Original article

Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma

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Background: Mortality rates associated with pancreatic resection for cancer have steadily decreased with time, but improvements in long-term survival are less clear. This prospective study evaluated risk factors for survival after resection for pancreatic adenocarcinoma.

Methods: Data from 366 consecutive patients recorded prospectively between November 1993 and September 2001 were analysed using univariate and multivariate models.

Results: Fifty-eight patients (15·8 per cent) underwent surgical exploration only, 97 patients (26·5 per cent) underwent palliative bypass surgery and 211 patients (57·7 per cent) resection for pancreatic adenocarcinoma. Stage I disease was present in 9·0 per cent, stage II in 18·0 per cent, stage III in 68·7 per cent and stage IV in 4·3 per cent of patients who underwent resection. Resection was curative (R0) in 75·8 per cent of patients. Procedures included pylorus-preserving Whipple resection (41·2 per cent), classical Whipple resection (37·0 per cent), left pancreatic resection (13·7 per cent) and total pancreatectomy (8·1 per cent). The in-hospital mortality and cumulative morbidity rates were 2·8 and 44·1 per cent respectively. The overall actuarial 5-year survival rate was 19·8 per cent after resection. Survival was better after curative resection (R0) (24·2 per cent) and in lymph-node negative patients (31·6 per cent). A Cox proportional hazards survival analysis indicated that curative resection was the most powerful independent predictor of long-term survival.

Conclusion: Resection for pancreatic adenocarcinoma can be performed safely. The overall survival rate is determined by the radicality of resection. Patients deemed fit for surgery who have no radiological signs of distant metastasis should undergo surgical exploration. Resection should follow if there is a reasonable likelihood that an R0 resection can be obtained.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in the USA, with an overall 5-year survival rate of no more than 5 per cent[1]. The Whipple procedure has remained the core of surgical treatment for resectable pancreatic cancer and several specialized centres have recently reported 5-year survival rates of over 20 per cent[2–6]. It is not clear whether these improvements reflect positive patient selection, more radical resection or effects of adjuvant treatment strategies. Fortner[7] developed a more extended surgical procedure with the aim of increasing the resectability rate and improving long-term survival. More radical lymph node dissection has been implemented widely, particularly in Japan, with favourable 5-year survival rates, although most series are retrospective[2,7–10]. In contrast, two recent randomized trials could not detect an overall survival advantage for extended lymphadenectomy in patients with pancreatic adenocarcinoma, although subgroups of patients with positive lymph node involvement had a small survival benefit[11,12]. The value of more radical resection remains open to debate. Similarly, studies of the effects of adjuvant therapy following resection have produced mixed results. In the Gastrointestinal Tumour Study Group (GITSG) randomized controlled trial, there was a significant

survival benefit in patients receiving radiotherapy (40 Gy) combined with 5-fluorouracil (5-FU) compared with the control group[13,14]. In contrast, the European Organization for Research and Treatment of Cancer (EORTC) study of 114 patients with pancreatic cancer found no difference in median survival between patients who received adjuvant chemoradiation and untreated controls[15]. The most recent and largest trial, the European Study Group for Pancreatic Cancer (ESPAC) 1 trial, randomized 285 patients in a two-by-two factorial design (observation, chemoradiotherapy alone, chemotherapy alone or in combination with chemoradiation)[16]. A further 68 patients were randomly assigned to chemoradiotherapy or no chemoradiotherapy and 188 to chemotherapy or no chemotherapy. Although adjuvant chemoradiotherapy showed no survival benefit, there was evidence of improved survival with adjuvant chemotherapy.

The present study represents a recent single-centre experience with surgical treatment of pancreatic adenocarcinoma in a consecutive and prospectively recorded series of patients, with the aim of identifying independent predictors of survival.

Patients and methods

Between November 1993 and September 2001, data from 366 consecutive patients who had operation for histologically proven pancreatic adenocarcinoma were entered into a prospective database. Patients underwent a standardized preoperative evaluation consisting of contrast-enhanced abdominal computed tomography in combination with endoscopic retrograde cholangiopancreatography (1993–1998) or magnetic resonance imaging (1998–2001). Patients with prolonged obstructive jaundice and altered liver function underwent preoperative endoscopic biliary stenting. Surgical exploration was performed to determine resectability. Resection was performed in the absence of haematogenous metastases and when no gross retroperitoneal tumour infiltration or complex vascular infiltration was evident. Limited invasion of the portal or superior mesenteric vein was not regarded as a contraindication to resection. The surgical techniques for classical and pylorus-preserving pancreatoduodenectomy, and total pancreatectomy have been described previously[17,18]. All patients who underwent curative pancreatoduodenectomy (R0 resection) received a standardized systematic lymph node dissection encompassing the lymph nodes of the hepatoduodenal ligament, along the common hepatic artery and the coeliac trunk, the right side of the superior mesenteric artery and the retropancreatic area between the aorta and vena cava. Palliative bypass surgery usually comprised hepaticojejunostomy with a Roux-en-Y loop combined with a gastric bypass procedure, although a minority of patients underwent a single bypass procedure depending on the intraoperative findings. The remaining patients underwent surgical exploration only.

Pancreatic adenocarcinoma was staged following the tumour node metastasis system of the Union Internacional Contra la Cancrum (UICC)[19]. Resected specimens were examined, noting the tissue diagnosis, tumour size, grade, lymph node involvement, resection margin and any vascular perineural and lymphatic infiltration. A curative resection (R0) was characterized by a specimen with clear resection margins and no gross tumour mass remaining at the operation site or in other organs. R1 resection was defined as microscopic involvement of the resection margin. A resection was classified as R2 when macroscopic tumour remained at the operation site. All perioperative and postoperative complications were recorded prospectively. Eighty-three patients were recruited into the randomized controlled ESPAC-1 trial, which examined the benefit of adjuvant chemotherapy and radiotherapy in patients with resectable pancreatic adenocarcinoma[16]. Following bypass surgery, selected patients received palliative chemotherapy with either 5-fluorouracil (5-FU), gemcitabine or a combination of both. The mortality rate included all in-hospital deaths. Delayed gastric emptying was defined as the need for a nasogastric tube for more than 10 days after operation. A pancreatic fistula was defined as persistent drainage of more than 30 ml amylase-rich fluid (more than 5000 units) per day for more than 10 days. A biliary fistula was diagnosed if bilirubin-rich fluid was drained for more than 5 days. Bleeding was defined as the need for more than 2 units of packed red blood cells more than 24 h after operation, or reoperation for bleeding.

Statistical analysis

Variables were analysed by means of Fisher's exact test, χ^2 test or Mann–Whitney U test as appropriate using SPSS® Statistical Software (SPSS, Chicago, Illinois, USA). Survival analysis was performed by the Kaplan–Meier method and differences between survival curves were assessed by means of the log rank test. Twenty-nine factors were included in the survival analysis. Testing all the factors in univariate analysis was the first step in an explorative data analysis; data were not corrected for multiple testing. Variables with $P \leq 0{\cdot}100$ were included in a multivariate stepwise regression survival analysis of patients undergoing resection using the Cox proportional hazard model. Applying a Bonferroni or Holm–Bonferroni

correction indicated that only a few of the factors were still significant prognostic variables. $P < 0.050$ was considered statistically significant.

Results

Operations were performed by ten consultant surgeons. To ensure that operative strategies and techniques were consistent, one surgeon attended or performed 52 per cent of all procedures. The surgical procedures are listed in *Table 1*. Demographic details were comparable in patients undergoing resection or palliative surgery (*Table 2*).

Clinical data for patients who underwent resection are given in *Table 3*. Operative findings and tumour

Table 1 Surgical procedures performed in 366 patients with pancreatic adenocarcinoma

	No. of patients
Resection	211 (57·7)
Pylorus-preserving Whipple resection	87 (23·8)
Classical Whipple resection	78 (21·3)
Pancreatic left resection	29 (7·9)
Total pancreatectomy	17 (4·6)
Bypass procedure	97 (26·5)
Double bypass procedure	59 (16·1)
Gastrojejunostomy	20 (5·5)
Hepatojejunostomy	18 (4·9)
Surgical exploration	58 (5·8)
Laparotomy	48 (13·1)
Diagnostic laparoscopy	10 (2·7)

Values in parentheses are percentages.

Table 3 Clinical details of patients who underwent curative or non-curative resection for pancreatic adenocarcinoma

	Curative resection ($n = 160$)	Non-curative resection ($n = 51$)	P§
Age (years)*	68 (24–87)	69 (44–86)	0·781
Sex			
M	86 (53·8)	26 (51)	0·730
F	74 (46·3)	25 (49)	
ASA grade			
I–II	116 (72·5)	40 (78)	0·401
III–IV	44 (27·5)	11 (22)	
Bodyweight (%)*†	93 (75–100)	90 (75–100)	0·250
Duration of symptoms (weeks)	4 (1–77)	8 (1–52)	0·012
Diabetes mellitus	27 (16·9)	14 (27)	0·107
Cardiac disease	33 (20·6)	14 (27)	0·300
COPD	19 (11·9)	1 (2)	0·033
Jaundice‡	54 (33·8)	8 (16)	0·010
Albumin < 30 g/l	25 (15·6)	8 (16)	0·995
Creatinine > 150 mmol/l	13 (8·1)	2 (4)	0·309
Biliary imaging	106 (66·3)	32 (63)	0·542
Biliary drainage	67 (41·9)	15 (29)	0·104

Values in parentheses are percentages unless indicated otherwise; *values are median (range). The resection was not considered curative (R+) in 51 patients (24·2 per cent) for the following reasons: macroscopic tumour remnant in 31 patients (R2 resection; 16 patients with infiltration of the superior mesenteric artery, five with infiltration of the coeliac trunk and ten with gross involvement of the portal or mesenteric vein) and microscopic infiltration of the resection margin in 20 patients (R1 resection). †Bodyweight as a percentage of premorbid bodyweight; ‡bilirubin level > 100 μmol/l. ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease. §Fisher's exact test or χ^2 test for qualitative variables and Mann–Whitney *U* test for quantitative variables.

Table 2 Clinical details of patients who underwent resection, palliative surgical bypass or exploration

	Resection ($n = 211$)	Palliative bypass ($n = 97$)	P§¶	Exploration ($n = 58$)	P§**
Age (years)*	66 (24–87)	68 (39–91)	0·360	66 (36–85)	0·630
Sex†			0·352		0·736
M	112 (53·1)	57 (59)		22 (38)	
F	99 (46·9)	40 (41)		36 (62)	
ASA grade†			0·483		0·184
I–II	156 (73·9)	68 (70)		47 (81)	
III–IV	55 (26·1)	29 (30)		11 (19)	
Operating time (min)*	420 (180–780)	245 (130–365)	0·001	105 (40–250)	0·001
Blood loss (ml)*	1500 (200–22 000)	500 (100–3000)	0·001	100 (0–600)	0·001
Hospital stay (days)*	16 (4–118)	14 (6–40)	0·001	9 (1–29)	0·001
Morbidity†	93 (44·1)	32 (33)	0·076	5 (9)	0·001
Deaths†	6 (2·8)	0 (0)	0·093	0 (0)	
Survival (months)‡	16 (13, 19)	6 (5, 7)	0·001	7 (4, 10)	0·282

*Values are median (range); †values in parentheses are percentages; ‡values are median (95 per cent confidence interval). ASA, American Society of Anesthesiologists. §Fisher's exact test or χ^2 test for qualitative variables and Mann–Whitney *U* test for quantitative variables. ¶Resection *versus* palliative by pass; **palliative bypass *versus* exploration.

Table 4 Operative and histopathological findings, hospital stay and postoperative morbidity in patients undergoing resection

	Curative resection ($n = 160$)	Non-curative resection ($n = 51$)	P§
Operative findings			
Pancreatic head resection	126 (78·8)	39 (76)	0·208
Total pancreatectomy	15 (9·4)	2 (4)	0·163
Pancreatic left resection	19 (11·9)	10 (20)	0·718
Operating time (min)*	420 (180–780)	415 (180–750)	0·641
Blood loss (ml)*	1500 (300–22 000)	1500 (200–5000)	0·845
Transfusion (units of PRBCs)*	2 (0–38)	2 (0–17)	0·681
Tumour characteristics			
Diameter (cm)*	3 (1–8)	3 (2–6)	0·087
Vessel invasion	25 (15·6)	36 (71)	0·001
Positive lymph nodes	113 (70·6)	41 (80)	0·025
Well differentiated (G1)	21 (13·1)	7 (14)	0·029
Tumour stage (UICC)			
I	17 (10·6)	2 (4)	0·145
II	30 (18·8)	8 (16)	0·620
III	108 (67·5)	37 (73)	0·498
IV	5 (3·1)	4 (8)	0·147
ICU stay (days)*	2 (1–21)	2 (1–19)	0·471
Hospital stay (days)*	16 (4–118)	16 (7–65)	0·958
Postoperative morbidity			
Local complications†	52 (32·5)	15 (29)	0·680
Fistula			
Pancreatic	3 (1·9)	0 (0)	0·325
Other	1 (0·6)	0 (0)	0·254
Systemic complications‡	36 (22·5)	10 (20)	0·663
Relaparotomy	6 (3·8)	1 (2)	0·534
Deaths	4 (2·5)	2 (4)	0·595

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Delayed gastric emptying, bleeding, wound sepsis, abscess, other; ‡cardiopulmonary, renal, sepsis, neural, other. PRBC, packed red blood cells; UICC, Union Internacional Contra la Cancrum; ICU, intensive care unit. §Fisher's exact test or χ^2 test for qualitative variables and Mann–Whitney U test for quantitative variables.

characteristics are summarized in *Table 4*. The tumour was located in the pancreatic head in 175 patients who had pancreatic resection (82·9 per cent), in the body in 12 (5·7 per cent) and in the tail in 19 patients (9·0 per cent). In five patients (2·4 per cent) the whole gland was involved. There were 28 well differentiated (13·3 per cent), 143 moderately differentiated (67·8 per cent) and 40 poorly differentiated (19·0 per cent) tumours. In 51 patients (24·2 per cent), the resection was not considered curative; 31 of these patients underwent R2 resection (16 with infiltration of the superior mesenteric artery, five with infiltration of the coeliac trunk and ten with gross involvement of the portal or mesenteric vein) and 20 had R1 resection. Twenty-six patients underwent segmental resection of the portal vein (18 who had curative resection and eight non-curative resection).

According to the UICC classification system[19], stage I disease was present in 19 patients (9·0 per cent), stage II in 38 (18·0 per cent), stage III in 145 (68·7 per cent) and stage IV in nine patients (4·3 per cent). Mean tumour size was 3·1 cm and only 8·1 per cent of patients who underwent resection had a lesion larger than 4 cm. The overall cumulative morbidity rate after resection was 44·1 per cent. Complications were registered in 56 per cent of patients after total pancreatectomy, 52 per cent after classical Whipple resection, 40 per cent after pylorus-preserving Whipple resection and 16 per cent after left pancreatic resection. Delayed gastric emptying was the most frequent complication following pancreatoduodenectomy, and occurred in 24 per cent of patients. After resection there were three pancreatic fistulas (1·4 per cent) which resolved spontaneously and a biliary fistula that required reoperation (0·5 per cent). The incidence of septic complications after resection was 3·8 per cent (eight patients). Three intra-abdominal abscesses occurred which were drained interventionally. Reoperation was performed in seven patients (3·3 per cent); the most frequent indication for relaparotomy was postoperative haemorrhage (three patients). The mortality rate after resection was 2·8 per cent (six patients).

Patients who had portal vein resection had a significantly higher postoperative morbidity rate than those who did not (17 of 26 *versus* 76 of 185 patients; $P = 0·019$). There were significantly more bleeding complications (six of 26 *versus* three of 185; $P = 0·001$), more infections (nine of 26 *versus* 18 of 185; $P = 0·001$) and more cardiopulmonary complications (eight of 26 *versus* 22 of 185; $P = 0·042$). The postoperative mortality rate was increased after portal vein resection but this difference was not statistically significant (two of 26 *versus* four of 185; $P = 0·161$).

Eighty-three patients were recruited into the ESPAC-1 trial. Thirty-five of these were randomized to surgery only. Twenty patients received adjuvant chemotherapy, 14 underwent adjuvant radiotherapy and seven patients underwent combined chemoradiotherapy. Seven patients did not complete the adjuvant therapy for various reasons. Sixty-one patients (63 per cent) received palliative chemotherapy following bypass surgery. Median follow-up was 21 (range 6–96) months. The overall median survival time was 16·4 (95 per cent confidence interval 13 to 19) months after resection and 6·1 (95 per cent c.i. 5 to 7) months after bypass ($P = 0·001$) (*Fig. 1*). Median survival after exploration was 7·3 (95 per cent c.i. 4 to 10) months ($P = 0·282$ in comparison to bypass procedures).

Overall 1-, 3- and 5-year actuarial survival rates after resection were 67·1, 23·4 and 19·8 per cent respectively

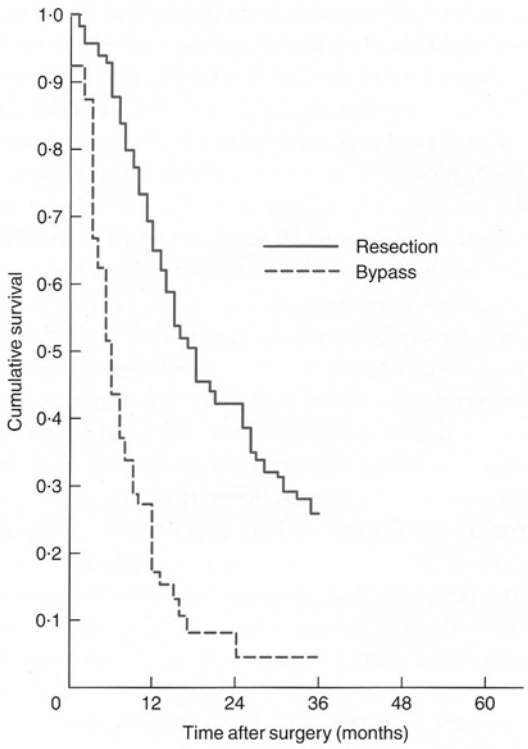

Fig. 1 Kaplan–Meier survival curves for patients who had palliative bypass surgery or pancreatic resection for pancreatic adenocarcinoma. $P < 0{\cdot}001$ (log rank test)

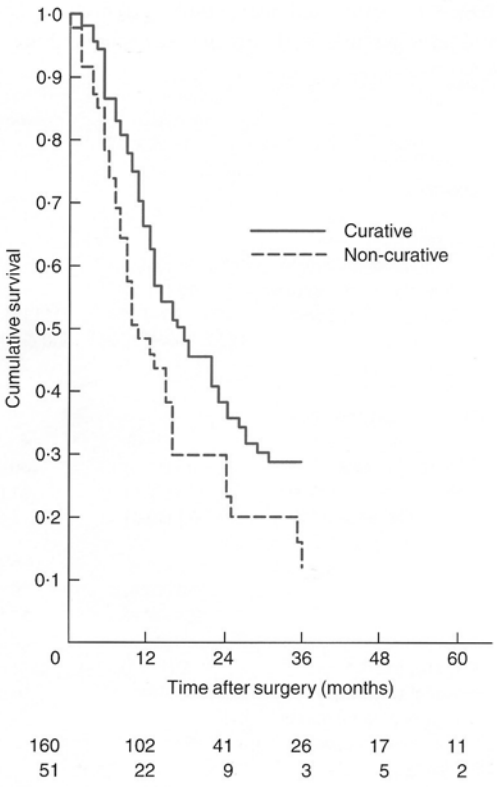

Fig. 2 Kaplan–Meier survival curves for patients who had curative or non-curative resection. $P < 0{\cdot}001$ (log rank test)

(*Fig. 2*). The actual 5-year survival rate was 16·5 per cent. Survival data related to R status are summarized in *Table 5*. For the whole group of 51 patients who had R+ resection, the 5-year survival rate was 4·3 per cent and the median survival time was 11·5 (95 per cent c.i. 9 to 13) months, compared with 24·2 per cent and 20·1 (95 per cent c.i. 14 to 26) months in those who had R0 resection ($P < 0{\cdot}001$).

In lymph node-negative patients, the 5-year actuarial survival rate was 31·6 per cent and median survival time was 26·2 (95 per cent c.i. 11 to 41) months, compared with 12·4 per cent and 16·1 (95 per cent c.i. 12 to 18) months in patients with lymph node involvement ($P = 0{\cdot}007$) (*Fig. 3*). Although lymph node-negative patients had a better overall survival, there was a wide range in survival in these patients (4–90 months). There was a similar wide range in patients with lymph node involvement (range 2–96 months). Survival correlated less strongly with tumour stage according to the UICC staging system; the median survival time was 26·1 (95 per cent c.i. 9 to 43) months for patients with stage I disease, 21·2 (95 per cent c.i. 1 to 41) months for those with stage II tumours and 15·5 (95 per cent c.i. 12 to 18) months for patients with stage III disease ($P = 0{\cdot}094$). The results of the univariate analysis of factors potentially influencing survival are shown in *Table 6*.

Table 5 Survival after resection in 211 patients with pancreatic adenocarcinoma

	No. of patients*	Median survival (months)†	*P*‡
R0 resection	160 (75·8)	20·1 (14, 26)	
R1 resection	20 (9·5)	15·3 (10, 20)	0·574
R2 resection	31 (14·7)	9·8 (8, 12)	0·001

Values in parentheses are *percentages or †95 per cent confidence intervals. Survival analysis was performed by the Kaplan–Meier method; ‡*versus* R0 (log rank test).

The actuarial survival of patients recruited in the ESPAC-1 trial was similar to that of patients who were not included (median survival 16·4 months (95 per cent c.i. 13 to 19) *versus* 20·1 (95 per cent c.i. 11 to 29) months). No survival benefit was noted for patients who received either adjuvant chemotherapy or radiotherapy or the combined regimen according to the ESPAC-1 protocol (median

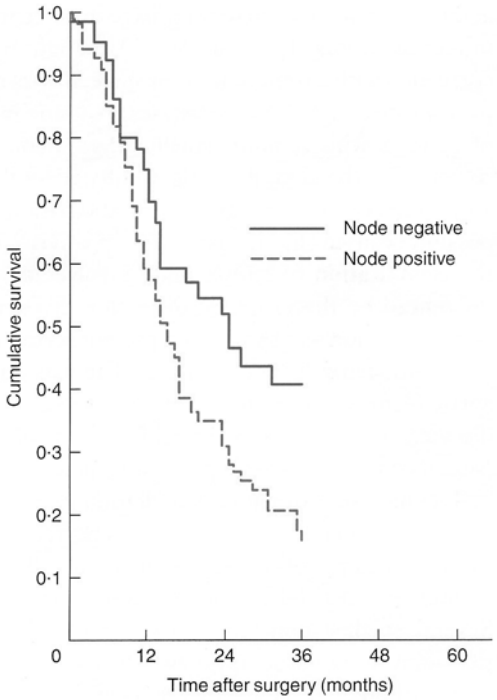

Fig. 3 Kaplan–Meier survival curves for patients with pancreatic adenocarcinoma who had positive or negative lymph nodes. $P = 0{\cdot}007$ (log rank test)

survival 14·9 (95 per cent c.i. 11 to 19) months compared with 18·1 (95 per cent c.i. 13 to 23) months in those who had no adjuvant treatment; $P = 0{\cdot}888$). Adjuvant chemotherapy according to the ESPAC-1 protocol had no influence on patient survival (median survival 18·8 (95 per cent c.i. 7 to 31) months compared with 18·2 (95 per cent c.i. 14 to 22) months in those who had no adjuvant chemotherapy; $P = 0{\cdot}531$).

Non-curative resection, lymph node involvement, nerve and vascular infiltration, and prolonged hospital stay were associated with shortened survival (*Table 6*). Multivariate analysis using a stepwise Cox regression model identified only curative resection as a significant independent determinant of long-term survival ($P = 0{\cdot}002$) (*Table 7*).

Discussion

Pancreatic adenocarcinoma is one of the most aggressive human malignancies. It is generally resistant to most cytotoxic agents and radiotherapy. Surgical resection remains the only potentially curative treatment. The high perioperative mortality rate and poor long-term survival[20–22] traditionally associated with resection have given way more recently to a perioperative mortality rate of less than 5 per cent and a 5-year survival rate of more than 10 per cent in experienced centres[3,23,24].

Comparing the present long-term results and those of other recent studies from high-volume centres, there are considerable differences in 5-year survival rate after pancreatic resection, ranging from 6·8 to 25 per cent in Western institutions; even higher survival rates have

Table 6 Potential risk factors affecting survival following resection in 211 patients with pancreatic adenocarcinoma

Variable	Subcategories	P^*
Sex	M, F	0·854
Age (years)	≤ 70, > 70	0·101
Weight loss > 10%	Yes, no	0·309
Duration of symptoms (weeks)	≤ 5, > 5	0·878
ASA grade	≤ 2, > 2	0·691
Bilirubin > 100 μmol/l	Yes, no	0·331
Diabetes mellitus	Yes, no	0·539
COPD	Yes, no	0·885
Cardiac history	Yes, no	0·187
Haemoglobin level	Normal, abnormal	0·394
Creatinine > 150 μmol/l	Yes, no	0·112
Vein resection	Yes, no	0·106
Curative resection	Yes, no	0·001
Operating time (h)	≤ 7, > 7	0·236
Transfusion (units)	≤ 2, > 2	0·610
Tumour diameter	≤ 3, > 3	0·232
Tumour localization	Head, distal	0·627
Tumour staging	UICC classification	0·147
Blood vessel infiltration	Yes, no	0·028
Lymphatic invasion	Yes, no	0·241
Neural invasion	Yes, no	0·037
Peripancreatic invasion	Yes, no	0·230
Lymph nodes	Positive, negative	0·025
Tumour differentiation	Well, poor	0·150
Postoperative hospital stay (days)	≤ 17, > 17	0·017
ICU stay (days)	≤ 2, > 2	0·188
Reoperation	Yes, no	0·058
Complications	Yes, no	0·288
Adjuvant therapy	Yes, no	0·994

COPD, chronic obstructive pulmonary disease; UICC, Union Internacional Contra la Cancrum; ICU, intensive care unit. Survival analysis was performed by the Kaplan–Meier method. *Log rank test.

Table 7 Significant factors affecting survival after resection for pancreatic adenocarcinoma in 211 patients by multivariate analysis using Cox's proportional hazard model

	β coefficient	Standard error	Hazard ratio	P
Curative resection	−0·678	0·214	0·51 (0·34, 0·78)	0·002

Values in parentheses are 95 per cent confidence intervals.

been obtained in Japanese studies[2,3,21,25–29]. Although it is difficult to compare the Japanese staging system with the classification used in Western countries (American Joint Committee on Cancer or UICC), large retrospective Japanese studies have not reported better overall survival rates than those from Western institutions following resection for pancreatic cancer[9]. Many factors might contribute to differences in survival. Variations in patient selection, retrospective studies, and patient accrual over a long time frame with changes in tumour staging methods and operative techniques are all confounding factors. Some studies do not distinguish between curative resection and procedures with gross or microscopically involved resection margins, which further limits their comparability. Moreover, actuarial survival is a postulated number based on the Kaplan–Meier curve, which is influenced by the mean follow-up period and the mortality rate per time increment. In contrast, actual 5-year survival is rarely published and is significantly lower than actuarial 5-year rates. A review of 15 recent series representing 2075 resections revealed an actual 5-year survival rate of only 4 per cent[30], which is identical to that in the historical review of Gudjonsson in 1987[20]. In the present series, the actual 5-year survival rate was 16·5 per cent following resection for pancreatic adenocarcinoma.

Certain subgroups of patients have a considerably better prognosis. Previous reports have identified lymph node involvement, tumour size and status of the resection margin as the strongest prognostic factors[27,29–32]. The combination of tumour size less than 2 cm and negative lymph nodes was associated with better long-term outcome in several studies, although this subgroup represents a small minority of patients with pancreatic cancer. In the present series, 27·0 per cent of patients had UICC stage I or II disease, a greater proportion than in other large series. Multivariate regression analysis failed to recognize tumour size, stage or lymph node involvement as independent prognostic factors. Only curative surgery (microscopically negative resection margins and no gross tumour mass remaining) proved to be an independent predictor of survival. There may be a number of reasons for this. The referral policy has a strong influence on the surgical patient population. The mean tumour size was 3·1 cm and only 8·1 per cent of patients who underwent resection had a neoplasm larger than 4 cm, as opposed to other recent series in which tumour size was greater than 4 cm in up to 32 per cent of patients[29,33]. The experience from the Johns Hopkins' group is comparable to that of the present authors, with a mean tumour size of 3 cm and 36 per cent of patients harbouring tumours smaller than 2 cm[4], suggesting that the percentage of patients treated at an earlier stage is increasing in referral centres, with an influence on long-term outcome. Although tumour size is correlated with advanced tumour stage, it is recognized that para-aortic lymph node metastases are found in 40 per cent of patients with tumours smaller than 2 cm. One of the reasons for the disappointing results is local recurrence around the coeliac axis, mesenteric and para-aortal region, possibly caused by lymph node involvement[34]. Thus, the classification of lymph node involvement is strongly influenced by the extent of dissection. Systematic lymph node dissection was used in the present series; nodes at the hepatoduodenal ligament, the coeliac axis and the para-aortic regions were removed from patients with resectable disease. This increases the likelihood of designating patients correctly as node positive or node negative.

The inclusion of patients undergoing adjuvant therapy merits comment. The GITSG reported a significant survival benefit following treatment of 40 Gy radiation combined with 5-FU therapy following resection[13,14]. Several smaller non-randomized studies have indicated that adjuvant radiotherapy may reduce the local recurrence rate, although a large randomized trial organized by the EORTC did not detect improved local control or a survival advantage[10,15,35,36]. The large European ESPAC trial, which compared external beam radiotherapy (EBRT) of 40 Gy (plus 5-FU) with systemic follow-on chemotherapy (folinic acid followed by 5-FU for 6 months) and a combination of these treatments with a control group, did not detect a beneficial effect for adjuvant radiotherapy or combined treatment[16]. There was, however, a significant survival advantage following adjuvant chemotherapy (median survival 19·7 months in 238 patients who had chemotherapy *versus* 14 months in 235 patients without; $P < 0{\cdot}001$). As the results of the published studies regarding the value of adjuvant treatment seem contradictory, patients who received adjuvant therapy, including those recruited to the ESPAC-1 trial, were included in the present survival analysis. Adjuvant therapy showed no survival benefit overall or when subgroups of patients receiving adjuvant chemotherapy or radiotherapy were compared individually. It therefore seemed appropriate to include such patients in the multivariate regression analysis of risk factors influencing survival.

This prospective audit of a large consecutive and recent series of patients with pancreatic adenocarcinoma demonstrated a strong association between curative surgery and long-term survival. This was the only independent prognostic factor in multivariate analysis. Curative resection still forms the core of successful therapy for patients with pancreatic cancer. Future studies should

address the challenge of earlier diagnosis and establish the role of extended lymph node dissection and adjuvant treatments to improve further the outcome after resection of pancreatic cancer.

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