ELSEVIER

European Journal of Cancer 40 (2004) 549–558

European Journal of Cancer

www.ejconline.com

Surgical treatment of pancreatic adenocarcinoma: actual survival and prognostic factors in 343 patients

K.F.D. Kuhlmann[a], S.M.M. de Castro[a], J.G. Wesseling[b], F.J.W. ten Kate[c], G.J.A. Offerhaus[c], O.R.C. Busch[a], T.M. van Gulik[a], H. Obertop[a], D.J. Gouma[a,*]

[a]*Department of Surgery, Academic Medical Center from the University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands*
[b]*Laboratory of Experimental Hepatology, AMC Liver Center, Academic Medical Center from the University of Amsterdam, Amsterdam, The Netherlands*
[c]*Department of Pathology, Academic Medical Center from the University of Amsterdam, Amsterdam, The Netherlands*

Received 30 September 2003; accepted 3 October 2003

Abstract

Survival data of patients with pancreatic carcinoma are often overestimated because of incomplete follow-up. Therefore, the aim of this study was to approach complete follow-up and to analyse survival and prognostic factors of patients who underwent surgical treatment for pancreatic adenocarcinoma. Between 1992 and 2002, 343 patients underwent surgical treatment for pancreatic adenocarcinoma. One hundred and sixty patients underwent a resection with a curative intention and 183 patients underwent bypass surgery for palliation. Follow-up was complete for 93% of patients. Median survival after resection and bypass was 17.0 and 7.5 months, and 5-year survival was 8% and 0, respectively. In multivariate analysis, tumour-positive lymph nodes, non-radical surgery, poor tumour differentiation, and tumour size were independent prognostic factors for survival after resection. For patients treated with bypass surgery, metastatic disease and tumour size independently predicted survival. In conclusion, actual survival of patients with pancreatic adenocarcinoma is disappointing compared with the actuarial survival rates reported in the literature. The independent prognostic factors for survival of patients who underwent surgical treatment for pancreatic adenocarcinoma are tumour-related.

Keywords: Pancreatic ductal adenocarcinoma; Adenocarcinoma; Surgery; Pancreaticoduodenectomy; Gastric bypass; Biliary bypass; Palliative care; Survival; Prognostic factors

1. Introduction

Pancreatic cancer is a highly lethal disease. The incidence in the United States of America (USA) and Western Europe is 10/100 000 per year and approaches mortality. The overall 5-year survival is less than 4% and has hardly improved over the last two decades [1]. Pancreaticoduodenectomy is still the only treatment with a curative potential. However, 80% of patients are not eligible for surgical resection because of local spread or metastatic disease at the time of diagnosis [2,3]. Thus, most patients are palliatively treated to improve the quality of their remaining life.

Endoscopic or transhepatic stenting are effective for short-term relief of jaundice, but stent exchanges are needed frequently and therefore cause considerable morbidity [4]. Surgical bypass procedures (biliary, gastric or both) can offer optimal long-term palliation of obstructive jaundice and can prevent or treat gastrointestinal obstruction [5]. Furthermore, a chemical coeliac plexus nerve block can easily be performed during laparotomy and can effectively manage pain in patients with unresectable pancreatic cancer [6].

Survival rates and prognostic factors for patients who underwent surgical treatment for pancreatic adenocarcinoma have been reported before. However, many studies include a limited number of patients, cover a long period of time, analyse all periampullary tumours (including ampullary, distal bile duct and duodenal tumours) or have limited follow-up with an estimated

* Corresponding author. Tel.: +31-20-5662166; fax: +31-20-6914858.
E-mail address: d.j.gouma@amc.uva.nl (D.J. Gouma).

0959-8049/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2003.10.026

survival [7–19]. These estimated actuarial curves may show better survival results than the actual survival.

The present study represents a large single centre series including 343 patients who underwent surgical treatment for histologically-proven pancreatic adenocarcinoma. Only 23 patients were alive at the end of follow-up and therefore Kaplan–Meier survival curves approach the actual survival. Earlier studies of our department have focused on the survival and the prognostic factors of periampullary tumours, but not on pancreatic adenocarcinoma alone [13,15,20–22]. Therefore, our aim was to evaluate the survival of patients with histologically-proven pancreatic adenocarcinoma and to analyse the prognostic factors for survival after resection or bypass surgery at the time of diagnosis.

2. Patients and methods

In the 10-year period from January 1992 to December 2001, a total of 759 consecutive patients underwent surgical treatment (resection in 459 patients and bypass in 300 patients) for a periampullary mass. In 358 of 759 patients pancreatic adenocarcinoma was confirmed histologically. Fifteen patients, who were initially treated elsewhere, were referred to our centre in a late stage of the disease for symptoms of gastric obstruction. These 15 patients were excluded. The remaining 343 patients were selected and data were obtained from a prospectively collected database.

2.1. Operative procedures

Of these 343 patients, 329 (96%) underwent an exploratory laparotomy with the intention to perform a resection. The indications to perform a bypass were metastatic disease or locally advanced tumour due to involvement of the portal vein, major arteries or infiltration of the mesocolon or retroperitoneum. When irresectability was assessed at exploratory laparotomy, histological conformation was obtained using frozen sections. The remaining 14 patients directly underwent bypass surgery because the tumour proved irresectable at diagnostic work-up. In these patients, non-surgical palliation was not considered because symptoms of gastric obstruction were present.

Of the 343 patients, 160 patients underwent a standard resection (group 1) as described in Ref. [23]. A pylorus-preserving pancreaticoduodenectomy was performed in 133 and a classic Whipple's procedure in 27 patients. Reconstruction was performed with a single retrocolic jejunal limb reconstruction. In 33 patients with minimal venous ingrowth, portal or superior mesenteric vein resection was performed.

Hundred and eighty three patients underwent palliative bypass surgery (group 2), 157 a double bypass (hepaticojejunostomy and gastroenterostomy) and 26 patients a single bypass (hepaticojejunostomy: $n=15$, gastroenterostomy: $n=10$, and pancreaticojejunostomy: $n=1$). Ninety patients underwent bypass surgery for metastatic disease and 93 patients for a locally advanced tumour.

2.2. Pathology

During surgery, frozen sections of the resection margins were taken for histological examination. A frozen section was taken of the pancreatic resection margin in 22% of the patients and in 43% of the patients of the bile duct margin. Frozen sections of the other resection margins (superior mesenteric artery, portal vein and duodenal resection margins) were only taken if indicated. In the case of a tumour-positive frozen section, re-resection was performed.

In the operating room, the surgeon marked the resection margins at the resection specimen at the level of bile duct, pancreatic duct, superior mesenteric artery and portal vein margin. Resection specimens were analysed for location, size and differentiation of the tumour and for the status of lymph nodes and resection margins. In the bypass group, the tumour size was assessed by preoperative imaging or was estimated during the operation. The histological tumour differentiation in this group was assessed in biopsies of the tumour.

Tumours were categorised according to the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) 1997 classification. When margins at the superior mesenteric artery or portal vein were positive, tumours were classified as stage IVa, even when ingrowth could not be proven histologically.

2.3. Patient evaluation and follow-up

Pre-operative parameters studied were: patients' characteristics, symptoms at the time of operation and pre-operative American Society of Anesthesiologists (ASA) score. Peri-operative parameters included surgical complications: anastomotic leakage (more than three times serum amylase or leakage proven at laparotomy), haemorrhage, abdominal abscess, wound infection, and delayed gastric emptying (stomach drainage for longer than 10 days postoperatively or intolerance for normal food intake for longer than 2 weeks postoperatively), general complications (e.g., cardio-pulmonary complications and urinary tract infections), relaparotomy during the admission for initial surgery, post-operative hospital stay, in-hospital mortality, blood transfusion (defined as packed red blood cells (PRC) within the first 24 h postoperatively and during hospital stay) and adjuvant or palliative chemotherapy and/or radiotherapy. All patients were followed for survival analysis

on a regular basis in the outpatient clinic. Follow-up ended in April 2003. When follow-up was incomplete, the general practitioner or referring physicians outside our centre were contacted.

2.4. Statistics

Differences between group 1 and 2 were analysed applying Chi-square test, ANOVA or Kruskall–Wallis test. Survival was measured from the day of surgery until death or until the last day of the follow-up period. Hospital mortality was included in the survival analysis. Survival was analysed with the Kaplan–Meier method. The log-rank test was used to compare differences in survival between the groups. Statistical significance was considered if $P<0.05$. After univariate analysis, all significant prognostic factors were entered into a Cox regression model to determine independent predictors of survival. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 10.1.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient population

The two groups (group 1: resection and group 2: bypass) were comparable in terms of age and sex distribution, pre-operative ASA-score and jaundice at the time of presentation. In group 2, significantly more patients presented with pain ($P=0.01$). Adjuvant or palliative chemo- and radiotherapy were not equally distributed over the two groups because of the different regimes followed during the 10-year inclusion period. Patients' characteristics are summarised in Table 1.

3.2. Peri-operative parameters

Median post-operative hospital stay was significantly longer in group 1 (20 versus 12 days with a range of 8–222 versus 4–43, respectively). There was no hospital mortality in group 1 and 2% (4 patients) in group 2. One patient died of cardiac complications, one of pulmonary complications due to carcinomatous pleuritis, one of abdominal sepsis, and one of pulmonary insufficiency due to pneumonia.

Anastomotic leakage (7% versus 1%, $P=0.01$), abdominal abscess (10% versus 3%, $P=0.01$) and gastrointestinal obstruction (14% versus 7%, $P=0.03$) occurred significantly more frequently after resection. Haemorrhage, wound infection, and general complications were not significantly different between groups. One or more relaparotomies were performed in 9% of patients in group 1 and in 4% of patients in group 2, which was not significantly different ($P=0.07$). Patients in group 1 received significantly more packed cells in the first 24 h (1.1 versus 0.2 units of packed cells, $P<0.01$) and during their hospital stay (2.2 versus 0.5 units of packed cells, $P<0.01$) than patients in group 2. Peri-operative parameters are summarised in Table 2.

3.3. Pathology

Six of 35 frozen sections of the pancreatic resection margin (17%) and two of 69 frozen sections of the bile duct margin (3%) were tumour-positive and subsequent re-resection was performed.

Table 1
Patients' characteristics

	Resection group 1 ($n=160$)	Bypass group 2 ($n=183$)	P-value
Gender			
Male	76 (48)	104 (57)	NS
Female	84 (53)	79 (43)	NS
Age (years) (median (range))	64 (43–84)	62 (33–78)	NS
Pre-operative ASA-score[a]			
1	38 (25)	36 (20)	NS
2	87 (57)	102 (58)	NS
3	27 (18)	39 (22)	NS
4	1 (1)	0	NS
Presenting symptoms			
Pain (abdominal and/or back)	62 (39)	98 (54)	0.01
Jaundice	148 (93)	168 (92)	NS
Adjuvant or palliative therapy			
Radiotherapy	3 (2)	27 (15)	<0.01
Chemotherapy	3 (2)	13 (7)	0.02
Radio/chemotherapy	9 (6)	13 (7)	NS

Numbers in parentheses represent percentages or range. ASA: American Society of Anesthesiologists, NS, non-significant (P value $\geqslant 0.05$).
[a] Some data are missing in these subgroups.

Table 2
Peri-operative parameters

	Resection group 1 ($n=160$)	Bypass group 2 ($n=183$)	P-value
Surgical procedure			
PPPD	133 (83)	–	–
PD	27 (17)	–	–
Double bypass	–	157 (86)	–
Single bypass	–	26 (14)	–
Postoperative stay days (median)	20 (8–222)	12 (4–43)	<0.01
Hospital mortality	0 (0)	4 (2)	NS
Complications (overall)	67 (42)	54 (30)	0.02
Anastomotic leakage	11 (7)	2 (1)	0.01
Haemorrhage	9 (6)	4 (2)	NS
Abdominal abscess	16 (10)	6 (3)	0.01
Delayed gastric emptying	22 (14)	12 (7)	0.03
Wound infection	9 (6)	12 (7)	NS
General	36 (23)	35 (19)	NS
Relaparotomy	15 (9)	8 (4)	NS
PRC units (median)			
First 24 h	1.1 (0–12)	0.2 (0–4)	<0.01
During hospital stay	2.2 (0–22)	0.5 (0–14)	<0.01

Numbers in parentheses represent percentages or range. PRC, packed red blood cell; NS, non-significant (P value $\geqslant 0.05$).

The tumour diameter in group 1 was significantly smaller than in group 2 (2.8 versus 3.4 cm, $P<0.01$). There was no difference in tumour differentiation between the two groups. In group 1, 68% of the patients had one or more positive lymph node(s) in the resection specimen. Fifty per cent of patients had tumour-positive resection margins. The margin at the superior mesenteric artery was tumour-positive in 37 patients, in 36 patients the dissection planes, in 31 patients the pancreatic resection margin, in 29 patients the margin at the portal vein, in 4 the resection margin of the bile duct and in 3 patients the resection margin of the proximal duodenum was tumour-positive. In group 2, metastatic disease was present in 49%.

Table 3
Pathology and tumour characteristics

	Resection group 1 ($n=160$)	Bypass group 2 ($n=183$)	P-value
Tumour size (cm) (median (range))	2.8 (0.8–6.8)	3.4 (1.0–10.0)	<0.01
0–0.9 cm	3 (2)	0	
1–1.9 cm	24 (15)	5 (3)	
2–2.9 cm	62 (39)	45 (25)	
3–3.9 cm	44 (28)	67 (37)	
4–4.9 cm	17 (11)	43 (23)	
5–5.9 cm	7 (4)	14 (8)	
6–6.9 cm	2 (1)	1 (1)	
7–10 cm	0	3 (2)	
Margins not well defined	1 (1)	5 (3)	
Tumour differentiation			
Poor	42 (26)	25 (29)	NS
Poor-intermediate	31 (19)	15 (17)	NS
Intermediate	64 (40)	39 (45)	NS
Intermediate-high	10 (6)	1 (1)	NS
High	13 (8)	7 (8)	NS
Not determined	0	96	
Tumour-positive lymph nodes	109 (68)	ND	–
Tumour-positive resection margins	80 (50)	–	–
Metastatic disease	0	90 (49)	<0.01

Numbers in parentheses represent percentages or range. NS, Non-significant (P value $\geqslant 0.05$); ND, not determined.

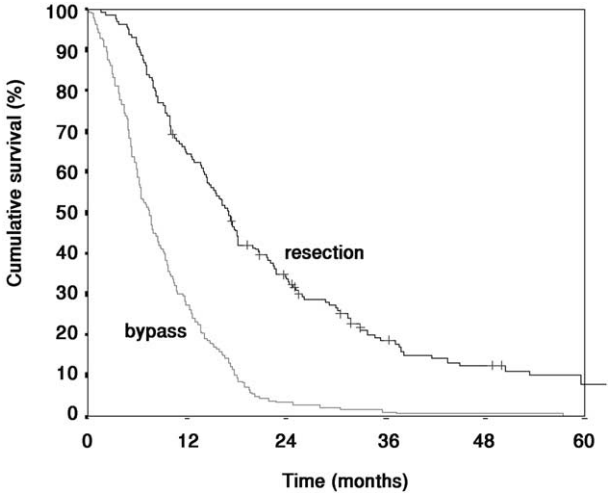

Fig. 1. Kaplan–Meier survival curves of patients after resection and bypass. Censored patients are indicated with a cross. *P*-value: <0.01.

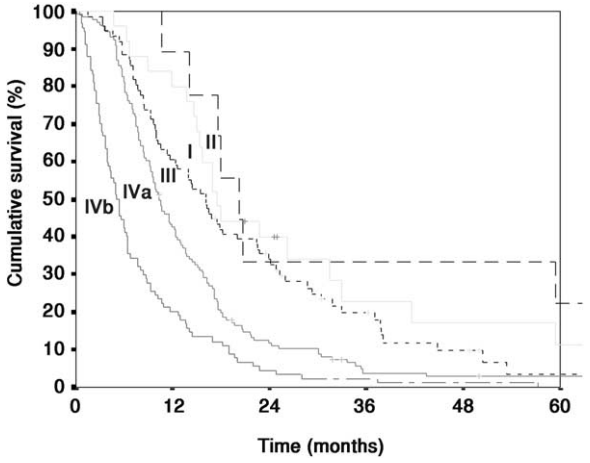

Fig. 2. Kaplan–Meier survival curves of all patients who underwent surgery for pancreatic adenocarcinoma (resection and bypass) divided by the AJCC/UICC 1997 classification. Overall *P*-value: <0.01.

In group 1, most patients had stage III (49%) or stage VIa (29%) disease according to the AJCC/UICC 1997 classification. In group 2, there was an equal distribution between stage VIa and VIb disease (Table 3).

3.4. Follow-up and survival

At the end of follow-up in April 2003, 22 patients (6%) were alive (all in group 1) and 320 patients (93%) were followed until death. One patient was lost to follow-up in group 1 due to emigration. The median follow-up was 16.9 months in group 1 and 7.5 months in group 2. Median follow-up of the living patients was 31.8 months (17.3–134.0 months).

Median survival for group 1 was 17.0 months and for group 2 7.5 months, with a 1, 2 and 5-year survivals of 64%, 34% and 8% in group 1 and 27%, 3% and 0 in group 2. Fig. 1 shows the Kaplan–Meier survival curves for the two groups. In the survival curve of group 1, the 23 patients that were alive at the end of follow-up or lost to follow-up were censored as depicted. There were seven actual 5-year survivors in this series (range 60.2–134.0 months). The survival of all patients divided by the AJCC/UICC 1997 classification is shown in Fig. 2.

3.5. Prognostic factors for survival (univariate analysis)

In group 1, 4 of the 24 analysed variables (tumour size, tumour differentiation, lymph nodes status and resection margins) significantly influenced survival. In group 2, 10 variables influenced survival: radiotherapy, post-operative hospital stay, haemorrhage, abdominal abscess, delayed gastric emptying, relaparotomy, more than four PRC's during admission, metastatic disease, tumour size and UICC classification.

Table 4
Multivariate analysis of prognostic factors predicting favourable survival

Tested factor	Reference factor	Hazard ratio (95% Confidence Interval)	*P*-value
Group 1 (resection):			
Tumour-positive node(s)	Negative node(s)	**1.58** (1.08–2.31)	**0.02**
Tumour-positive resection margins	Negative margins	**1.57** (1.10–2.23)	**0.01**
Poor tumour differentiation	Poor-intermediate	**1.31** (1.13–1.52)	**<0.01**
Tumour size	1 cm decrease	**1.25** (1.06–1.48)	**0.01**
Group 2 (bypass):			
Metastatic disease present	Absent	**1.43** (1.05–1.95)	**0.03**
Tumour size	1 cm decrease	**1.15** (1.01–1.31)	**0.03**
Haemorrhage present	Absent	2.96 (0.75–11.60)	0.12
Delayed gastric emptying present	Absent	1.73 (0.86–3.49)	0.12
Hospital stay > median	⩽Median	1.35 (0.76–2.40)	0.30
Relaparotomy	No relaparotomy	1.67 (0.66–4.20)	0.28
Abdominal abscess present	Absent	1.25 (0.38–4.11)	0.71

Bold: independent prognostic factors.

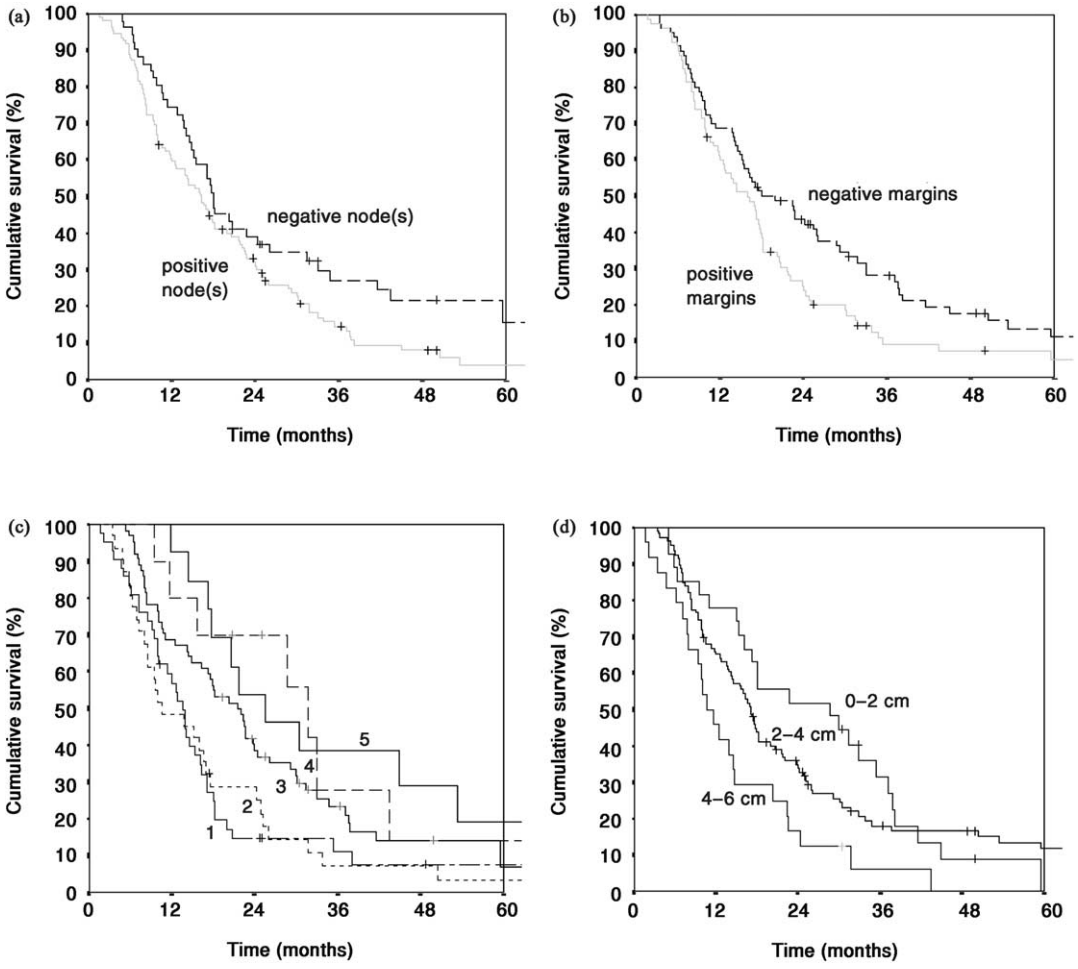

Fig. 3. Kaplan–Meier survival curves of patients who underwent a resection (group 1) for pancreatic adenocarcinoma according to the independent prognostic factors. a: lymph nodes, b: resection margins, c: tumour differentiation (1 = poor, 2 = poor-intermediate, 3 = intermediate, 4 = intermediate-high, 5 = high) and d: tumour size in cm (patients with a tumour size >6 cm ($n=2$) are not depicted).

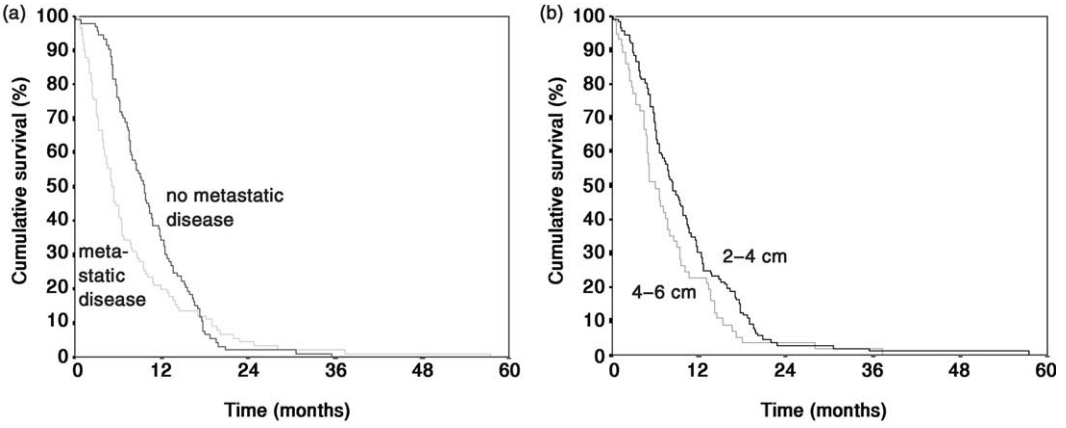

Fig. 4. Kaplan–Meier survival curves of patients who underwent a bypass (group 2) for pancreatic adenocarcinoma according to the independent prognostic factors. a: metastatic disease, b: tumour size (patients with a tumour size <2 cm ($n=5$) and >6 cm ($n=4$) are not depicted).

Table 5
Patient numbers, study period, median survival, 5-year survival, number of 5-year survivors and mortality in large series of resections for pancreatic carcinoma published in English literature since 1992

Study, *journal*, year [Ref.]	Patient no.	Study period	Median survival (months)	5-year survival (%)	No. of 5-year survivors	Mortality
Geer and colleagues, *Am J Surg* 1993 [7]	146	1983–1990	18	24	10	3.4
Nitecki and colleagues, *Ann Surg* 1995 [8]	174	1981–1991	17.5	6.8	nst	2.9
Allema and colleagues, *Cancer* 1995 [15]	67	1981–1991	nst	15	nst	7.4
Yeo and colleagues, *Ann Surg* 1995 [16]	201	1970–1994	15.5	21	22	5.0
Sperti and colleagues, *Br J Surg* 1996 [9]	113	1970–1992	nst	12[a]	9	15.0
Yeo and colleagues, *Ann Surg* 1997 [14]	282	1990–1996	18	nst[b]	nst	1.4
Millkan and colleagues, *Am Surg* 1999 [18]	75	1980–1997	13	17	6	4.0
Wenger and colleagues, *Dig Surg* 2000 [10]	158	1981–1996	13.8	11.8	nst	7.3
Sohn and colleagues, *J Gastroint Surg* 2000 [19]	616	1984–1999	17	17	33	2.3
van Geenen and colleagues, *Eur J Surg Oncol* 2001 [13]	108	1992–1998	16	nst	nst	0
Kedra and colleagues, *Hepatogastroenterology* 2001 [17]	136	1980–1999	18	15.2	nst	8
Ahmad and colleagues, *Am J Gastroenterol* 2001 [11]	125	1990–1998	16	19	9	3
Lim and colleagues, *Ann Surg* 2003 [12]	396	1991–1996	17.6	nst[c]	0	nst
This study	160	1992–2001	17.0	7.8	7	0

nst, not stated in article.
[a] Hospital mortality (17 patients) excluded.
[b] 3-year survival: 30%.
[c] 3-year survival 34.3%.

3.6. Independent prognostic factors for survival (Cox regression model)

For group 1, resection margins, lymph node status, tumour differentiation and tumour size were entered in the multivariate analysis. These four variables all independently predicted the survival. One or more tumour-positive lymph nodes predicted a poor survival with a hazard ratio of 1.58 (95% Confidence Interval (CI) 1.08–2.31), tumour-positive resection margins with a hazard ratio of 1.57 (CI 1.10–2.23), low tumour differentiation with a hazard ratio of 1.31 (CI 1.13–1.52) and tumour size (compared with a tumour that is 1 cm smaller) with a hazard ratio of 1.25 (CI 1.06–1.48) (Table 4 and Fig. 3).

For group 2, seven of 10 variables that were significant in the univariate analysis were entered in the multivariate analysis. Radiotherapy was not entered because different radiotherapy regimes were used during the 10-year period and because confounding was possible due to patient selection. The factor >4 PRC's during admission was not entered because patients who received more than four PRC's also suffered from a post-operative haemorrhage. Therefore, only haemorrhage was entered. The AJCC/UICC 1997 classification was not entered because this factor was represented by the factor metastatic disease. Of these seven factors that were entered in the multivariate analysis, only metastatic disease (hazard ratio 1.43, CI 1.05–1.95) and tumour size (hazard ratio 1.15, CI 1.01–1.31) independently predicted a poor survival. The data are summarised in Table 4 and Fig. 4.

4. Discussion

The present study shows the outcome of a single-centre analysis of the survival in 343 patients after surgical treatment for histologically-proven pancreatic adenocarcinoma during a 10-year period between 1992 and 2002. Although resection is still the only treatment with a curative potential, long-term survival was limited. The median and 5-year survival after resection was only 17 months and 8%, and 7.5 months and zero after a surgical bypass. Independent prognostic factors that predicted a poor survival for patients after resection were tumour-positive lymph nodes, tumour-positive resection margins, poor tumour differentiation grade and tumour size. After bypass surgery, metastatic disease and tumour size were independent prognostic factors.

The median survival after resection is comparable, but 5-year survival is generally lower than rates reported the literature (Table 5) [7–19]. The low 5-year survival can partly be explained by the fact that in the present study the follow-up of all patients was nearly completed. Only 22 (6.4%) of 343 patients were alive at the end of the follow-up in April 2003 and only 1 patient (0.3%) was lost to follow-up. Therefore, in this study the actuarial survival computed by the Kaplan–Meier method approaches the actual survival. When the Kaplan–Meier method is used to perform survival calculations, the percentage of 5-year survival increases when increasing numbers of patients are censored or lost to follow-up. This phenomenon occurs frequently in series of patients with pancreatic carcinoma and was described by Gudjonsson, who stated that survival

improves when the amount of censored data increases [24]. Yeo and colleagues, who reviewed 650 pancreaticoduodenectomies in 1997, have endorsed this viewpoint and state that their Kaplan–Meier curves lose accuracy after a 2-year period because of a short period of follow-up of 12 months [14]. In most series published in literature, the period of follow-up is not given and information about censored patients is lacking. Therefore, 5-year survival data should be interpreted with some restraint. Certainly because the numbers of actual 5-year survivors, if stated, is mostly well below 10% of the total number of studied patients (Table 5). When we once again analyse the 67 patients treated in our centre between 1983 and 1992 (published by Allema and colleagues in 1995 [15]), we find that one patient is lost-to-follow up because he returned to his native country and all other patients died. The 5-year survival of these 67 patients is 7.9%, while this was 15% in the original article, indicating the effect of incomplete data. The median and 5-year survival after bypass surgery is comparable with literature, although few studies have been published recently [5,25].

The median survival of patients after resection, which was performed as a standard resection without extended lymph node resection, is in agreement with the literature during the last decade. Although resections were macroscopically radical during surgery, our study shows a high rate of positive resection margins after resection. In these patients, the resection should be considered as a palliative treatment. Concerning the margins of the superior mesenteric artery or portal vein it is shown in literature that a wedge resection does not lead to prolonged survival [21]. The rate of tumour-positive resection margins at the pancreatic margin is high, certainly because a re-resection of this margin can be performed easily. Of the 31 patients with a tumour-positive pancreatic margin, in 12 patients this margin was the only tumour-positive margin. Therefore, these patients could theoretically have benefited from a frozen section and subsequent pancreatic re-resection. As a result of these findings, we have adapted our policy in terms of taking frozen sections routinely.

In-hospital mortality after pancreaticoduodenectomy is decreasing. Cameron [26] and Yeo [14] from Johns Hopkins reported studies with series of 145 and 190 consecutive pancreaticoduodenectomies, without mortality. However, these resections concerned heterogeneous groups of patients with malignant as well as benign disease. To our best knowledge, the present study is the first series with a zero hospital mortality in 160 consecutive resections for pancreatic adenocarcinoma. In a previous study in our hospital of 176 patients who underwent resection between 1983 and 1992, mortality was 7.4% for patients who underwent a resection for pancreatic carcinoma [15]. Although there was no mortality after resections for pancreatic adenocarcinoma, the overall mortality for the total group of patients after pancreaticoduodenectomy was 1.5% in the period from 1992 to 1998 [13]. Low mortality was found after resections for pancreatitis and pancreatic carcinoma and a higher mortality after resections for ampullary and bile duct carcinoma. This difference could be due to the lower incidence of major complications like anastomotic leakage, in which the quality of the pancreatic remnant and dilatation of the pancreatic duct plays an important role [27]. Furthermore, the preoperative selection procedure may play a role. The selection of patients with tumours other than pancreatic carcinomas could have been less stringent, because of their better prognosis. The mortality after palliative bypass was low (2%).

Morbidity after pancreaticoduodenectomy is also decreasing, our rates for the three major surgery-related complications after a pancreaticoduodenectomy were for anastomotic leakage 7%, haemorrhage 6% and abdominal abscess 10%. This is in agreement with the literature [28].

Irresectability of the tumour occurred in 53% of the patients and was mostly assessed during explorative laparotomy. Although less invasive palliative treatments such as stenting and laparoscopic bypass procedures are possible and are in fact first choice when irresectability has been shown at radiological staging, bypass surgery at the time of laparotomy is efficient to prevent later biliary and duodenal obstruction [29]. A recent randomised study which compared bypass surgery with endoscoping stenting showed no benefit for patients allocated to the endoscopic treatment. Furthermore, survival after bypass surgery was longer while procedure-related morbidity and mortality were comparable [30]. In the present study, morbidity after bypass surgery is low and hospital stay is relatively short. In combination with an acceptable hospital mortality, a surgical bypass is a safe and efficient treatment option for patients with irresectable pancreatic adenocarcinoma found at explorative laparotomy.

In the past, the role of an additional prophylactic gastrojejunostomy has been discussed. Lillemoe and colleagues demonstrated in a randomised trial that a gastrojejunostomy supplementary to biliary bypass decreases the incidence of late gastric outlet obstruction, without a higher mortality and morbidity [5]. A randomised trial in our centre between 1999 and 2002 shows comparable results [31]. In the present study, most patients (84%) with an irresectable tumour underwent a double bypass. Thirteen patients (7.1%) needed reoperation after bypass surgery because of late gastrointestinal obstruction (7/157 after double bypass and 6/26 after single bypass).

The independent prognostic factors found in the resection group were related to tumour characteristics. During the last decade, various studies showed tumour-

related prognostic factors after resection [7–19]. Therefore, the biology of pancreatic adenocarcinoma seems responsible for the poor prognosis. In the light of the finding that tumour-positive resection margins and lymph nodes are independent prognostic factors, one could consider to study the effect of an extended lymph node resection in a large randomised controlled trial. However, two single centre randomised trials could not show a survival benefit after an extended lymph node resection [32,33]. Chemo-radiation therapy has also been found to be an independent factor for survival in the literature [11;12;19]. However, patient selection may be responsible for this finding in these retrospective studies. In the bypass group, only metastatic disease and tumour size were independently prognostic for survival. These factors are also related to the aggressiveness of the tumour and the stage of the disease.

Although mortality and morbidity have decreased rapidly after pancreatic surgery, survival of pancreatic cancer remains poor. Therefore, new treatment modalities, such as immunotherapy, molecularly-targeted therapies and gene therapy, are crucial to specifically target pancreatic adenocarcinoma. These new therapies must reach the primary tumour and, even more importantly, must reach distant metastases and micrometastases. A combined eradication of both the primary tumour and the (micro)metastatic tissue is the only way to improve the survival of these patients with a poor prognosis.

Acknowledgements

All authors certify that there are no affiliations with or involvement in any organisation, person or entity with a direct financial interest in the subject matter or materials discussed in this manuscript.

References

1. Greenlee RT, Murray T, Bolden S, *et al*. Cancer statistics, 2000. *CA Cancer J Clin* 2000, **50**, 7–33.
2. Sener SF, Fremgen A, Menck HR, *et al*. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the National Cancer Database. *J Am Coll Surg* 1999, **189**, 1–7.
3. Tan HP, Smith J, Garberoglio CA. Pancreatic adenocarcinoma: an update. *J Am Coll Surg* 1996, **183**, 164–184.
4. Smith AC, Dowsett JF, Russell RC, *et al*. Randomised rial of endoscopic stenting versus surgical bypass in malignant low bile-duct obstruction. *Lancet* 1994, **344**, 1655–1660.
5. Lillemoe KD, Cameron JL, Hardacre JM, *et al*. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. *Ann Surg* 1999, **230**, 322–328.
6. Lillemoe KD, Cameron JL, Kaufman HS, *et al*. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. *Ann Surg* 1993, **217**, 447–455.
7. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. *Am J Surg* 1993, **165**, 68–72.
8. Nitecki SS, Sarr MG, Colby TV, *et al*. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? *Ann Surg* 1995, **221**, 59–66.
9. Sperti C, Pasquali C, Piccoli A, *et al*. Survival after resection for ductal adenocarcinoma of the pancreas. *Br J Surg* 1996, **83**, 625–631.
10. Wenger FA, Peter F, Zieren J, *et al*. Prognosis factors in carcinoma of the head of the pancreas. *Dig Surg* 2000, **17**, 29–35.
11. Ahmad NA, Lewis JD, Ginsberg GG, *et al*. Long term survival after pancreatic resection for pancreatic adenocarcinoma. *Am J Gastroenterol* 2001, **26**, 2609–2615.
12. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. *Ann Surg* 2003, **237**, 74–85.
13. van Geenen RC, van Gulik TM, Offerhaus GJ, *et al*. Survival after pancreaticoduodenectomy for periampullary adenocarcinoma: an update. *Eur J Surg Oncol* 2001, **27**, 549–557.
14. Yeo CJ, Cameron JL, Sohn TA, *et al*. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997, **226**, 248–257.
15. Allema JH, Reinders ME, van Gulik TM, *et al*. Prognostic factors for survival after pancreaticoduodenectomy for patients with carcinoma of the pancreatic head region. *Cancer* 1995, **75**, 2069–2076.
16. Yeo CJ, Cameron JL, Lillemoe KD, *et al*. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. *Ann Surg* 1995, **221**, 721–731.
17. Kedra B, Popiela T, Sierzega M, *et al*. Prognostic factors of long-term survival after resective procedures for pancreatic cancer. *Hepatogastroenterology* 2001, **48**, 1762–1766.
18. Millikan KW, Deziel DJ, Silverstein JC, *et al*. Prognostic factors associated with resectable adenocarcinoma of the head of the pancreas. *Am Surg* 1999, **65**, 618–623.
19. Sohn TA, Yeo CJ, Cameron JL, *et al*. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000, **4**, 567–579.
20. Obertop H, Gouma DJ. Improved results for resection of periampullary adenocarcinoma. *HPB Surg* 1996, **10**, 125–128.
21. van Geenen RC, ten Kate FJ, de Wit LT, *et al*. Segmental resection and wedge excision of the portal or superior mesenteric vein during pancreatoduodenectomy. *Surgery* 2001, **129**, 158–163.
22. Gouma DJ, van Gulik TM, de Wit LT, *et al*. Complications after resection of biliopancreatic cancer. *Ann Oncol* 1999, **10**(Supp. 4), 257–260.
23. Obertop H, Pedrazzoli S. Current views on surgical treatment of pancreatic cancer. *Dig Surg* 1999, **16**, 263–264.
24. Gudjonsson B. Survival statistics gone awry: pancreatic cancer, a case in point. *J Clin Gastroenterol* 2002, **35**, 180–184.
25. Engelken FJ, Bettschart V, Rahman MQ, *et al*. Prognostic factors in the palliation of pancreatic cancer. *Eur J Surg Oncol* 2003, **29**, 368–373.
26. Cameron JL, Pitt HA, Yeo CJ, *et al*. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. *Ann Surg* 1993, **217**, 430–435.
27. Yeo CJ, Cameron JL, Lillemoe KD, *et al*. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. *Ann Surg* 2000, **232**, 419–429.
28. Halloran CM, Ghaneh P, Bosonnet L, *et al*. Complications of pancreatic cancer resection. *Dig Surg* 2002, **19**, 138–146.
29. van den Bosch RP, van der Schelling GP, Klinkenbijl JHMPG, *et al*. Guidelines for the application of surgery and endoprostheses

in the palliation of obstructive jaundice in advanced cancer of the pancreas. *Ann Surg* 1994, **219**, 18–24.
30. Nieveen van Dijkum EJ, Romijn MG, Terwee CB, *et al*. Laparoscopic staging and subsequent palliation in patients with peripancreatic carcinoma. *Ann Surg* 2003, **237**, 66–73.
31. van Heek NT, de Castro SMM, van Eijck CH, *et al*. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer, a prospective randomized multi-center trial with special focus on assessment of quality of life. *Ann Surg* 2003, **238**, 894–902.
32. Yeo CJ, Cameron JL, Lillemoe KD, *et al*. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. *Ann Surg* 2002, **236**, 355–366.
33. Pedrazzoli S, DiCarlo V, Dionigi R, *et al*. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. *Ann Surg* 1998, **228**, 508–517.