

Pancreatico-duodenectomy: 5-year experience

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Abstract

Background: Pancreatico-duodenectomy is the only potentially curative treatment of pancreatic cancer and is considered one of the most technically demanding and challenging procedures. Survival after surgery of pancreatic cancer is still poor.

Aim of the study: was to estimate the resectability rate of pancreatic and periampullary tumors presenting with jaundice and to assess the outcome of tumors treated by pancreatico-duodenectomy.

Patients and methods: Throughout a 5-year period from 2006 to 2011, 378 patients presented with tumors involving the head of pancreas or periampullary region. Pancreatico-duodenectomy was performed for 65 (17.2%) patients with resectable tumors. Follow up was done for 3 years. Univariate and multivariate analyses were done for factors affecting the postoperative survival.

Results: Resectability was feasible in 17.2% of patients. After pancreatico-duodenectomy, complications occurred in 32.3% of patients. Pylorus preservation did not affect the rate of complications. The 1-, 2- and 3-year survival rates were 64.6%, 43.1% and 35.4% respectively. Survival more than 3 years was significantly related to tumor diameter up to 3cm, free resection margin, absence of lymph nodes involvement, well differentiation of the tumors and periampullary tumors. By multivariate regression analysis, tumor diameter not exceeding 3cm and absence of lymph nodes involvement were found to be the most predictive factors correlated to survival more than 3 years.

Conclusion: The malignant pancreatic tumors have a low resectability rate. Most of pancreatic tumors present in late stages. Tumors not exceeding 3cm in diameter and absence of lymph nodes involvement were predictive of probable 3 year survival.

Key words: Pancreatic carcinoma, jaundice, resectability, surgical outcome.

Introduction:

Pancreatic cancer is one of the most lethal human tumors and is currently the fifth leading cause of cancer death for men and the sixth for women. Ductal pancreatic adenocarcinoma is the most common pathological type (90% of pancreatic cancer) and is one of the most aggressive human malignancies^{1,2}.

Pancreatico-duodenectomy (PD) is the only potentially curative treatment of pancreatic cancer and is considered one of the most technically demanding and challenging procedures. Although there has been constant progress in surgical techniques and advances in perioperative care with a modern interdisciplinary approach, prognosis is still life-threatening even after curative resection.^{3,4} The aim of this study was to estimate the

resectability rate of pancreatic and periampullary tumors presenting with jaundice and to assess the outcome of the tumors treated by pancreaticoduodenectomy.

Patients and methods:

This study was approved by the Committee of Ethics in Faculty of Medicine, University of Alexandria. This study was performed from March 2006 to October 2011.

Three hundred and seventy eight consecutive patients with obstructive jaundice due to mass in the pancreatic head or periampullary region were studied prospectively. The studied patients were subjected to detailed medical history, full clinical examination and laboratory investigations including liver function tests

and tumor markers (CA 19-9 and carcinoembryonic antigen). Imaging included abdominal ultrasonography, abdominal CT and cholangiography for all patients. ERCP was performed for 302 (79.9%) patients and MRCP for 120 (31.7%) patients. Both ERCP and MRCP were performed for 44 (11.6%) patients. Preoperative endoscopic stents were inserted in 26 (6.8%) patients, with serum bilirubin > 20mg/dl, to alleviate the jaundice and improve the patient fitness.

The data obtained by the previous workup were used for preoperative assessment of the patients. Diagnostic laparoscopy was performed for 9 patients with suspicious resectability.

Pylorus preserving pancreaticoduodenectomy was performed for 19 patients while conventional pancreaticoduodenectomy was performed for 46 patients according to the preference of the surgeon. Pancreatico-jejunal anastomosis by duct to mucosa method was the preferred technique. Dunking method was used for patients with small caliber of pancreatic duct and soft pancreas. Postoperative histopathological examination was done for excised specimens.

Postoperative follow up was done every 3 months. This included clinical assessment, liver function tests, tumor markers, abdominal ultrasonography and CT.

Statistics:

Data are presented, when appropriate, as median and percentage. The Fisher's exact and chi-squared tests were performed for univariate analyses of categorical values. Logistic regression was performed for multivariate model with P values and 95% confidence intervals estimated by the Wald method. A value of $p < 0.05$ was considered statistically significant. All data analyses were performed with the Statistical Package for the Social Sciences version 18 software (SPSS, Inc., Chicago, IL).

Results:

The studied patients were 228 (60.3%) males and 150 (39.7%) females. Their median age was 56 years. Their clinical presentations included jaundice in 378 (100%) patients, dyspepsia in 320 (84.6%) patients, abdominal

pain in 356 (94.2%) patients, weight loss in 312 (82.5%) patients and abdominal mass (palpable liver or gall bladder) in 108 (28.5%) patients. The laboratory workup showed anemia (less than 70% of normal) in 66 (17.5%) patients, elevated serum bilirubin in 378 (100%) patients with a median of 10.51mg/dl, elevated tumor markers: CA 19-9 and/or carcinoembryonic antigen (CEA) in 301(79.6%) patients. The abdominal ultrasonography showed the presence of pancreatic mass in 263 (69.6%) patients, dilated biliary tract in 375 (99.2%) patients and ascites in 24 (6.3%) patients. Advanced unresectable tumors could be diagnosed by ultrasonography in 85(22.5%) patients who showed liver metastases or ascites. Abdominal CT revealed pancreatic head tumor in 352 (93.1%) patients and periampullary tumor in 26 (6.9%) patients, vascular invasion of major vessels (superior mesenteric vessels or portal vein) in 223(59%) patients, enlarged peri-pancreatic and/or para-aortic lymph nodes in 193 (51%) patients and liver metastases in 56 (14.8%) patients. Associated co-morbidities were present in 45 (11.9%) patients including diabetes mellitus in 23 patients, hypertension in 14 patients, liver cirrhosis in 5 patients and chronic pulmonary disease in 3 patients. Exploration was done for 70 patients. On exploration, five patients were found unresectable due to major vascular invasion in 2 patients, peritoneal seeding in 2 patients and liver metastases in one patient. These operative findings of unresectability were missed by preoperative imaging. Pancreatico-duodenectomy could be performed for 65 (17.2%) patients. Pancreatico-jejunosotomy was performed by duct to mucosa method in 57 (87.7% of operations) patients and by dunking method in 8 (12.3%) patients. Operative time ranged from 290 to 430 minutes with a median of 325 minutes; while the median intraoperative blood loss was 700ml. The hospital stay ranged from 9 to 34 days with a median 12 days for uncomplicated patients and 26 days for complicated patients.

Postoperative complications occurred in 21 (32.3%) patients. These complications are shown in **Table(1)**. Five patients (7.7%) died in the perioperative period. Two patients died due to complicated pancreatic fistula, one

patient died due to severe bleeding, one patient died due to severe renal shutdown on top of diabetic nephropathy and another patient died due to cholestatic jaundice complicated by liver failure. Pancreatic fistula occurred in 9 patients (13.8%). No significant difference was found in rates of postoperative complications between pylorus-preserving pancreaticoduodenectomy and conventional pancreaticoduodenectomy. These were 31.5% and 32.6% respectively. Follow up revealed that 1-, 2- and 3-year survivals were 64.6%, 43.1% and 35.4% respectively. This is shown in **Figure(1)**.

The cause of disease-related mortality was tumor recurrence. Recurrence was revealed by

abdominal CT as a mass at the resection area or pancreatic remnant, multiple para-aortic lymph nodes, liver metastases and/ or omental deposits.

By univariate analysis, survival more than 3 years was significantly related to tumor diameter not exceeding 3cm, free resection margin, negative lymph nodes, well differentiation of the tumors and periampullary tumors. This is shown in **Table(2)**. By multivariate regression analysis, tumor diameter not exceeding 3cm and absence of lymph nodes involvement were found to be the most predictive factors correlated to survival more than 3 years. This is shown in **Table(3)**.

Table (1): Postoperative complications (morbidity).

Complications	Number of patients (n=65)	%
Pancreatic fistula	9	13.8
Delayed gastric emptying	6	9.2
Wound infection	3	4.6
Haemorrhage	1	1.5
Renal failure	1	1.5
Cholestatic Jaundice	1	1.5

Table (2): Relationship between tumor pathological criteria and survival.

	Number of patients (n=65)		Total <3year survival		<1 year survival (n=23)		1-2 year survival (n=14)		2-3 years survival (n=5)		>3 years survival (n=23)		p ₁
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Tumor diameter													
2-3cm	26	40.0	8	19.0	2	8.7	3	21.4	3	60.0	18	78.3	p<0.001*
>3-5cm	39	60.0	34	81.0	21	91.3	11	78.6	2	40.0	5	21.7	
p2							FEp= 0.346		FEp= 0.027*		FEp<0.001*		
Tumor location													
Pancreatic head	57	87.7	40	95.2	23	100.0	13	92.9	4	80.0	17	76.9	FEp = 0.019*
Periampullary	8	12.3	2	4.8	0	0.0	1	7.1	1	20.0	6	26.1	
p2							FEp = 0.378		FEp = 0.179		FEp =0.022		
Resection margin													
Free	47	72.3	24	57.1	9	39.1	10	71.4	5	100.0	23	100.0	FEp <0.001*
Involved	18	27.7	18	42.9	14	60.9	4	28.6	0	0.0	0	0.0	
p2							FEp = 0.091		FEp= 0.041*		FEp <0.001*		
Lymph nodes													
Positive	24	36.9	24	57.1	18	78.3	6	42.9	0	0.0	0	0.0	MCp <0.001*
Negative	40	36.1	18	42.9	5	21.7	8	57.1	5	100.0	23	100	
p2							MCp= 0.070		MCp= 0.003*		MCp<0.001*		
Pathological type													
Adenocarcinoma	60	92.3	37	88.1	18	78.3	14	100.0	5	100.0	23	100.0	FEp = 0.152
Others	5	7.7	5	11.9	5	21.7	0	0.0	0	0.0	0	0.0	
p2							FEp = 0.135		FEp = 0.550		FEp= 0.049*		
Differentiation													
Well	56	86.2	33	78.6	17	73.9	11	78.6	5	100.0	23	100.0	FEp = 0.021*
Poor	9	13.8	9	21.4	6	26.1	3	21.4	0	0.0	0	0.0	
p2							FEp = 1.000		FEp = 0.553		FEp= 0.022*		

p₁: p value between non survivor and >3 years survival

p₂: p value between <1 year survival with (1-2 year survival, 2-3 years survival and >3years survival)

p: p value for Chi-square test

MCp: p value for Monte Carlo test

FEp: p value for Fisher Exact test

*: Statistically significant at p ≤ 0.05

Table (3): Multivariate regression analysis for tumor diameter, tumor location, resection margin, lymph nodes and tumor differentiation.

	B	Sig	OR	95% CI (lower – upper)
Tumor diameter <3cm	1.982	0.030	7.258*	(1.209 – 43.572)
Tumor location	1.581	0.277	4.858	(0.282 – 83.820)
Resection margin	18.586	0.998	1.2x10 ⁸	--
Negative lymph nodes	3.739	0.005	42.076*	(3.146 – 562.824)
Tumor differentiation	18.348	0.999	92980961	--

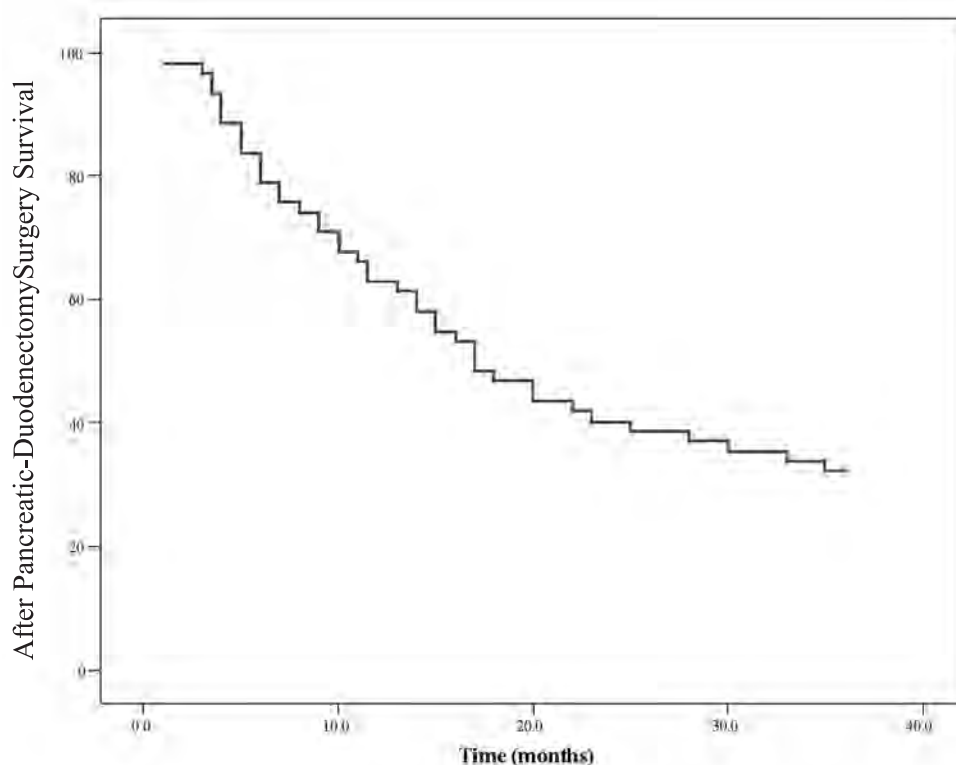


Figure (1): Kaplan Meier survival curve.

Discussion:

Surgical treatment of pancreatic cancer is the only modality that can offer a chance of long-term survival. Many studies found that potentially curative surgery is an option for only 15% of all patients with pancreatic adenocarcinoma.⁵ In this study, 65 patients (17.2 %) had resectable tumors. Complications occurred in 33.9% of patients; while 1-, 2- and 3-year survival rates were 64.6%, 43.1% and 35.4% respectively.

Despite improvements in imaging modalities, a high incidence of unresectable disease, is still found at the time of surgery. It is important to identify patients who are candidates for curative resection and to spare

patients with unresectable disease the risks associated with surgery and allow them proper palliation.^{5,6} Staging laparoscopy may identify locally advanced disease and small peritoneal or hepatic lesions not identified by noninvasive imaging.⁶ In this study, diagnostic laparoscopy was used in 9 patients with suspicious resectability and was found beneficial to detect unresectable tumors in 4 patients.

A multivariate analysis showed that neoplasms larger than 4.5cm, low leucocytic count (<9500/mm), high bilirubin levels (>137micromol/L) and tomographic tumor invasion are independent factors predicting unresectability.⁷

In this study, 313 (82.8%) patients had unresectable tumors. The reasons for unresectability in these patients were involvement of major vessels (superior mesenteric, portal vein, or celiac trunk), local spread and/or metastasis (hepatic or peritoneal).

The high incidence of lymphatic and perineural invasion of pancreatic cancer results in poor loco-regional control. In addition, sentinel lymph node mapping is not technically feasible in pancreatic cancer. Radical pancreatico-duodenectomy may achieve better loco-regional control, but is accompanied by increasing morbidity.⁸

Complete resection (R0) remains the only potentially curative treatment of pancreatic ductal adenocarcinoma. R1 resection was defined as microscopic evidence of tumor < or =1mm from a resection margin. The rate of microscopic margin involvement (R1) varies markedly in the literature (from 5 to 85%) and R1 resections are frequently underreported. Involvement of transection margins in contrast to mobilization margins defines a group whose outcome is significantly worse. Better survival in the resection group and similar perioperative risk would support the decision to perform pancreatico-duodenectomy even when there is the possibility of incomplete microscopic clearance. In most of the patients, complete loco-regional surgical eradication of malignant tissue is impossible. Patients selected for resection have been shown to have an advantage over operative bypass in terms of length of survival.⁹⁻¹²

Pancreatic surgery has been improved dramatically. Perioperative mortality rates after Whipple's procedure in the 1980s exceeded 20%, but nowadays it is less than 5% in high volume centers. Currently, postoperative morbidity is considerable, about 30-50% and survival rate is still low. Overall 5-year survival rate was reported less than 4%.^{2,13}

Postoperative complications of PD are still frequent and severe. The pancreatic fistula represents the most relevant complication. The standard and meticulous surgical technique with good postoperative care would support early detection of complications and improvement of outcome. There is evidence that delayed gastric emptying can be

responsible for 50% of morbidity after PD. Preservation of the pylorus and extent of lymph node removal have no impact on the incidence of delayed gastric emptying.^{14,15} The method of pancreatic anastomosis is crucial. The isolated defunctioned duct-to-mucosa pancreatico-jejunostomy is a safe procedure offering good functional results.^{16,17} In this study, incidence of pancreatic fistula was significantly less after duct to mucosa than dunking pancreatico-jejunostomy.

Preoperative biliary drainage by endoscopic stenting is associated with a high incidence of infective complications. There is no support of the routine use of biliary stenting prior to pancreatico-duodenectomy.¹⁸ In this study, preoperative stenting was used in 26 patients with serum bilirubin > 20mg/dl.

In this study, both pylorus-preserving and conventional pancreatico-duodenectomy had no different impact on the outcome. Other studies showed no evidence of relevant differences in morbidity, survival and quality of life between both techniques, if the principles of viable and tumor free margins are followed.^{1,19}

In this study, 1-, 2- and 3-year survival rates after pancreatico-duodenectomy were 64.6%, 43.1% and 35.4% respectively. Other studies reported median survival of R0, R1 and palliative bypass groups to be 27.2, 15.6 and 6.5 months respectively. While 1-, 2- and 5-year survival of R0 were 79 %, 48.3% and 21.5% respectively; and 1-, 2- and 5-year survival of R1 were 70%, 39.1 and 9.9% respectively. The 1- and 2-year survival of palliative surgical bypass group were reported to be 34% and 0% respectively.^{10,20}

Many factors are determinant of the outcome and survival after PD. Resection margin involvement is an important determinant of overall survival. The cut-off value of 2cm tumor diameter was not independently associated with outcome, however, tumor size was strongly associated with the risk of other adverse prognostic factors.^{21,22} Even after complete resection and adjuvant chemotherapy, the 5-year survival rate does not exceed 20-25%.²³

In this study, survival more than 3 years was significantly related to tumor diameter not

exceeding 3cm, free resection margin, absence of lymph nodes involvement, well differentiation of the tumors and periampullary tumors. By multivariate regression analysis, tumor diameter not exceeding 3cm and absence of lymph nodes involvement were found to be the most predictive factors correlated to survival more than 3 years.

In patients with vascular invasion, partial resection of superior mesenteric or portal vein can be done followed by application of a vein graft. It was found that postoperative morbidity and survival in patients with partial resection of superior mesenteric vein or portal vein were similar to those patients without vein resection.^{24,25}

Conclusion:

The malignant pancreatic tumors have a low resectability rate. Most of pancreatic tumors present in late stages. Tumors not exceeding 3cm in diameter and absence of lymph nodes involvement were predictive of probable 3 year survival after pancreatico-duodenectomy.

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