] This protocol was developed on basis of the results of GITSG.[8,22] The choice of radiation dose of 50 Gy was a compromise between the 40 and 60 Gy doses used in the GITSG study. By using the dose of 50 Gy in fractions of 2 Gy, the actual treatment time was limited to 5 weeks. A treatment split of 2-3 weeks was considered valuable to allow acute reactions to therapy to subside. Toxicity was scored according to the common toxicity criteria scale (CTC) of the World Health Organisation (WHO).

Subkop?

In-hospital records and follow-up

Patients were seen every three months at the outpatient clinic the first two years after operation, thereafter every six months. During follow-up additional investigations were performed when there was any clinical suspicion of tumour recurrence. Locoregional and/or distant recurrence was diagnosed by using ultrasonography or trifasic CT-scan and Ca19-9 was used as tumour marker. If possible histological confirmation was obtained.

All patients except one underwent routine US or trifasic CT (US was used routinely during 1989 to 1995 later on trifasic CT-scan was used routinely). The first two

years, follow-up using US or CT was performed every 3 months and thereafter every six months, or more frequently as indicated.

(Sub)Kop?

Statistics

Survival was calculated from the date of surgery on an actuarial basis using the Kaplan-Meier method. Statistical analysis was performed using the Chi-square test and the Fisher's exact test. A p-value below 0.05 was considered statistically significant.

Results

During a 10-year period a total of 54 (21%) patients out of 250 had positive resection margins. Thirty-three patients were treated post-operatively whereas 21 patients did not receive any adjuvant treatment. In this period 33 patients with R1 resections were included in the EORTC-trial, 14 were randomised for the control arm and 19 for chemoradiotherapy.[3] All other patients (n=21) was offered chemoradiotherapy however, this therapy had to start within 8 weeks after surgery. Four patients refused therapy and another 3 patients had prolonged recovery (more than 8 weeks) after surgery. These patients were included in the control group. Patient's characteristics and operative procedures are described in table 1.

Pathology

Staging for all pancreatic adenocarcinoma is shown in table 2. In the treated group most positive margin(s) were found at the posterior part of the resection specimen, namely at the portal vein, superior mesenteric artery, the processus uncinatus or peripancreatic tissues. One patient had a positive resection margin at the common bile duct and three patients had a positive resection margin (perineural invasion) at the transsection site of the pancreas.

TABLE 1 **Patient's characteristics and operative procedures**

Patients	***No additional therapy***	***Radiotherapy and 5-FU***
Total	21	33
Gender		
Male	12	18
Female	9	15
Age (years)	59 [43-65]	60 [39-76]
PPPD	14	21
Whipple	7	12

Table 2 **Staging**

TNM classification	*No additional therapy* (n=21)	*Radiotherapy and 5-FU* (n=33)
Stage II	5	5
Stage III	7	16
Stage IV	9	12
R-1	10	17
R-2	11	16
Positive margins/areas		
pancreas	1	3
bile duct	2	1
duodenum	1	0
uncinate process*	17	29

* the level uncinate process: adjacent to the SMV, portal vein, or SMA)

In the control group 20 patients had positive resections margins at the posterior part of the resected specimen (superior mesenteric vein and artery and the portal vein) and one at the transsection site of the pancreas and was due to perineural invasion.

There were no statistical differences between both groups regarding patient's characteristics, post-operative morbidity and tumour stage.

Radiotherapy & 5-FU, morbidity

Radiation was started within two months after operation. All patients successfully fulfilled the treatment schedule. Eight patients had no morbidity, 13 patients experienced complaints, mostly of gastrointestinal origin. Grade III toxicity meant that medication was needed to alleviate symptoms. Grade III nausea occurred in 6 patients, four of them had concomitant diarrhea grade III. No patient needed to stop radiation and 5-FU therapy due to morbidity. No hospitalisation was necessary.

Follow-up

In the treatment group 59 postoperative CT-scans and 54 US were performed. In the control group 47 CT-scans and 17 US were performed. There was no statistically significant difference between both groups according to number of follow-up scans.

Survival analysis is complete for all but one patient, this patient emigrated. Local recurrence and/or distant metastases in both groups are shown in table 3. Local recurrence was found in 6 patients in the group of patients that received adjuvant therapy versus 16 patients in the group that did not receive adjuvant therapy (p=0.001). Metastatic disease was seen in 25 patients in the treatment group and in 18 patients in the control group (p=0.8). In the treatment group development of both local and distant disease was found in 3 patients versus 13 in the group of patients that received surgery alone (p=0001). Median time to recurrence

TABLE 3 **Recurrent disease and distant metastases in the no additional therapy and the radiotherapy & 5-FU group**

Recurrent disease	*No additional therapy* (n=21)	*Radiotherapy & 5-FU* (n=33)	*P-value*
Local recurrence	16	6	
No local recurrence	4	27	0.001
Distant metastases	18	25	
No metastases	2	8	0.8
Both	13	3	0.001
No local recurrence or metastases	4	1	0.3
Lost to FU	1	0	0.7

Median time to recurrence was 7.8 months in the No additional treatment group versus 12.7 months in the

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(both metastatic and local recurrence) was 7.8 months in the no-treatment group versus 12.7 months in the treatment group (p=0.43). Overall time to recurrence is shown in figure 2.

Pathology proven recurrence was obtained in 14 patients of the treatment group and in 11 patients of the control group (p=0.9)

Median survival in the no additional treatment group was 13.7 months versus 12.8 months in the radiotherapy & 5-FU group (p=0.9). Three patients in the radiotherapy

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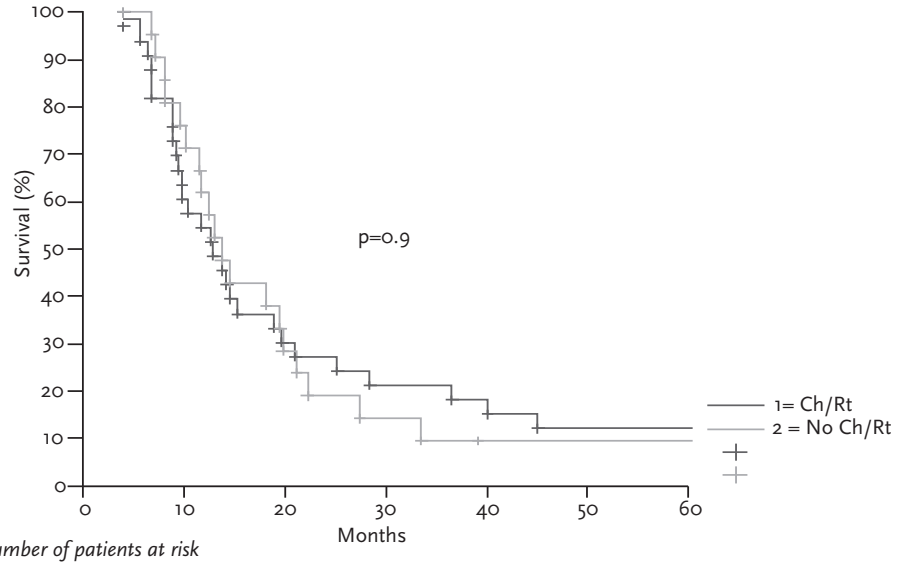
FIGURE 1 **Survival (Kaplan-Meier) for patients with irradical resected adenocarcinoma and adjuvant therapy (5-FU/RT) versus patients with irradical resected adenocarcinoma and no-additional therapy (p=0.9)**

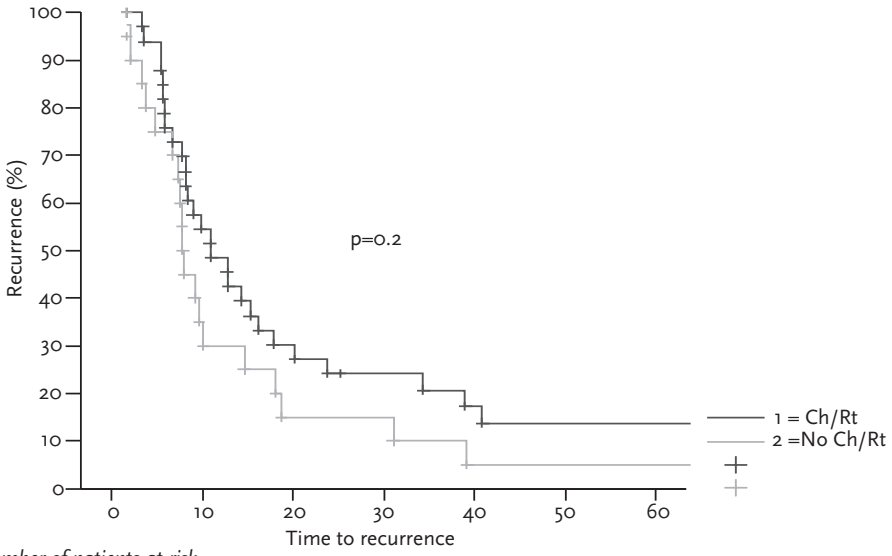


Number of patients at risk

No Ch/Rt	21	16	6	3	1	1	1
Ch/rt	33	20	10	7	6	4	4

Klopt de verticale uitlijning van de Number of patients at risk bij de figuren, alsmede de cijfers?

FIGURE 2 **Time to recurrence in months (Kaplan-Meier) for patients with irradical resected adenocarcinoma and adjuvant therapy (5-FU/RT) versus patients with irradical resected adenocarcinoma and no-additional therapy (p=0.2)**



Number of patients at risk

No Ch/Rt	21	13	3	3	1	1	1
Ch/rt	33	16	9	7	5	4	4

& 5-FU group are still alive 140, 88 and 70 months after initiation of treatment. In the no-treatment group one patient is still alive after 132 months. Survival curves are shown in figure 1.

Discussion

After potentially curative resection for cancer of the pancreatic head, the 1-year survival estimate is 50% to 60%, 2-year survival is 15% to 35%, and 5-year survival is 5% to 20%.[23,24] Even after macroscopically radical resection recurrence rates might run up to 97%.[23,24] The sites of failure most frequently found are local, in the resected region and in the liver. Even when peroperative frozen sections are negative for tumour, definitive paraffine coupes can show perineural and/or vasoinvasive invasion (in the circumferential area) missed in the frozen section.

Because of the high recurrence percentages development of adjuvant treatment strategies seems to be logical and they have been studied extensively. Prospective data however, are rare and are available from both the Gastrointestinal Stage Study Group (GITSG), ESPAC-1 and from Klinkenbijl et al..[3,8]

In the GITSG randomised study of adjuvant chemoradiotherapy (5-FU 500 mg/m^2 for 6 days and 4 Gy EBRT) following pancreaticoduodectomy, 24% of the patients in the adjuvant arm could not begin chemoradiotherapy until more than 10 weeks after surgery because of prolonged recovery time.[8] Similar findings were more recently reported by Klinkenbijl et al. (EORTC) with a drop-out percentage of 20%. In the EORTC-study, 218 patients who had undergone pancreaticoduodenctomy for pancreatic carcinoma of either the pancreas or the periampullary region were randomised to receive either chemoradiotherapy (40 Gy EBRT in a split course and 5-FU given as continuous infusion at a dose of 25 mg/kg per day during radiotherapy) or no further treatment. Of the 207 eligible patients, 114 (55%) had pancreatic cancer; the median survival was 17.1 months for those who received chemoradiotherapy and 12.6 months for those who received surgery alone (p=0.099).[3] The recently reported interim and final results of the European Study Group of Pancreatic Cancer (ESPAC)-1 study suggest that chemotherapy rather than chemoradiotherapy, is the essential component of adjuvant therapy.[4,6] The ESPAC-1 trial was a four arm study with a 2*2 factorial design that compared the effects of adjuvant chemoradiotherapy (5-FU and 40 Gy in a split course) adjuvant chemotherapy (5-FU and folonic acid) chemoradiotherapy followed by chemotherapy and observation alone following panreaticoduodenctomy for pancreatic and periampullary adenocarcinomas. After a median follow-up period of 10 months, 227 (42%) were alive. The overall results showed no benefit for chemoradiotherapy (median survival time 15.5 months in 175 patients with chemoradiotherapy vs 16.1 months in 178 patients without (p=0.24) There was, however, evidence of a survival benefit for chemotherapy (median survival time 19.7 months in 238 patients with chemotherapy vs. 14.0 months in 235 patients without (p=0.0005).

In conclusion, the ESPAC-1 study showed no survival benefit for adjuvant chemoradiotherapy, but revealed a potential benefit for adjuvant therapy, justifying further randomised controlled trials of adjuvant chemotherapy for pancreatic cancer.

Comparing our results in patients who underwent R-1 and R-2 resections with the results of these studies which included both R-0 and R-1 resected patients, we may conclude that chemoradiotherapy indeed does not prolong survival in patients who underwent irradical resections for pancreatic cancer. Median survival in the no additional treatment group was 13.7 months (9–33 months) versus 12.8 months (4-93 months) in the radiotherapy & 5-FU group (p=0.9). Remarkable fact was that three patients in the radiotherapy & 5-FU group are still alive 140, 88, and 70 months after initiation of treatment. Two of them had stage II (UICC) moderate/well differentiated tumours whereas the other patient had moderate differentiated stage III tumour. These patients are alive without progression of disease suggesting their tumours behave biologically different compared to the other patients. This phenomenon has

been previously reported by Neoptolemos, Geer and Brennan.[5,25] They suggested that R-1 status is being linked to the underlying biological phenotype. The three survivors in the treatment group suggest that there is difference in aggressiveness between R-1/R-2 resected tumours also which might be explained by a better response on chemoradiotherapy resulting in long term survival.

The study of Klinkenbijl et al. did not find differences in local recurrence between both groups.[3] ESPAC-1 showed a significant lower recurrence free survival rate in patients treated with chemoradiotherapy and a significant higher recurrence free survival rate in patients treated with chemotherapy alone.[6] Suggesting chemoradiotherapy has a deleterious effect on survival. No information is given about difference in local and distant recurrence of the R-1 and R-2 resections in the chemoradiotherapy group.[6]

Looking closely to our results, it is important to note that chemoradiotherapy provides a better local control compared to patients that received a resection alone. In the end distant (mainly liver) metastasis remains the underlying death cause in the group that was treated with 50 Gy radiation and concomitant 5-FU radiotherapy. Evaluating the results of the EORTC and ESPAC-1 it seems that chemoradiotherapy does not provide survival benefit. Evaluating our results it appears that most patients treated with chemoradiotherapy died because of metastatic disease rather than local relapses. Therefore treatment strategies other than locally given chemoradiotherapy must be designed to prevent or retard metastatic disease.

The rationale for such treatment has been provided by Link et al. and Ozaki et al..[26-28] In a study of extended radical resections of pancreatic cancer combined with regional adjuvant chemotherapy which was performed using hepatic artery and/or portal vein infusion and intraoperative radiotherapy, reported a survival improvement as compared with standard radical surgery with a 5-year survival rate of 32%. Since the main concerns after R-1 or R-2 resections is to get local control at the pancreatic site and, to prevent distant metastases particularly in the liver, regional chemotherapy and irradiation might be an effective strategy. This is an intriguing adjuvant treatment concept[26] and a randomised trial to test this hypothesis is currently underway.

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Chapter 7

Locally advanced pancreatic cancer treated with radiation and 5-fluorouracil

A first step to neoadjuvant treatment?

Dig Surg. 2005;22(3):191-7

Abstract

Aim of the study
A retrospective analysis was performed, in two institutions, of patients with histologically proven locally advanced pancreatic cancer without distant metastases. The aim of this analysis is to assess whether chemoradiotherapy provides survival benefit for patients with locally advanced pancreatic cancer.

Methods
Forty-five patients from Erasmus Medical Centre (Erasmus MC), Rotterdam, received 5-FU and radiotherapy and, 38 patients from the Academic Medical Centre Amsterdam (AMC) was offered best supportive care. Radiotherapy consisted of 50 GY external upper abdomen radiation in two courses, concomitant with intravenous 5-FU 25 mg/kg/24 hours continuously on the first 4 days of each treatment course.

Results
The treatment protocol was completed in 38 out of 45 patients (84%) without complications. Radiological response was evaluated in 38 patients. Ten patients (26%) showed a partial response, stable disease in 6 (16%) patients and progressive disease in 22 (58%) patients. A second look operation was performed in 8 out of 10 patients (72%) showing radiological response, in three patients the tumour could be resected. Median overall survival time for the Erasmus MC group (n=45) was 9.8 months compared to 7.6 months when best supportive care was performed (AMC group, p=0.04).

Conclusion
Although overall survival remains poor, treatment with 5-FU and radiotherapy might benefit some patients with locally advanced pancreatic cancer.

Introduction

Pancreatic cancer has a dismal prognosis, with an overall 5-year survival rate of only 0-4%.[1] At the time of presentation, approximately 40% of the patients with pancreatic cancer already have metastatic disease; only 10% to 20% of patients are candidates for resection and 40 % to 50% have locally advanced disease that is not amenable to a microscopically radical surgical treatment.[2] Since 1982 Erasmus MC has offered treatment to patients with locally advanced non-resectable adenocarcinoma without presence of distant metastases and with a Karnofsky performance score of 80 or more.[3] Treatment consisted of local radiotherapy combined with 5- fluorouracil (5-FU).

The value of this combined treatment was suggested by the results of a comparative trial conducted by the Gastro Intestinal Tumour Study Group (GITSG), showing better survival after a combination of 5-FU and radiotherapy, as compared to radiation alone.[4,5] In contrast to the high response rates reported for combined modality therapy in oesophageal and rectal cancer, chemoradiotherapy for pancreatic cancer rarely achieves a complete radiographically or histopathologically response.[6] In recent years several studies showed possible beneficial effect on survival when chemoradiotherapy was given for locally advanced pancreatic cancer. Reported median survival ranged between 9 and 13 months. However non of these studies are adequately randomised clinical trials.[3,7-15] In most studies overall survival of the treated patients was retrospectively evaluated and compared with historical controls, who did not receive any form of treatment. Before initiating a prospective randomised trial we first wanted to analyse our data and consider the overall survival in relation to a group of patients who received best supportive care.

The aim of this analysis is to evaluate the radiologic and clinical response in all patients who started chemoradiation and to assess whether our chemoradiotherapy protocol provides survival benefit in patients with locally advanced pancreatic cancer.

Materials and Methods

All patients with suspected locally advanced disease without metastases on CT scan, underwent an explorative laparotomy at two University hospitals in the Netherlands (EMC and AMC) were studied. At the EMC all patients were offered chemoradiation, whereas at the AMC not all patients received treatment (see description below).

Both centres locally advanced disease was defined as tumour in growth in the mesenteric root (superior mesenteric vein and/or portal vein, hepatic or superior mesenteric artery confirmed by biopsy at vessel location), transverse mesocolon or mesentery of the small bowel (at the ligament of Treitz), and positive regional lymph nodes at other stations than those to be removed en bloc with the pancreatoduodenectomy. The resectable nodes are described by the Japanese Pancreas Society Classification.[16]

Histopathological biopsies of the primary tumour were obtained during operation in all cases to confirm the diagnosis. In addition biopsies of suspected lymph nodes outside the resection area were taken. For this study, only patients with tumours smaller than 6 cm and a Karnofsky performance status of > 80 points were included. Positive lymph nodes (proven by biopsy) had to be located within the radiation field otherwise patients were excluded.

Between May 1982 and January 1998, 45 of 190 patients with incurable disease had locally advanced pancreatic cancer without metastases. They were offered com-

bined radiotherapy and 5-FU after discharge from hospital at the EMC. In order to compare the results of chemoradiotherapy in the EMC, patients who underwent a bypass between 1992 and 1998 in the AMC for locally advanced disease and only observed after discharge from hospital were selected. Of the 82 patients with locally advanced disease during this time period, 16 patients were excluded since they had histologically proven positive lymphnodes outside the radiation field. Forty-four patients (Study Group) underwent either high dose radiotherapy (n=20), chemo-radiation (n=4) or chemotherapy alone (n=4) in trial settings. The remaining 38 patients (Excluded Group) served either as controls or did not participate in any study. To eliminate any selection bias, the study group (SG) was compared with the excluded group (EG). Postoperative complications were comparable (SG 34% vs. EG 23%, p=0.367) as was the case for postoperative hospital stay (SG 10 days vs. EG 11 days, p=0.204) and tumour size (SG 3.6 cm. vs. EG 3.5 cm., p=0.461) The Karnofsky performance status was > 80 points for both the SG and EG group. The complete group of patients from the AMC is also described in detail elsewhere [9,15,17].

Radiotherapy

Radiotherapy was given according to Erasmus MC Daniel den Hoed Clinic protocol consisting of 50 Gy EBRT in two courses, with a split-course of 2-3 weeks, combined with intravenous 5-FU. Radiotherapy started at a mean of 48 days postoperatively. Till the end of the 1980s 5-FU was given in a dose of 375 mg/m^2 as a bolus injection 4-6 hours before radiation on the first 4 days of each treatment course. From 1990, and currently, 5-FU is given as a continuous infusion with a dose of 25 mg/kg/24 hours, with a maximum of 1500 mg, the first 4 days of both radiation courses. This protocol was developed on basis of the results of GITSG.[16,17] The choice of radiation dose of 50 Gy was a compromise between the 40 and 60 Gy doses used in the GITSG study. By using the dose of 50 Gy in fractions of 2 Gy, the actual treatment time was limited to 5 weeks. A treatment split of 2-3 weeks was considered valuable to allow acute reactions to therapy to subside.

We are aware that today this treatment technique is suboptimal, but at the time it was considered acceptable according to the GISTSG data. The first course consisted of 13 times 2 Gy, followed after the split, by 12 times 2 Gy, 5 days per week. Radiation technique involved multiple-field treatment planning using computed tomography (CT). Megavolt energy of 25 MV was preferred, although occasionally 4, 6 or 8 MV was used. Three-field plans using wedges were more common.

The target volume comprised the tumour and first lymph nodes stations as seen on the planning CT, adding 10 mm for the planning target volume.

The main concern was protection of the kidneys (a renography was always performed) and spinal cord. Technical details of the radiotherapy protocol have been previously published.[18] According to our protocol, one third of the kidneys should not receive a dose higher than 20 Gy, taking also into account the renography. The maximal radiation dose accepted for the spinal cord was 50 Gy. Toxicity was scored according to the common toxicity criteria scale (CTC) of the World Health Organisation (WHO).

After completion of chemoradiotherapy, patients were given a two months break before re-staging, to allow for recovery of blood counts, side effect of radiation, and overall functional activity. Tumour size on restaging CT was compared to initial CT tumour size in the treatment group only by measuring.

Response Assessment

CT-scan was planned two months after chemoradiotherapy regimen was completed.

Partial response was defined as a greater than 50% decrease in tumour size for at least 4 weeks without disease progression at another site. Bidimensionally measurable tumours must have had a 50% decrease in tumour size, as measured by multiplication of the greatest diameter by the perpendicular diameter, whereas unidimensional tumours must have had a 30% decrease at linear tumour measurement. Stable disease was defined as no significant change in measurable or evaluable disease for at least 4 weeks, no appearance of new areas of malignant disease, and no decrease in malignant disease by greater than 50% or increase by greater than 25%. Progression was defined as a greater than 25% increase in area of any malignant lesion greater than 2 cm^2, or appearance of any new lesion at another site.

Specimens of resections after chemoradiotherapy were evaluated for size, tumour margins, and degree of differentiation and lymph node status.

Statistics

Survival was calculated from the date of operation until October 2002, on an actuarial basis using the Kaplan-Meier method. Comparison of survival was done only for patients with pancreatic adenocarcinoma, using the log-rank test. To test for differences between the treatment group and the control group the Chi-Square Test or Mann-Whitney test was used. P-values (two sided) less then 0.05 were considered significant.

Results

Patient's characteristics are listed in Table 1. There were no significant differences regarding age, sex and tumour characteristics between both groups. Use of gastro/biliary by-pass and preoperative stents differs between both groups (see discussion).

As far as could be defined, no ampullary tumours were included in this study. A majority of patients had locally advanced disease due to direct tumour invasion either in large vessels or transverse mesocolon found during explorative laparotomy.

Toxicity

Thirty-eight out of 45 patients (85%) completed the planned regimen of chemoradiotherapy. Three patients (7%) discontinued from treatment; In one patient treatment was discontinued due to nonreversible haematological (grade III) toxicity and two patients refused further treatment because of severe (grade III) nausea and vomiting. Neither grade four toxicity nor treatment- related deaths were observed. Details of toxicity grade for all patients who started chemoradiotherapy are summarised in Table 2.

TABLE 1 **Patients characteristics and pathology (data given are number of patients or mean (range)**

	EMC	***AMC***	***p-value***
No. of patients	45	38	
Age in years [means (SD)]	62 (41-80)	65 (45-78)	n.s
Sex (M/F)	29/16	17/21	p= 0.81
Laparotomy			
Tumour growth in transverse mesocolon	7	9	n.s.
Regional lymph nodes*	17	12	n.s.
Tumour growth in large vessels (mesenteric artery/vein and vena porta)	24	20	n.s.
Pathology type			
Adenocarcinoma	45	38	n.s.
Tumour location			
Head	44	38	
Corpus	1		n.s.
Bypass surgery			
Biliary bypass	28	38	0.001
Gastrojejunal bypass	21	38	0.001
Pre-operative stent	19	27	0.001

*Positive lymph nodes outside the resected specimen but within the radiation field

Table 2 **Toxicity**

WHO	*Grade 1*	*Grade 2*	*Grade 3*
Haematological toxicity			
Leucocytopenia	1	0	1
Thrombocytopenia	0	0	1
Anaemia	0	0	1
Non-haematological toxicity			
Nausea/emesis	3	2	10
Diarrhoea	3	3	8
Fever	0	3	1
Pain	1	2	2

(Data given are number of patients)

Radiological Tumour Response

Four patients stopped treatment due to development of malignant ascites, proven by cytology during chemoradiotherapy. For 38 patients who received the full treatment, evaluation of local tumour response was planned two months after chemoradiotherapy regimen was completed. Ten patients (10/38; 26%) had shown a partial response on CT-scan, 6 (6 /38; 16%)had stable local disease and 22(22/38; 58%) showed tumour progression either local or at distant sites. Loco regional progression was found in 11 patients (24%), liver metastases were found in 11 patients (24%). Three out of 22 patients with progressive disease, developed concomitant metastases elsewhere, one patient developed lung metastases, one patient bone metastases and one patient developed peritoneal metastases.

Eight of 10 patients, who had shown tumour regression and were free of metastatic disease on CT-scan, underwent a second-look operation, between 4 and 6 months after chemoradiotherapy. Two patients refused surgical re-exploration because of general conditions. In three patients a resection could be performed. Definitive histological diagnosis demonstrated that all tumours were adenocarcinomas, two resections were radical (R-0) and one was an irradical (R-1) resection. Overall in only 2 patients (5%) of the total group who started chemoradiotherapy curative resection could be performed. The remaining patients failed to demonstrate adequate tumour regression to be considered resectable at the second-look laparotomy.

Subkoppen? Toch...?

Survival

Overall median survival for the EMC group (n=45, including 3 resected patients) that received radiotherapy and 5-FU was 9.8 months [CI 7.6-12.0] and 7.6 months [CI 6,2-9.0] for the AMC control group (n=38) (p= 0.046). The survival curve is shown in Figure 1. Survival for the three patients who underwent a resection for

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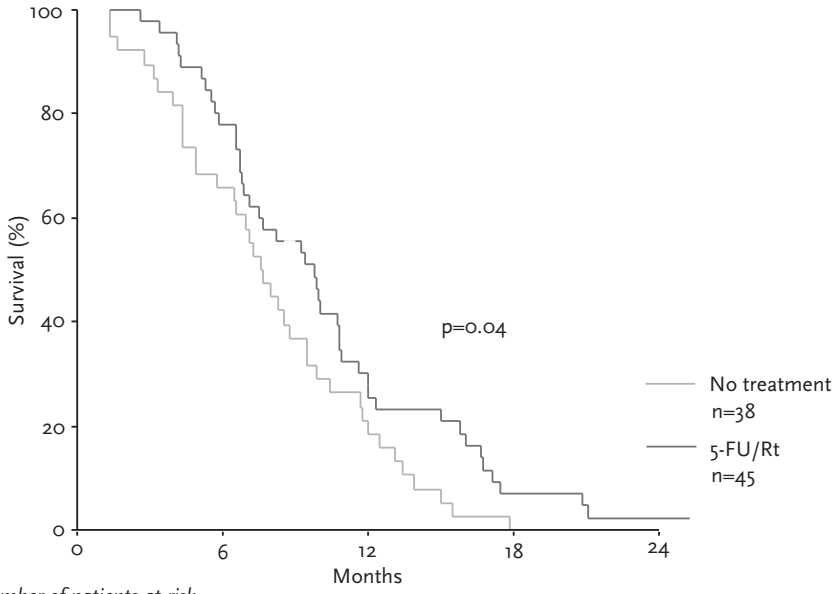
FIGURE 1 **Overall survival. The solid curve represents the treated group from the EMC (n=45) and the dotted curve represents the control group from the AMC (n=38)**



adenocarcinoma was 11, 15, and 157 months. If these three patients are not included in the survival analysis median survival is 9.2 [6.35-12.05] in the EMC group (n=42) vs. 7.6 months in the AMC group (p=0.1).

Discussion

In the Netherlands surgery for pancreatic cancer is partly centralized in two major centres, the AMC and the Erasmus MC. This study was designed to evaluate the radiologic and clinical response of chemoradiotherapy, which routinely was offered to patients with locally advanced pancreatic cancer at the Erasmus MC. The overall survival of these patients was compared with a group of similar patients who received best supportive care at the AMC. Of the 45 patients who started our chemoradiation protocol, 38 patients (84%) received full treatment.

Toxicity associated with chemoradiotherapy was relatively low. Three patients had grade III toxicity and four patients developed malignant ascites during therapy. Grade 3-4 haematological toxicity was observed in 6.5 % of the patients. Nausea was the most common non-haematological toxicity with this treatment; 25% of the

patients experienced this adverse effect and 2 patients refused to continue the treatment. This is similar to toxicity reported by other studies using 5-FU radiotherapy regimens.[4,5,7,8,10-12,14,22 26,27,30-35]

There was a significant difference in bypass surgery and use of biliairy stents. In the AMC every patient with locally advanced disease underwent a double bypass in trial setting.[38,39] In the EMC only patients with signs of obstruction peri- and postoperatively underwent a bypass. That explains the difference between both groups. Difference in preoperative stent using can also be explained by a different policy in both institutions. In the EMC a stent is used only when patients do have clinical and lab signs of obstructive jaundice. In the AMC every patient gets a preoperative stent.

Two months after completion of the chemoradiation already 22 patients (58%) showed progression of disease. In this study 26% of patients showed a response and 16% had stable disease after two months which is again comparable to international results.[3,7-9,11,12,19-23,27-29] However, only two patients (5%) of the total group underwent a R-0 resection. Distant metastasis, especially in the liver (11 patients in this study) is the most important cause of death in pancreatic cancer[32-34], and was found in 11 patients in this study two months after finishing chemoradiotherapy. Eight patients who had shown tumour regression underwent a second look laparotomy followed by resection in three patients. All three patients had histopathologically proven adenocarcinoma after resection. In two cases a radical (R0) resection and one had an irradical (R1) resection was performed. Median survival for these three patients was 83 months (11,15, >157(still alive)). Remarkably, two patients were not found to have positive resections margins or positive lymphnodes, which suggests that preoperative chemoradiotherapy, may yield pathologic down staging for patients with locally advanced pancreatic cancer.

Pilepich and Miller et al. have also described this concept of down staging. They performed a second-look laparotomy in 11 of 17 patients after preoperative irradiation. The tumour could be resected in six of them, and two patients were still alive after 5 years. However, in this small series the resectability at first laparotomy was in doubt for at least 5 patients.[34]

Recently Kastl et al.[25] described a combination of radiotherapy, chemotherapy and mitomycin which was given to 27 patients with locally advanced pancreatic cancer. A second look relaparotomy was performed in sixteen patients. In ten patients the tumour could be resected. Although this study shows an improved resectablility median survival remained poor (9 months).[25]

Although these groups are very similar (Table 1), care must be taken to draw conclusions because selection bias might have occurred. The control group may be partly selected in terms of patients who did not prefer radiotherapy for instance due to general conditions. High dose radiotherapy (70-72 Grays) without subsequent chemotherapy was offered in a phase II study at the AMC, to evaluate the effect of

radiotherapy on pain control.[9,15] So the control group in our study consisted of patients in a poor condition and therefore it is even more surprising that the benefit of chemoradiotherapy in means of survival is so poor. The radiotherapy group in the AMC-study had a median survival time of 11 months (10 months from the start of radiotherapy) which is comparable with the results in the EMC group.[9]

This study shows a small survival benefit for patients with unresectable locally advanced adenocarcinoma of the pancreas treated with radiotherapy and 5-FU (9.8 months versus 7.6 in the control group p=0.046). This is comparable to results published in international literature in which survival ranges from 9-14 months.[3,7-12,14,19-31]

Ishii et al.[10] reported in a recent trial the results of 20 patients who were treated with 5-FU (200mg/m^2/d) infusion + radiotherapy (50.4 Gy over 25 fractions) for locally advanced pancreatic cancer similar to those reported in this study. Ten percent of Ishii's patients achieved partial radiographic response and tumour remained stable in 80%. The median overall survival was 10.3 months.[10]

A more recent randomised trial of 31 patients by Shinchi et al.[12] found a significantly better survival for the patients treated with external-beam radiotherapy and continuous 5-FU (13.4 versus 6.4 months). However, as in our study their survival curves separate immediately after surgery. The difference at this point is 7 months, suggesting a worse prognosis for the control group at the time of admission.[12]

In a study by De Lange et al.[36] gemcitabine-radiotherapy was found to yield a similar median survival (10 months). In some studies Cisplatin is found to have some value when added to the 5-FU or Gemcitabine regimens.[20,36] The rationale for this addition is that 5-FU and Gemcitabine are primarily used as a radiosensitizers and therefore have a local effect; Cisplatin might help to target the disease more effectively at distant locations of (micro-) metastasis.

Of the studies discussed above only one (Shinchi et al.) was designed as a randomised clinical trial, however the results should be interpreted with caution because only 31 patients were enrolled and an adequate power analysis was lacking. All other studies are cohort studies.

According to the present study we cannot conclude that there is a clear benefit using 5-FU and radiotherapy for patients with locally advanced pancreatic cancer. The significant difference in survival appearing in figure 1 is most likely due to the worse prognosis of patients who did not receive radiotherapy. The beneficial effect of chemoradiotherapy should be expected after a few months so that the two curves would only begin to separate some time after the completion of treatment. In fact the curves separate immediately after surgery, making the conclusion viable that a worse prognosis is most obvious the reason for this significant difference. Despite some positive reports in the literature there is no level one evidence that subscribes the positive effect of chemoradiotherapy in patients with locally advanced pancreatic carcinoma. To draw final conclusions, randomised clinical trials are necessary. The

lack of efficacy of the above mentioned modalities gives rise to the question whether further modifications of this multimodality approach could lead to better clinical results. Data from the MD Anderson showed promising results for patients with resectable pancreatic cancer treated with either rapid-fractionation chemoradiotherapy and intra-operative chemoradiotherapy.[37] They reported a overall median survival of 19 months which compares favourably with recently reported series of patients treated by pancreaticoduodenectomy alone, and to those treated with combined post-operative adjuvant 5-FU-based chemoradiotherapy (median survival 11-20 months). However in patients with locally advanced pancreatic carcinoma no such positive results with 5-FU and radiotherapy alone have been reported yet.

Lymph Node Group Classification by the JPS

Group	*Carcinoma pancreatic head*	*Carcinoma of the pancreatic body-tail*
1	13,17	8,11,18
2	6,8,12,14	7,9,14,15
3	1,2,3,4,5,7,9,10,11,15,16,18	5,6,12,13,17,17,16,16

Numbers and names of lymph nodes: 1, right cardial;2, left cardial;3, along the lesser curvature of the stomach; 4, along the greater curvature of the stomach;5, suprapyloric;6, infrapyloric; 7, along the left gastric artery; 8, along the common hepatic artery; 9 around the celiac artery; 10, splenic hilum; 11, along the splenic artery; 12, in the hepatoduodenal ligament; 13, on the posterior surface of the pancreatic head; 14, along the superior mesenteric artery; 15, along the middle colic artery; 16, around the abdominal aorta; 17, on the anterior surface of the pancreatic head; 18, along the inferior margin of the pancreatic body-tail

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Chapter 8

Summary and conclusions

Surgery for pancreatic cancer offers a low success rate, but it provides the only likelihood of cure (chapter 2). Modern series show that, in experienced hands, the standard Whipple procedure is associated with a five-year survival of 10 to 20% with a perioperative mortality rate of less than 5%. The most feared complication is leakage of the pancreaticojejunostomy which is the main cause for postoperative mortality.[31] Many patients will develop recurrent disease within two years after curative treatment. This occurs usually either at the site of resection or in the liver. This suggests the presence of micrometastases at the time of operation. Negative lymphnodes are the strongest predictor for long-term survival. Other predictors for a favourable outcome are tumour size, radical surgery and a histopathologically well-differentiated tumour. Adjuvant therapy so far has only shown modest results, with 5-FU and folonic acid chemotherapy to date the only proven agent able to increase survival. Long term survival is observed in only a very small group of patients contradicting the published actuarial survival rates of 10-45%.

Assessment of clinical benefit from surgery and adjuvant therapy should therefore not only be based on actuarial survival but also on progression-free survival, actual survival, median survival and quality of life (QOL) indicators. Survival in surgical series is usually calculated by actuarial methods. Without information on the total number of patients, the number of actual survivors and a clear definition of the subset of patients, actuarial survival curves can prove to be misleading.

Use of molecular diagnostics and markers in the assessment of tumour biology, may in future reveal important subtypes of this type of tumour and may possibly, predict the response to adjuvant therapy. Defining the subtypes of pancreatic cancer will hopefully lead to target specific, less toxic and finally more effective therapies.

In the international literature pylorus-preserving pancreaticoduodenectomy (PPPD) has been associated with a higher incidence of delayed gastric emptying, resulting in a prolonged period of post-operative nasogastric suctioning.[1-4] Another controversy of the pylorus-preserving pancreaticoduodenectomy for patients with malignancy is the radicality of the resection.[5] In a retrospective study from our center we found that the PPPD is associated with a shorter operation time, less blood loss, shorter hospital stay and the same amount of positive resection margins as for the standard Whipple procedure.[1]

A prospective randomized multi-center study was performed to assess whether the results of PPPD equalize those of the standard Whipple operation, especially with respect to duration of surgery, blood loss, hospital stay, delayed gastric emptying and survival (chapter 3).

We found that the incidence of delayed gastric emptying in this study of 170 consecutive patients was similar after PPPD and Whipple resection. Postoperative nasogastric drainage period was comparable in both groups. As far as the duration

of operation, blood loss, hospital stay and postoperative weight loss are concerned, there were also no significant differences. The PPPD operation seems to be as radical as a standard Whipple procedure for periampullary and pancreatic head cancer. Long-term survival and disease free survival did not exhibit significant differences.

Thus in conclusion both procedures are equally effective for treatment of pancreatic cancer. With respect to radical resection, morbidy, mortality and survival our results are confirmed by the latest literature.[6,7] However, the latest review by Diener et al. showed that intra operative blood loss and duration were significantly reduced in the PPPD group.[6]

Pancreatic cancer has a dismal prognosis. Periampullary adenocarcinoma, however, has a better prognosis and is thought to be a biologically different tumor. Yet even after radical (R-0) resection of pancreatic cancer survival remains poor and most patients may still die of disseminated disease. Adjuvant therapy may only be of marginal benefit. Aim of this study was to find clinical, pathological and molecular factors that could predict long-term survival after R-0 resection for pancreatic and periampullary cancer (chapter 4).

After multivariate analysis the following factors were isolated.

Alinea?

Gender, pre-operative pain, tumor differentiation, nodal status were all independent prognostic factors for pancreatic and periampullary cancer. In literature these features have all been described before.[16-24] Over expression of EGF-R in pancreatic cancers appeared to have a negative effect on survival. The EGF family and its receptors are known to be involved in tumor progression and mediate growth of pancreatic cancer. Since this has been proved, EGFR has been a target for new treatment strategies. It is the aim of these treatments to interrupt the EGFR signal introduction and so inhibit tumor growth. Some very interesting approaches have been launched lately. The most promising is usage of EGFR antibodies e.g. C225, erlotinib and Herceptin. Treatment with these antibodies combined with gemcitabine and radiotherapy have been tested in nude mise with high rates of apoptosis and growth inhibition.[8] A Phase III trail by Moore et al showed promising results. [27] In a this multicenter randomized trial a total of 569 patients with advanced non-resectable pancreatic cancer were randomly assigned to receive standard gemcitabine plus erlotinib (100 or 150 mg/d orally) or gemcitabine plus placebo in a double-blind, international phase III trial. Overall survival based on an intent-to-treat analysis was significantly prolonged on the erlotinib/gemcitabine; median 6.24 months v 5.91 months). Progression-free survival was significantly longer with erlotinib plus gemcitabine with an estimated HR of 0.77 (95% CI, 0.64 to 0.92; P = .004).

In the near future further development of EGFR targeted therapies might reveal even better results. Our data support the rationale to use these drugs in adjuvant targeted therapy modalities.

The role of adjuvant chemoradiation for resectable pancreatic cancer has long been under discussion. So far only adjuvant chemotherapy has shown significant survival benefit.[9,25]

We reported the long-term follow-up results of our multicenter study, which assessed the role of chemoradiation in resectable pancreatic cancer (chapter 5).

In the initial short-term results a trend toward increased survival was found in the pancreatic head cancer group treated with chemoradiation. However this was not a significant finding.[15] The long-term results show again that overall survival did not differ between the two treatment groups. The 10-year overall survival was 18% in the whole population of patients (8% in the pancreatic head cancer group and 29% in the periampullary cancer group). Patients with pancreatic cancer may survive over 10 years. Only 1 of 31 cases recurred after year 7. Thus it seems that follow-up should at least extent a term of 7 years.

So far this is the only study on pancreatic cancer with a long-term follow up exceeding 10 years. Where most studies report actuarial survival we report more than 10 years actual survival. The results indicate no benefit of adjuvant chemoradiation over observation in patients with resected pancreatic cancer or periampullary cancer. This conclusion is confirmed by the results of the ESPAC-1 trial in which chemoradiation even showed a deleterious effect on survival.[9]

The reason for relative ineffective treatment of chemoradiation or chemotherapy might be found in the heterogeneity of solid tumors with high and low mitotic areas. It is believed that tumor hypoxia, which is common in pancreatic cancer, plays an important role in local and systemic tumour progression, leading to a more aggressive phenotype.[28,29,30] Recent data by Graeber et al demonstrated increased levels and growth of p53(tumor suppressor gene) mutated cells under low oxygen conditions. Clinical tumor treatment with chemotherapy and/or radiotherapy is based on disruption of the cell cycle particularly in cells with high mitotic activity, in other words tumor cells. High proliferating cells however consume a lot more oxygen than dormant cells. Sufficient oxygenation is of pivotal importance to achieve an adequate response on chemo/radiotherapy. The reason for the poor response of pancreatic cancer on chemoradiation might be the low oxygenation of the inner tumor cells.

Further our results show that curative surgery offers long-term survival of 8% for patients with pancreatic head cancer. Metastases still occur up to seven years. This makes long-term follow-up necessary in trials which evaluate the effect of adjuvant treatment.

Current challenges for the treatment of resectable pancreatic cancer is to improve survival by multimodality approaches to treatment in the hope to create more efficient agents. Chemoradiation has no role anymore in the treatment of resectable

pancreatic cancer. Until know only chemotherapy treatment confers a modest but significant survival advantage.[9,25,26,27]

Among patients treated with surgery alone, liver metastasis occur in up to 50%, peritoneal recurrence in 25%, and local recurrence occurs in 50-80%. Even after a macroscopically curative resection, tumour cells might be observed by microscopy at one or more edges of the resected specimen in 20% to 51% (R-1), which might account for the high local recurrence. Therefore a rationale for chemoradioation in this group seems reasonable.[13]

An analysis was performed in patients who underwent an irradical resection (R-1 and R-2) for pancreatic cancer (chapter 6). Thirty-three patients were treated with therapeutic chemoradiotherapy. To evaluate the effect of therapy on survival and recurrence, this group was retrospectively compared to a group of 21 patients that did not receive chemoradiotherapy.

Adjuvant chemoradiotherapy clearly gave a significant better local control. However, treatment with 5-FU and radiotherapy did not improve survival due to distant metastases. In only a few patients this therapy probably prolongs survival, however no randomised clinical trials are available at this time. More effective treatment methods have to be designed to prevent metastatic disease and improve survival.

No role for adjuvant chemoradiation has been found so far. However the effect of chemoradiation for patients with locally advanced pancreatic cancer remains unclear.[10-14]

A retrospective analysis was performed, in two institutions, of patients with histological proven locally advanced pancreatic cancer without distant metastases (chapter 7). The aim of this analysis is to assess whether chemoradiotherapy provides survival benefit for patients with locally advanced pancreatic cancer.

The treatment protocol was completed in 38 out of 45 patients (84%) without complications. Radiological response was evaluated in 38 patients. Ten patients (26%) showed a partial response, stable disease in 6 (16%) patients and progressive disease in 22 (58%) patients. A second look operation was performed in 8 out of 10 patients (72%) showing radiological response, in three patients the tumour could be resected. Median overall survival time for the Erasmus MC group (n=45) was 9.8 months compared to 7.6 months when best supportive care was performed (AMC group, p=0.04).

Although overall survival remains poor, treatment with 5-FU, folonic acid and radiotherapy might benefit some patients with locally advanced pancreatic cancer. Its future role needs to be assessed in randomised trials. Recently Moore et al.[27] published the first phase III trial known todate that showed significant survival benefit (1 year 23%, treatment vs 17% no treatment) for patients treated with Gemcitabine

and targeted therapy for EGFR (erlotinib) in order to disrupt the signal pathway and inhibit tumor growth. Hopefully even better agents can be designed in order to improve survival more significantly.

Conclusion

Today, surgery provides the only likelihood of cure for patients having pancreatic cancer. Centralization of surgery has helped a great deal in lowering mortality rates. Modern series show that, in experienced hands, pancreatic surgery is associated with a perioperative mortality rate between 0.5% and 5%, and a five-year survival of 10-20%.

In this thesis two surgical procedures for treating periampullary and pancreatic cancer, the PPPD and the Whipple operation, show equal survival and morbidity results. These procedures can be carried out with acceptable morbidity and mortality.

Chemoradiotherapy given as split course (total 40 Gy) with concomitant 5-FU (25 mg/kg/day) and folonic acid, is ineffective as adjuvant treatment after resection of pancreatic cancer. Up to date only one multicenter trial (ESPAC-1) shows that adjuvant chemotherapy offers a significant (actuarial) survival increase, however survival benefit remains marginal (a few months). More evidence is needed before chemotherapy can be standardized as adjuvant treatment after resection for pancreatic cancer.

In patients with locally advanced cancer survival benefit might occur, although define proof by randomized multicentre studies has yet to be given.

The molecular mechanism of pancreatic cancer should be revealed in the near future and might help to develop and design more specific and effective adjuvant and neoadjuvant therapies, for instance targeting therapy with an EGFR antibody. In this thesis EGFR proofs to have negative effect on survival. Therefore EGFR targeted therapy might reveal a new era in treatment of pancreatic cancer. Lately treatment strategies using EGFR targeted therapies have been published and show promising results although the measured affects on survival are moderate.

It is a harsh conclusion that in the last decades all our effort to improve survival by adjuvant and neoadjuvant strategies has resulted in only modest survival advantage without any standard approved adjuvant protocol. Even worse is the fact that proven inefficient chemoradiation as adjuvant treatment is still widely used in some countries.

To counter this trend we need effort from oncologist, surgeons as well as the medical industry to give patients with this devastating disease new hope. New, more effective agents need to be developed and tested. Because of the long accrual times in most multicenter trails, valuable time is lost before conclusions can be drawn.

Therefore we plea for centralization. Performing pancreas surgery in high volume setting not only reduces the risk of mortality and morbidity but also shortens trial durations. Patients have the right and the need to know as quick as possible if a new agent is effective or not. By cooperating extensively in multidisciplinary and multicenter setting it must be possible to shorten time schedules needed for clinical trials. Together with a search for more effective regiments such as targeted therapy against EGFR and effort to unravel the whole genome of pancreatic cancer this era must bring the define solution in the cure pancreatic cancer.

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Samenvatting en conclusies

Een operatieve behandeling van alvleesklierkanker heeft een geringe kans op slagen, maar vormt de enige mogelijkheid tot genezing (hoofdstuk 2). Hedendaagse operatiereeksen tonen aan dat, wanneer uitgevoerd door zeer ervaren chirurgen, de standaard Whipple procedure gepaard gaat met een overlevingspercentage van 10 tot 20% in 5 jaar tijd met een peri-operatief sterftecijfer van minder dan 5%. De meest gevreesde complicatie is lekkage van de pancreaticojejunostomie hetgeen de hoofdoorzaak is van postoperatieve sterfte.[31] Bij een groot aantal patiënten zal de ziekte terugkeren binnen twee jaar na de curatieve behandeling. De ziekte komt meestal terug op de plaats van resectie of in de lever. Dit doet vermoeden dat er micro-uitzaaiingen waren ten tijde van de operatieve behandeling. Negatieve lymfeklieren zijn de beste voorspellers van langdurig herstel. Andere voorspellers van een gunstig resultaat zijn de grootte van de tumor, radicale chirurgie en een tumor die zich histopathalogisch gunstig onderscheidt. Adjuvante therapie heeft tot nog toe slechts magere resultaten opgeleverd, met tot op heden 5-FU en foliumzuur chemotherapie als enige bewezen middelen om de overlevingskans te vergroten. Langdurige overleving wordt slechts bij een klein aantal patiënten geconstateerd en dit spreekt de gepubliceerde actuariële overlevingspercentages van 10-45% tegen. De beoordeling van de klinische voordelen van een operatieve behandeling en adjuvante therapie dient niet slechts gebaseerd te worden op actuariële overleving maar ook op progressievrije overleving, feitelijke (actual) overleving, mediane overleving en de kwaliteit van leven (QOL) indicatoren. Overleving in operatieve reeksen wordt meestal berekend door middel van actuariële methoden. Zonder informatie over het totale aantal patiënten, het aantal feitelijke overlevingen en een duidelijke omschrijving van de samenstelling van de groep patiënten, kunnen actuariële overlevingscurven misleidend blijken te zijn.

Het gebruik van moleculaire diagnostiek en markers bij de beoordeling van de tumorbiologie, kan in de toekomst belangrijke subtypen van deze tumor openbaren en mogelijk de reactie op adjuvante therapie voorspellen. De ontrafeling van de

subtypen alvleesklierkanker resulteert hopelijk in doelgerichte, minder toxische en uiteindelijk effectievere therapieën.

In de internationale vakliteratuur wordt de maagpoortbehoudende pancreaticoduodenectomie (PPPD) in verband gebracht met een grotere incidentie van vertraagde maaglediging, hetgeen resulteert in een verlengde periode van postoperatieve nasogastrische afzuiging[1-4]. Nog een controverse van de maagpoortbehoudende pancreaticoduodenectomie voor patiënten met kwaadaardige tumoren is de mate van radicaliteit van de resectie[5]. Door middel van een retrospectief onderzoek vanuit ons centrum kwamen wij tot de conclusie dat PPPD in verband wordt gebracht met een kortere operatieduur, minder bloedverlies, een kortere ziekenhuisopname en dezelfde hoeveelheid positieve resectiemarges als bij de standaard Whipple ingreep.[1]

Er werd een prospectief multi-centeronderzoek uitgevoerd om vast te stellen of de PPPD resultaten gelijk zijn aan die van de standaard Whipple operatie, in het bijzonder met betrekking tot de operatieduur, het bloedverlies, de duur van de ziekenhuisopname, vertraagde maaglediging en de overleving (hoofdstuk 3).

Wij concludeerden dat de incidentie van vertraagde maaglediging in dit onderzoek bij 170 opeenvolgende patiënten gelijk was na de PPPD en Whipple resectie. De periode waarin postoperatieve nasogastrische afzuiging moest worden toegepast was van vergelijkbare duur in beide groepen. Er waren geen opmerkelijke verschillen wat betreft de duur van de ingreep, het bloedverlies, de duur van de ziekenhuisopname en het postoperatieve gewichtsverlies. De PPPD-operatie lijkt even ingrijpend te zijn als een standaard Whipple procedure voor periampullaire en alvleesklierkopkanker. Er werden geen belangrijke verschillen aangetroffen bij langdurige overleving en ziektevrije overleving.

We kunnen daarom de conclusie trekken dat beide procedures evenredig effectief zijn bij de behandeling van alvleesklierkanker. Met betrekking tot drastische resectie, ziekte, sterfte en overleving worden onze resultaten bevestigd door recente literatuur.[6,7] Een recente beoordeling door Diener e.a. toonde echter aan dat intraoperatief bloedverlies en duur aanmerkelijk waren verminderd bij de PPPD groep.[6]

Alvleesklierkopkanker gaat gepaard met een slechte prognose. Bij een periampullair adenocarcinoom wordt daarentegen een betere prognose gegeven en het lijkt zo te zijn dat deze tumor biologisch gezien afwijkt van de alvleesklierkoptumor. In beide gevallen echter, is zelfs na radicale (R-0) resectie van de tumor, de overlevingskans klein en de meeste patiënten sterven alsnog als gevolg van uitzaaiingen. Adjuvante therapie voegt hier vaak weinig positiefs toe. Het doel van dit onderzoek was om klinische, ziekte- en moleculaire factoren te ontdekken die de duur van overleving

zouden kunnen voorspellen na R-0 resectie van de alvleesklierkop- en periampullaire tumor (hoofdstuk 4).

Door middel van een multivariabele analyse werden de hiernavolgende factoren geïsoleerd.

Geslacht, preoperatieve pijn, tumor differentiatie en nodale status waren stuk voor stuk onafhankelijke prognostische factoren bij alvleeskler- en periampullaire tumoren. In de literatuur zijn deze kenmerken reeds beschreven.[16-24] Overexpressie van EGF-R bij alvleeskliertumoren bleek een negatief effect te hebben op de overleving. Het is bekend dat de EGF-familie en haar receptoren meespelen bij de ontwikkeling van de tumor en de indirecte groei van alvleeskliertumoren. Na deze bekendmaking werd EGFR het doelwit van nieuwe behandelmethoden. Het doel van deze behandelingen is om de EGFR signaalwegen te onderbreken en op deze wijze de groei van de tumor te remmen. Enkele interessante aanpakken zijn recentelijk uitgevoerd en een van de meest veelbelovende aanpakken is het gebruik van EGFR antilichamen zoals bijv. C225, erlotinib en Herceptin. Behandelingen met deze antilichamen in combinatie met gemcitabine en radiotherapie zijn getest op naakte muizen met een hoge mate van apoptose en groeiremming.[8] Een door Moore e.a. uitgevoerd fase III onderzoek bracht eveneens veelbelovende resultaten.[27] Bij dit internationaal gerandomiseerd multicenteronderzoek, werd een totaal aantal van 569 patiënten met inoperabel alvleesklierkanker in een vergevorderd stadium willekeurig uitgekozen om te worden behandeld met standaard gemcitabine plus erlotinib (100 of 150 mg/d oraal) of met gemcitabine plus placebo. De algehele levensduur bij een zogenaamde 'intent-to-treat' analyse werd aanzienlijk verlengd in het geval van de erlotinib/gemcitabine; (gemiddeld 6,24 maanden versus 5,91 maanden). De progressievrije overleving was van aanzienlijk langere duur bij het gebruik van erlotinib plus gemcitabine, met een geschatte HR van 0,77 (95% CI, 0,64 tot 0,92; P = ,004).

In de nabije toekomst zal de verdere ontwikkeling van EGFR-gerichte therapieën wellicht nog betere resultaten opleveren. Onze gegevens ondersteunen de grondgedachte deze medicijnen te gebruiken bij op adjuvante therapie gerichte modaliteiten.

De rol van adjuvante chemoradiatie bij operatief verwijderbare alvleeskliertumoren is reeds lang een onderwerp van discussie. Tot nog toe heeft alleen adjuvante chemotherapie een aanzienlijke verlenging van de levensduur aangetoond.[9,25]

We berichtten de follow-up resultaten op lange termijn van ons gerandomiseerde multicenteronderzoek waarin de rol van chemoradiatie bij de behandeling van operatieve alvleeskliertumoren wordt beoordeeld (hoofdstuk 5).

Bij de eerste resultaten op korte termijn constateerden we een verlenging van de levensduur bij de groep patiënten met een alvleesklierkoptumor die behandeld

werden met chemoradiatie. Dit was echter een trend maar nog geen significant verschil.[15] De resultaten op lange termijn gaven wederom aan dat er geen verschillen waren in de algehele overleving bij de twee behandelde groepen. De algehele overleving binnen 10 jaar was 18% bij de totale groep patiënten (8% bij de groep met alvleesklierkopkanker en 29% bij de groep met periampullaire kanker). Patiënten met alvleesklierkanker kunnen meer dan 10 jaar overleven. Een aantal patiënten kreeg een recidief na 5 jaren overleving een enkeling zelfs na 7 jaar. Hieruit blijkt, dat in geval van klinische studies, de follow-up periode een termijn van tenminste 7 jaar in beslag zou moeten nemen.

Tot op heden is dit het enige onderzoek naar alvleesklierkanker met een follow-up op lange termijn die de 10 jaar overschrijdt. Daar waar de meeste onderzoeken actuariële overleving aantonen kunnen wij een feitelijke overleving van meer dan 10 jaar aantonen. Helaas geven de resultaten aan dat adjuvante chemoradiatie geen toegevoegde waarde heeft ten opzichte van observatie bij patiënten met operatieve alvleesklierkanker of periampullaire kanker. Deze conclusie wordt bevestigd door de resultaten van het ESPAC-1 onderzoek dat aantoonde dat chemoradiatie zelfs een negatief effect heeft op de overleving.[9]

De reden voor de relatief ineffectieve behandeling met chemoradiatie zou kunnen worden toegeschreven aan de heterogeniteit van deze tumoren met hoge en lage mitotische gebieden. Men is van mening dat tumor hypoxia, veelvoorkomend bij alvleesklierkanker, een belangrijke rol speelt in de lokale en systemische tumorprogressie, en leidt tot een agressiever fenotype.[28,29,30] Recente gegevens van Graeber e.a. toonden toegenomen hoeveelheden aan alsmede groei van p53 (gen dat de tumor onderdrukt) gemuteerde cellen in omstandigheden met een laag zuurstofniveau. De klinische tumorbehandeling door middel van chemotherapie en/of radiotherapie is gebaseerd op de verstoring van de celcyclus en in het bijzonder van cellen met een hoge mitotische activiteit, ofwel tumorcellen. Snel vermenigvuldigende cellen nemen echter veel meer zuurstof op dan inactieve cellen. Voldoende oxygenatie is van zeer groot belang om een degelijke reactie te krijgen op de chemo/radiotherapie. De lage oxygenatie van de binnenste tumorcellen zou kunnen verklaren waarom alvleesklierkanker hier slecht op reageert.

Verder geven onze resultaten aan dat curatieve chirurgie een overlevingspercentage van 8% op lange termijn biedt aan patiënten met alvleesklierkopkanker. Het is daarmee vooralsnog de enige behandeling die curatie kan bieden, zij het dus met kleine percentages. Uitzaaiingen komen tot na 7 jaar na de operatie en behandeling nog voor. Hierdoor is een follow-up op lange termijn noodzakelijk bij onderzoeken waarbij het effect van adjuvante behandeling wordt geëvalueerd.

Op dit moment blijft het een uitdaging om bij de behandeling van operatieve alvleesklierkanker de levensduur te verbeteren, het meeste heil valt te verwachten een multimodale behandelingen in de hoop op deze wijze efficiënter en effectiever

pancreaskanker te kunnen gaan bestrijden. Chemoradiatie speelt niet langer een rol in de behandeling van operatieve alvleesklierkanker. Tot op heden geeft alleen een behandeling door middel van chemotherapie een bescheiden overlevingsvoordeel.[9,25,26,27]

Bij 50% van de patiënten die alleen operatief behandeld zijn komen later uitzaaiingen in de lever voor, bij 25% worden er buikvliesuitzaaingen geconstateerd, en bij 50%-80% keerde de ziekte op lokaal niveau terug. Zelfs na een macroscopisch curatieve resectie worden na microscopie bij 20% tot 51% (R-1) gevallen tumorcellen gevonden aan een of meerdere uiteinden van de operatief verwijderde monsters, wat in feite de hoge mate van lokale terugkeer verklaart. Daarom lijkt het motief voor chemoradiatie in deze groep een redelijke te zijn en werd zodoende aan patiënten aangeboden.[13]

Wij verrichten een analyse uitgevoerd bij patiënten die een niet radicale resectie van de alvleeskliertumor ondergingen (R-1 en R-2)(hoofdstuk 6). Drieëndertig patienten werden behandeld door middel van therapeutische chemoradiotherapie. Om het effect van de therapie op de overlevingskans en de kans op het terugkeren van de ziekte te kunnen evalueren, werd deze groep retrospectief vergeleken met een groep van 21 patiënten die geen chemoradiotherapie onderging.

Adjuvante chemoradiotherapie bewerkstelligde een zichtbaar betere lokale controle. Maar als gevolg van uitzaaiingen elders in het lichaam resulteerde de behandeling met 5-FU en radiotherapie niet in een langere levensduur. Deze vorm van therapie verlengt slechts bij een klein aantal patiënten de levensduur, maar er zijn op dit moment geen gerandomiseerde klinische onderzoeken beschikbaar. Effectievere behandelingsmethoden zullen moeten worden ontwikkeld om metastatische ziekte te voorkomen en de overlevingskansen te vergroten.

Vooralsnog is tot op heden geen rol weggelegd voor adjuvante chemoradiatie. Echter, het effect van chemoradiatie op patiënten met lokaal vergevorderde alvleesklierkanker blijft onduidelijk.[10-14]

In twee verschillende instellingen werd een retrospectieve analyse uitgevoerd bij patiënten met alvleesklierkanker in een vergevorderd stadium zonder uitzaaiingen elders in het lichaam (hoofdstuk 7). Het doel van deze analyse is om vast te stellen of chemoradiotherapie de levensduur verlengt bij patiënten met lokaal vergevorderde alvleesklierkanker.

Het behandelingsprotocol werd afgerond bij 38 van de in totaal 45 patiënten (84%) zonder dat er complicaties optraden. Bij 39 patiënten werd de radiologische reactie gemeten. Tien patiënten (26%) toonden een gedeeltelijke reactie, bij zes patiënten bleef de ziekte stabiel (16%) en bij 22 patiënten schreed de ziekte onverstoord voort (58%). Een tweede operatie werd uitgevoerd bij 8 van de 10 patiënten

(72%), waarbij radiologische reacties werden geconstateerd en bij drie patiënten kon de tumor operatief worden verwijderd. De mediane algehele overlevingduur bij de Erasmus MC groep (n=45) was 9,8 maanden vergeleken met 7,6 maanden bij de AMC groep (p=0,04).

Hoewel de algehele overleving gering blijft, zou de behandeling met 5-FU, foliumzuur en radiotherapie een gunstig effect kunnen hebben op sommige patiënten met alvleesklierkanker in een vergevorderd stadium. Een toekomstige rol voor deze behandeling dient te worden vastgesteld in gerandomiseerde onderzoeken.

Recentelijk hebben Moore e.a[27] het eerste fase III onderzoek gepubliceerd bij patiënten met waarbij een significante verlenging van de levensduur werd waargenomen. (1 jaar behandeling 23%, tegenover 17% bij geen behandeling) bij patiënten behandeld met Gemcitabine en gerichte EGFR-therapie (erlotinib) met als doel de signaalwegen te verstoren en de groei van de tumor te remmen. Hopelijk kunnen er nog betere middelen worden ontwikkeld om zodoende de levensduur aanzienlijk te kunnen verlengen.

Conclusie

Op dit moment biedt chirurgie de enige mogelijkheid tot genezing aan patiënten met alvleesklierkanker. De centralisatie van chirurgie heeft enorm bijgedragen aan de vermindering van het aantal sterfgevallen. Moderne operatiereeksen tonen aan dat, wanneer uitgevoerd door ervaren chirurgen, alvleesklierchirurgie gepaard gaat met een perioperatieve sterfte van 0,5% tot 5%, en een overleving bij vijf jaar van 10-20% .

In deze thesis tonen twee operatieve procedures voor de behandeling van periampullaire kanker en alvleesklierkanker, te weten de PPPD en de Whipple procedure, gelijke resultaten als het gaat om overleving en sterfte. Het uitvoeren van deze procedures gaat gepaard met acceptabele ziekte- en sterftecijfers.

Chemoradiotherapie toegepast als gespreide kuur (totaal 40 Gy) in combinatie met 5-FU (25 mg/kg/dag) en foliumzuur, blijkt ineffectief te zijn als adjuvante behandeling na het verwijderen van de alvleeskliertumor. Tot op heden heeft alleen een multicenteronderzoek (ESPAC-1) aangetoond dat adjuvante chemotherapie een significante (actuariële) toename van de overleving teweegbrengt, echter het overlevingsvoordeel blijft marginaal (slechts enkele maanden). Er is meer bewijs nodig voordat chemotherapie kan worden gestandaardiseerd als adjuvante behandeling na de resectie van een alvleeskliertumor.

Bij patiënten met kanker een vergevorderd stadium zou een overlevingsvoordeel kunnen optreden, hoewel duidelijk bewijs daarvoor bij gerandomiseerd uitgevoerde multicenteronderzoeken nog ontbreekt.

De moleculaire samenstelling van de alvleeskliertumor dient in de nabije toekomst te worden blootgelegd. Dit zou kunnen bijdragen aan de ontwikkeling van een EGFR antilichaam. In deze thesis blijkt EGFR een negatief effect te hebben op de overleving. Daarom zou op een op EGFR gerichte therapie een nieuw tijdperk kunnen inluiden in de behandeling van alvleesklierkanker. Onlangs zijn er behandelingsstrategieën gepubliceerd waarbij op EGFR gerichte therapieën werden toegepast. Deze tonen veelbelovende resultaten ten aanzien van respons hoewel de gemeten effecten op de overleving gering zijn.

Helaas moeten we de conclusie trekken dat in de laatste tientallen jaren alle inspanningen om de overlevingskans te verhogen middels toepassing van adjuvante en neoadjuvante strategieën slechts geresulteerd hebben in een summiere verlenging van de levensduur. Om deze trend tegen te gaan hebben we de hulp nodig van oncologen, chirurgen en de medische industrie om patiënten met deze moeilijk te behandelen ziekte nieuwe hoop te kunnen geven. Nieuwe, effectievere middelen zullen moeten worden ontwikkeld en getest. Doordat de meeste multicenteronderzoeken gepaard gaan met zeer lange looptijden verliezen we waardevolle tijd voordat er conclusies kunnen worden getrokken. Daarom pleiten wij voor centralisatie. Het uitvoeren van operaties op het gebied van alvleesklierkanker op brede schaal vermindert niet alleen het risico op ziekte en sterfte maar verkort eveneens de onderzoeksduur. Patiënten hebben immers het recht zo snel mogelijk te worden geïnformeerd wanneer een nieuw middel effectief blijkt te zijn of niet. Door op grote schaal samen te werken in een multidisciplinaire en multicenteromgeving zou het mogelijk moeten zijn om de duur van de klinische onderzoeken te verkorten. In combinatie met de ontwikkeling van effectievere regimenten zoals doelgerichte therapie tegen EGFR en de inspanningen om het gehele genoom van alvleesklierkanker te ontrafelen, zal het tijdperk dat nu aanbreekt een gerichte oplossing moeten kunnen brengen om te komen tot de genezing van alvleesklierkanker.

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Comma
Is dat wat?
+ witregels
weg.

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nlop. "m

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Ook hier
witregels er
uit gevist.
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Davidje! Lieve heerlijke kleine boef! Kus van je trotse pappie.

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Curriculum vitae

Hans Smeenk was born on March 4th, 1972 in Arnhem, The Netherlands. After finishing high school he continued his education at the VU Amsterdam. In February 2001 he received his medical degree and started a combined research and clinical registrar at the Erasmus MC, Rotterdam under supervision of dr. Casper van Eijck and prof. dr. Hans Jeekel, financially supported by the Janivo Stichting. His was awarded at the EUGW Madrid 2003, the annual EPC meeting Liverpool 2003 and, at the 500th anniversary of the Royal College of Surgeons Scotland at the IHPBA Edinburgh 2006.

In January 2003 he started his surgical residency at the Erasmus MC in Rotterdam (prof.dr. Jaap Bonjer and later prof. dr. Jan IJzermans). He went on training in the Sint Fransiscus Gasthuis in Rotterdam, under supervision of dr. Cees Wittens and dr. Bert Kerver. For his last years of surgical training he moved to the Onze Lieve Vrouwe Gasthuis in Amsterdam (dr. Nico Out and later dr. Frank van der Heijden). Hans is happily married and has a beautiful son named David.

~~CV niet in NL?~~