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ORIGINAL ARTICLE

Longterm survival after pancreaticoduodenectomy for periampullary adenocarcinomas

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Abstract

Objectives: The aim of this study was to identify predictors for longterm survival following pancreaticoduodenectomy (PD) for pancreatic and other periampullary adenocarcinomas.

Methods: Clinicopathological factors were compared between short-term (<5 years) and longterm (≥5 years) survival groups. Rates of actual 5-year and actuarial 10-year survival were determined.

Results: There were 109 (21.8%) longterm survivors among a sample of 501 patients. Patients with ampullary adenocarcinoma represented 76.1% of the longterm survivors. Favourable factors for longterm survival included female gender, lack of jaundice, lower blood loss, classical PD, absence of postoperative bleeding or intra-abdominal abscess, non-pancreatic primary cancer, earlier tumour stage, smaller tumour size (≤2 cm), curative resection, negative lymph node involvement, well-differentiated tumours, and absence of perineural invasion. Independent factors associated with longterm survival were diagnosis of primary tumour, jaundice, intra-abdominal abscess, tumour stage, tumour size, radicality, lymph node status and cell differentiation. The prognosis was best for ampullary adenocarcinoma, for which the rate of actual 5-year survival was 32.8%, and poorest for pancreatic head adenocarcinoma, for which actual 5-year survival was only 6.5%.

Conclusions: The majority of longterm survivors after PD for periampullary adenocarcinomas are patients with ampullary adenocarcinoma. The longterm prognosis in pancreatic head adenocarcinoma remains dismal.

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Introduction

Pancreaticoduodenectomy (PD) is the treatment of choice for periampullary adenocarcinomas. An increase in experience and advances in perioperative care have reduced perioperative mortality following PD to <5% in high-volume centres.[1–7] Only 10–15% of patients presenting with pancreatic adenocarcinoma are technically resectable[8,9] and for those who do undergo resection, the prognosis remains poor, with median survival of 11–19 months.[1,8–26] Even the addition of adjuvant therapies has resulted in only modest improvements in survival. Several studies have reported on actual longterm survival beyond 5 years in patients subjected to resection for pancreatic or other periampullary cancers.[1,10–19,26–29] Clinical factors, such as lymph node metastasis, tumour size and resection margin, have been comprehensively studied with respect to determining short-term survival after PD for pancreatic and other periampullary cancers.[11,13,19,27,30] However, prognostic factors that may predict longterm survival are poorly understood.

The purpose of this study was to identify the predictors of longterm survival (≥5 years) in patients with pancreatic and other periampullary adenocarcinomas after PD. In addition, actual 5-year and actuarial 10-year survival rates in all patients with periampullary adenocarcinomas after PD were determined.

Materials and methods

Data for patients with pancreatic or other periampullary adenocarcinomas who underwent PD between 1974 and 2006 were

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Table 1 Demographics of patients with periampullary adenocarcinomas submitted to pancreaticoduodenectomy

Variable	Total	Survival <5 years	Survival ≥5 years	*P*-value
Patients, *n* (%)	501 (100%)	392 (78.2%)	109 (21.8%)	
Gender, *n* (%)				<0.001
Male	368 (73.5%)	303 (77.3%)	65 (59.6%)	
Female	133 (26.5%)	89 (22.7%)	44 (40.4%)	
Age, years				0.201
Median (range)	67 (25–89)	67 (25–89)	65 (34–89)	
Mean ± SD	64.6 ± 11.4	65.0 ± 11.4	63.4 ± 11.5	
Diagnosis of primary tumour, *n* (%)				<0.001
Pancreatic head	169	158 (93.5%)	11 (6.5%)	
Ampullary	253	170 (67.2%)	83 (32.8%)	
Distal CBD	52	42 (80.8%)	10 (19.2%)	
Duodenal	27	22 (81.5%)	5 (18.5%)	
Duration of symptoms, months, median (range)	1 (0–120)	1 (0–120)	1 (0–24)	0.514
Symptoms, *n* (%)				
No symptoms	9 (1.8%)	7 (1.8%)	2 (1.8%)	1.000
Jaundice	393 (78.4%)	320 (81.6%)	73 (67.3%)	0.002
Epigastric pain	219 (43.7%)	165 (42.1%)	54 (49.5%)	0.190
Body weight loss	177 (35.3%)	136 (34.7%)	41 (37.6%)	0.573
Nausea/vomiting	56 (11.2%)	46 (11.2%)	10 (9.3%)	0.606
Diabetes mellitus	77 (8.3%)	68 (17.3%)	9 (8.3%)	0.023
Serum CA 19-9, U/ml, median (range)	73 (0–18 545)	92 (0–18 545)	36 (2–12 000)	0.207
Serum CEA, ng/ml, median (range)	4 (1–143)	4 (1–143)	4 (1–19)	0.205
Chemotherapy, *n* (%)				0.204
No	275 (56.8%)	219 (57.9%)	56 (52.8%)	
Yes	209 (43.2%)	159 (42.1%)	50 (47.2%)	
Radiotherapy, *n* (%)				0.158
No	278 (57.6%)	222 (58.9%)	56 (52.8%)	
Yes	205 (42.4%)	155 (41.1%)	50 (47.2%)	

SD, standard deviation; CBD, common bile duct; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

retrieved from a prospectively collected database for pancreatic surgery. Data for patients with other malignancies, such as intraductal papillary mucinous neoplasms, mucinous cystadenocarcinoma, acinar cell carcinoma, solid pseudopapillary neoplasms and neuroendocrine carcinoma, were excluded from the analysis.

The number of surgeons who performed at least one PD during the study period was 26. Five surgeons each performed ≥15 PDs and 65.3% of all PDs were performed by two high-volume surgeons, each of whom performed ≥15 PDs per year. A standard resection without extensive retroperitoneal lymph node dissection was performed. The decision on whether the procedure should consist of a classical PD or a pylorus-preserving resection was left to the discretion of the operating surgeon. A pancreaticogastrostomy or pancreaticojejunostomy was used for pancreaticoenteric reconstruction. Curative resection was defined as a PD without evidence of any residual cancer at the resection margins, including the pancreatic neck and distal common bile duct (CBD) cut-ends, retroperitoneal margin, and superior mesenteric and portal vein grooves. A palliative resection was defined as including either gross or microscopic evidence of cancer at the resection margin. The definition of primary tumour origin was mainly based on pathological findings; however, image studies and gross findings were also taken into consideration for primary tumour origin when pathological determination was unclear. Postoperatively, patients were followed at 6-month intervals for ≥5 years or until death. Patients with operative mortality were included in this study. Patient who died from causes other than cancer were also included, but their data were censored for survival analysis.

Based on survival time, patients were stratified into two groups consisting of, respectively, short-term (<5 years) and longterm (≥5 years) survivors. Patient demographics, the pathological characteristics of tumours, surgical factors and risk factors were compared between these two groups. Actual 5-year survival in all

Table 2 Surgical factors and risks in pancreaticoduodenectomy (PD)

	Total	Survival <5 years	Survival ≥5 years	*P*-value
Operation time, h				0.161
Median (range)	7.5 (3.5–16)	7.5 (3.5–16)	8.5 (4.0–14)	
Mean ± SD	8.0 ± 2.3	7.8 ± 2.4	8.3 ± 2.0	
Surgeon volume, *n* (%)				0.294
High (≥15 PD/year)	406 (81.2%)	315 (80.6%)	91 (83.5%)	
Low (<15 PD/year)	94 (8.8%)	76 (19.4%)	18 (16.5%)	
Blood loss, ml				0.005
Median (range)	800 (50–5250)	800 (50–5250)	575 (100–2950)	
Mean ± SD	903 ± 618	954 ± 639	709 ± 487	
Pylorus-preserving PD, *n* (%)				0.048
No	288 (57.5%)	216 (55.1%)	72 (66.1%)	
Yes	213 (42.5%)	176 (44.9%)	37 (33.9%)	
Postoperative hospital stay, days, median (range)	26.0 (1–383)	26.0 (1–383)	26.5 (5–87)	0.531
Surgical morbidity, overall, *n* (%)	225 (44.9%)	174 (44.4%)	11 (10.1%)	0.665
Pancreatic leakage, *n* (%)	55 (11.10%)	44 (11.2%)	11 (10.1%)	0.863
Gastric atonia, *n* (%)	52 (10.3%)	40 (10.2%)	12 (11.0%)	0.859
Post-PD bleeding, *n* (%)	53 (10.6%)	49 (12.5%)	4 (3.7%)	0.007
Intraluminal post-PD bleeding, *n* (%)	31 (6.2%)	30 (7.7%)	1 (0.9%)	0.006
Extraluminal post-PD bleeding, *n* (%)	32 (6.4%)	28 (7.1%)	4 (3.7%)	0.267
Intra-abdominal abscess, *n* (%)	55 (11.0%)	35 (8.9%)	20 (18.3%)	0.009
Wound infection, *n* (%)	54 (10.8%)	39 (9.9%)	15 (13.8%)	0.294

SD, standard deviation.

patients with pancreatic and other periampullary adenocarcinomas after PD was determined. For patients who survived 5 years, actuarial 10-year survival was calculated.

PASW Statistics Version 18 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. All continuous data were expressed as the mean ± standard deviation (SD) or as the median (range), as appropriate. Comparisons of data between the primary groups were performed using a Student's *t*-test or Wilcoxon rank sum test, as appropriate, for continuous variables. Categorical variables were compared using a chi-squared or Fisher's exact test. *P*-values were derived from two-tailed tests. Survival was calculated following PD. Using the binary logistic regression model for all factors with a *P*-value of <0.2 after univariate analysis, multivariate analysis was performed to identify independent predictors of longterm survival of ≥5 years after PD. Cumulative survival was estimated using the Kaplan–Meier method and differences between subgroups were determined using a log-rank test. A *P*-value of <0.05 was considered to indicate statistical significance.

Results

A total of 501 patients with periampullary adenocarcinomas underwent PD during the study period. Of these, 109 (21.8%) were longterm survivors (≥5 years) and 392 (78.2%) were short-term survivors (<5 years). Among the 109 longterm survivors, 83 (76.1%) were operated for ampullary adenocarcinoma, 11 (10.1%) for pancreatic head adenocarcinoma, 10 (9.2%) for distal CBD adenocarcinoma, and five (4.6%) for duodenal adenocarcinoma. Univariate analyses of various factors associated with survival status are shown in Tables 1–3. Following multivariate analysis with a binary logistic regression model, diagnosis of the primary tumour, jaundice, intra-abdominal abscess, tumour stage, tumour size, radicality, lymph node status and cell differentiation were found to be independent predictors of longterm survival after PD (Table 4).

Of the 392 (78.2%) patients who died within 5 years of PD, 378 (96.4%) died as a result of recurrent disease. Fourteen (3.6%) patients were lost to follow-up. Patients with ampullary adenocarcinoma (32.8%) showed the highest actual 5-year survival rate, followed by those with distal CBD adenocarcinoma (19.2%) and duodenal adenocarcinoma (18.5%). The lowest actual 5-year survival was found in patients with pancreatic head adenocarcinoma (6.5%). Overall actual 5-year survival in patients with periampullary adenocarcinomas was 21.8% (109 patients were alive). The median length of survival was 21.0 months across all patients, 13.7 months in patients with pancreatic head adenocarcinoma, 28.9 months in those with ampullary

Table 3 Pathological parameters in patients with periampullary adenocarcinomas undergoing pancreaticoduodenectomy

	Total	Survival <5 years	Survival ≥5 years	*P*-value
Stage, *n* (%)				0.003
0	15 (3.0%)	10 (2.6%)	5 (4.6%)	
I	84 (16.8%)	56 (14.3%)	28 (25.7%)	
II	279 (55.7%)	217 (55.4%)	62 (56.9%)	
III	92 (18.4%)	83 (21.2%)	9 (8.3%)	
IV	31 (6.2%)	26 (6.6%)	5 (4.6%)	
Stage, *n* (%)				0.001
0 + I + II	387 (75.4%)	283 (72.2%)	95 (87.2%)	
III + IV	123 (24.6%)	109 (27.8%)	14 (12.8%)	
Tumour size, *n* (%)				0.006
≤2 cm	218 (43.5%)	158 (40.3%)	60 (55.0%)	
>2 cm	283 (56.5%)	234 (59.7%)	49 (45.0%)	
Tumour size, cm				0.020
Median (range)	2.5 (0.4–15)	2.5 (0.5–15)	2.0 (0.4–8)	
Mean ± SD	2.8 ± 1.6	2.9 ± 1.6	2.5 ± 1.4	
Radicality, *n* (%)				<0.001
Curative	422 (84.2%)	317 (80.9%)	105 (96.3%)	
Palliative	79 (15.8%)	75 (19.1%)	4 (3.7%)	
Lymph node involvement, *n* (%)				<0.001
Negative	302 (60.7%)	211 (53.8%)	93 (85.3%)	
Positive	197 (39.3%)	181 (46.2%)	16 (14.7%)	
Cell differentiation, *n* (%)				0.001
Good	61 (13.2%)	40 (11.0%)	21 (21.4%)	
Moderate	330 (71.6%)	259 (71.3%)	71 (72.4%)	
Poor	70 (15.2%)	64 (17.6%)	6 (6.1%)	
Perineural invasion, *n* (%)				<0.001
Negative	235 (62.0%)	176 (57.5%)	59 (80.8%)	
Positive	144 (38.0%)	130 (42.5%)	14 (19.2%)	
Lymphovascular invasion, *n* (%)				0.678
Negative	254 (67.0%)	203 (66.3%)	51 (69.9%)	
Positive	125 (33.0%)	103 (33.7%)	22 (30.1%)	

SD, standard deviation.

adenocarcinoma, 24.4 months in those with distal CBD adenocarcinoma, and 21.7 months in those with duodenal adenocarcinoma. Figure 1 shows actuarial survival curves for individual histological subtypes following PD.

Of the 109 actual 5-year survivors, 56 (51.4%) were alive at 10 years. A total of 24 (22.0%) 5-year survivors had died, 22 of them as a result of the disease process. Actuarial 10-year survival in actual 5-year longterm survivors according to histological subtype is shown in Table 5.

Discussion

Pancreaticoduodenectomy was previously abandoned by nihilistic surgeons confronted with patients diagnosed with periampullary adenocarcinomas because of the high surgical risk associated with the procedure and dismal survival outcomes, especially as pancreatic primary cancers were regarded as lethal.[10,17,31] However, decreasing perioperative mortality and encouraging improvements in survival since the 1990s have allowed PD to become the standard of care for patients with resectable periampullary adenocarcinomas.[8,10–17] Prognoses in periampullary adenocarcinomas vary and depend on the origin of the primary tumour. Patients with pancreatic head adenocarcinoma have the worst prognosis, with 5-year survival of 5–20% after resection.[9,11,19–32] Prognosis is better in ampullary adenocarcinoma, in which 5-year survival is 30–40%,[10,23,33–35] and duodenal adenocarcinoma, in which 5-year survival is 50–65%.[10,23,36] Furthermore, 5-year survival in distal CBD adenocarcinoma is approximately 20–30%.[10,33]

Table 4 Independent predictors of longterm survival [≥5 years after pancreaticoduodenectomy (PD)] by multivariate analysis in a binary logistic regression model

	Odds ratio	95% CI	*P*-value
Gender	1.015	0.348–2.965	0.798
Diagnosis of primary tumour (pancreatic versus non-pancreatic)	2.318	0.541–9.935	0.002
Jaundice	0.828	0.730–0.938	0.002
Epigastric pain	1.107	0.362–3.386	0.798
Diabetes mellitus	0.967	0.871–1.072	0.545
Radiotherapy	0.734	0.214–2.516	0.403
Operation time (<7.5 h versus ≥7.5 h)	1.039	0.266–4.053	0.312
Blood loss (<800 ml versus ≥800 ml)	0.522	0.180–1.511	0.136
Pylorus-preserving PD	1.673	0.435–6.438	0.415
Post-PD bleeding	1.200	0.178–8.106	0.907
Intra-abdominal abscess	1.257	0.869–1.817	0.003
Stage (I + II versus III + IV)	1.602	0.383–6.708	0.780
Tumour size (≤2.0 cm versus >2.0 cm)	0.384	0.127–1.162	0.006
Radicality (curative versus palliative)	0.500	0.072–3.496	0.015
Lymph node involvement	0.339	0.096–1.196	0.021
Cell differentiation (good + moderate versus poor)	0.000	0.000–1.265	0.028
Perineural invasion	1.177	0.817–1.695	0.085

95% CI, 95% confidence interval.

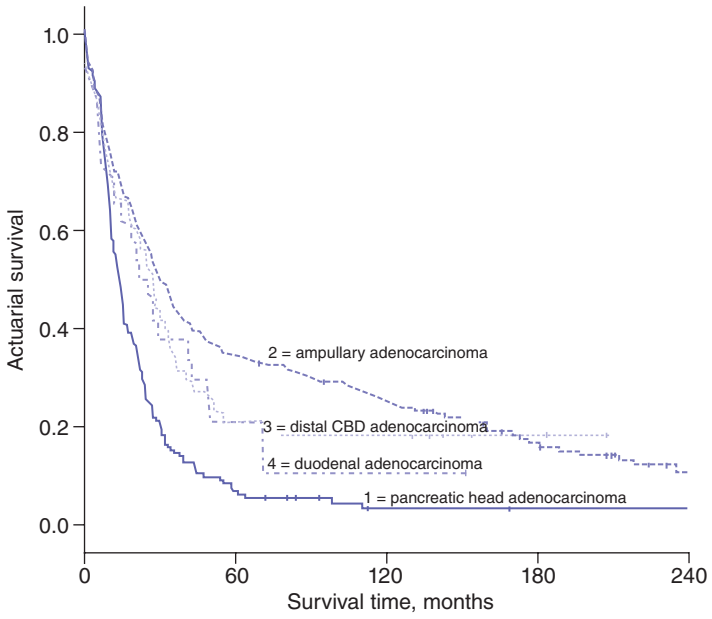
Table 5 Data for 10-year survival in longterm survivors (survival ≥5 years) of periampullary adenocarcinomas after pancreaticoduodenectomy

	Survival, months, median (range)	Actuarial 10-year survival	Patients alive, *n*
Periampullary adenocarcinomas (*n* = 109)	137.3 (60.8–341.1)	73.2%	56
Pancreatic head adenocarcinoma (*n* = 11)	112.5 (60.8–293.7)	49.1%	2
Ampullary adenocarcinoma (*n* = 83)	143.9 (62.4–341.1)	74.4%	46
Distal CBD adenocarcinoma (*n* = 10)	137.1 (62.0–208.1)	87.5%	7
Duodenal adenocarcinoma (*n* = 5)	84.4 (60.8–341.1)	50.0%	1

CBD, common bile duct.

Most of the 5-year survival rates reported in the literature are actuarial and represent estimates of 5-year survival after resection. In fact, few studies on periampullary adenocarcinomas report actual 5-year survival figures. It has been suggested that actuarial 5-year survival estimates may be higher than actual 5-year survival rates.[13,24] The current study reports actual 5-year survival in a large group of patients with a variety of periampullary adenocarcinomas, which enables a subgroup analysis. This confirms that a worse prognosis is associated with pancreatic head adenocarcinoma compared with the other disease subgroups. Because the numbers of patients surviving to 10 years is low, it was not possible to compare 10-year actuarial survival among patients with pancreatic head, distal CBD and duodenal adenocarcinomas by histological subgroup. However, patients with ampullary adenocarcinoma who survived to 5 years were found to have a 74.4% probability of surviving to 10 years, with the most likely cause of death being the disease process itself.

The clinicopathological characteristics contributing to longterm survival (i.e. ≥5 years) remain controversial.[12,13,29] Pathologic factors have been proposed as the most important prognostic indicators of longterm survival, and include non-pancreatic primary cancers, negative lymph node status, a low number of positive lymph nodes, smaller tumour size, curative resection, well-differentiated tumours, and no invasion of the extrapancreatic nerve plexus.[10–16,19,26,27,29,30] Surgical factors, such as curative resection with negative margins, that lack postoperative complications are independent variables that are significantly associated with longterm survival.[16,29] In the current study, many of these factors seemed to be important on univariate analysis. However, only primary tumour diagnosis, jaundice, intra-abdominal abscess, tumour stage, tumour size, radicality, lymph



Survival time	0 year	5 years	10 years	15 years	20 years
Number at risk					
Pancreatic head	169	12	8	8	8
Ampullary	253	88	70	57	51
Common bile duct	52	13	12	11	11
Duodenal	27	7	6	6	6

Figure 1 Actuarial survival following pancreaticoduodenectomy for periampullary adenocarcinomas in patients with (1) pancreatic head adenocarcinoma ($n = 169$), (2) ampullary adenocarcinoma ($n = 253$), (3) distal common bile duct (CBD) adenocarcinoma ($n = 52$) and (4) duodenal adenocarcinoma ($n = 27$). Subgroup comparisons showed: (1) versus (2), $P = 0.000$; (1) versus (3), $P = 0.001$; (1) versus (4), $P = 0.028$; (2) versus (3), $P = 0.352$; (2) versus (4), $P = 0.202$, and (3) versus (4), $P = 0.779$

node status and cell differentiation remained as independent factors associated with longterm survival. Some investigators have reported that patients with more advanced stages of cancer (i.e. a large tumour size and/or lymph node metastasis) can be cured by surgical resection.[12,13] This suggests that poor prognostic factors, such as large tumour size or lymph node metastasis, do not necessarily preclude an actual 5-year survival, and therefore active surgical resection with curative intent should be attempted in all patients with resectable disease.[12,13] Chemotherapy is currently the standard of care for pancreatic cancer. However, only 43.2% of patients in the present study received chemotherapy. This may partially explain why actual survival in this study was found to be lower than actuarial survival reported in the literature.

In summary, of patients submitted to PD, most longterm survivors are those with ampullary adenocarcinoma. Actual 5-year survival in patients with pancreatic ductal adenocarcinoma is 6.5%. This would appear to be significantly lower than reported actuarial 5-year survival figures. Independent factors associated with longterm survival were primary tumour diagnosis, jaundice, intra-abdominal abscess, tumour stage, tumour size, radicality, lymph node status and cell differentiation.

Conflicts of interest

None declared.

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