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Standards of pancreaticoduodenectomy in a tertiary referral centre in Hong Kong: retrospective case series

香港三級轉介中心的胰十二指腸切除術的水平：病例系列回顧

Objective. To evaluate the perioperative outcomes of pancreaticoduodenectomy in a tertiary referral centre in Hong Kong.

Design. Retrospective case series.

Setting. University teaching hospital, Hong Kong.

Patients. One hundred and forty patients who underwent pancreaticoduodenectomy from July 1989 through June 2001.

Main outcome measures. Mortality and morbidity.

Results. Overall hospital mortality among 140 patients was 2.9% (n=4), and 30-day operative mortality was 2.1% (n=3). There was no significant difference in the hospital mortality rate between 43 elderly patients aged 70 years or older and 97 younger patients (2.3% versus 3.1%). The overall morbidity rate was 38.6% (n=54). Intra-abdominal abscess (13.6%) and pancreaticojejunal anastomotic leakage (12.9%) were the two most common complications. Presence of co-morbid illness (risk ratio, 2.823; 95% confidence interval, 1.541-4.385; P=0.01), preoperative cholangitis (risk ratio, 2.565; 95% confidence interval, 1.166-5.643; P=0.02), and intra-operative blood loss ≥ 1.5 L (risk ratio, 2.236; 95% confidence interval, 1.132-6.213; P=0.03) were independent risk factors for post-operative morbidity.

Conclusions. Pancreaticoduodenectomy is associated with a low risk of operative death when performed in a tertiary referral setting in Hong Kong. The post-operative morbidity rate remains high, however. Further improvement by reducing intra-operative blood loss may help curtail the high postoperative morbidity.

目的：評估香港三級轉介中心的胰十二指腸切除的手術結果。

設計：病例系列回顧。

安排：大學教學醫院，香港。

患者：1989年7月至2001年6月期間進行胰十二指腸切除手術的140名病人。

主要結果測量：死亡率和併發症發生率。

結果：140名患者的整體住院死亡率是2.9% (n=4)，手術後30天的死亡率是2.1% (n=3)。43名70歲以上老年患者，與97名70歲以下的患者之間的住院死亡率無顯著差異 (2.3% 比 3.1%)。整體併發症發生率是38.6% (n=54)。腹腔膿腫 (13.6%) 和胰漏 (12.9%) 是兩個最常見的併發症。並存疾病 (RR=2.823; 95% CI, 1.541-4.385; P=0.01)，術前膽管炎 (RR=2.565; 95% CI, 1.166-5.643; P=0.02) 和術中失血多於1.5 L (RR=2.236; 95% CI, 1.132-6.213; P=0.03) 是手術後出現併發症的三個獨立的危險因素。

結論：在香港的三級轉介中心進行胰十二指腸切除手術的死亡率低。然而，手術後併發症發生率仍然偏高。減少術中失血可能會有助於降低手術後併發症的發生率。

Key words:

Morbidity;

Mortality;

Pancreaticoduodenectomy

關鍵詞：

併發症發生率；

死亡率；

胰十二指腸切除術

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Introduction

Pancreaticoduodenectomy is one of the most complex surgical procedures, and is associated with substantial operative mortality and morbidity rates. The first successful pancreaticoduodenectomy was performed by the German surgeon, Kausch, in 1912,¹ and the operation was popularised in 1935 by Whipple et al,² who reported three cases of pancreaticoduodenal resection. Until the 1980s, the operative mortality rate of pancreaticoduodenectomy was 20% to 25%, and at

one time some surgeons even proposed that this operation should be completely abandoned as a treatment for carcinoma of the head of the pancreas.^{3,4} A comprehensive review of the literature that included 1859 patients who underwent pancreatic resection for pancreatic cancer between 1980 and 1986 showed a mortality rate of 16%, which was unacceptably high when compared with other types of elective surgery.⁵ In the 1990s, several major centres in western countries reported dramatically reduced operative mortality rates as a result of improved surgical management and increased experience.⁶⁻¹⁴ Several studies have linked the improved operative outcomes after pancreaticoduodenectomy in the 1990s with concentration of case volume in tertiary referral centres.^{8-11,13,14} While an operative or in-hospital mortality rate of less than 5% had been achieved in high-volume centres, mortality rates in low-volume hospitals were still in the range of 13% to 20% in the 1990s.^{8-11,13,14} In centres with a case volume of more than 40 per year, a mortality rate of less than 2% has been reported.^{7,12}

The most common indication for pancreaticoduodenectomy is carcinoma of the head of pancreas.^{7,11,12} With the improved safety of pancreaticoduodenectomy, the operation is also considered an appropriate treatment for selected patients with chronic pancreatitis, which constitutes the second most common indication for the operation in western series.^{7,12} Pancreatic cancer is much less common in Hong Kong than in western countries. It is the fourth leading cause of cancer death in men and the fifth leading cause in women in the US,¹⁵ whereas in Hong Kong, it only ranks 16th in cancer incidence.¹⁶ Chronic pancreatitis due to alcoholism is also much less prevalent among the local population compared with western populations. Hence, the experience of pancreaticoduodenectomy among local institutions is expected to be low compared with western centres. It is unknown whether the current standards of pancreaticoduodenectomy in Hong Kong are on a par with western centres. This study evaluated the perioperative outcomes of 140 patients who underwent pancreaticoduodenectomy in a local tertiary referral centre during a 12-year period.

Methods

Between July 1989 and June 2001, 140 patients underwent elective pancreaticoduodenectomy at the Department of Surgery of the University of Hong Kong in Queen Mary Hospital. All patients were operated and managed by a team of surgeons specialised in hepatobiliary and pancreatic surgery. A retrospective study was performed by reviewing the records of these patients for clinical, laboratory, operative, and pathological data. Any postoperative complications and mortality were documented. Operative mortality was defined as death within 30 days of surgery, and hospital mortality was defined as any death that occurred during the admission for surgery.

All continuous variables were expressed as a mean and standard deviation (SD) and compared using the Student's *t*

test. Categorical variables were compared using the Chi squared test with Yates' correction or Fisher's exact test where appropriate. Univariate analysis was performed to evaluate the impact of 12 clinical and operative parameters on postoperative morbidity and mortality, including age, sex, any co-morbid illness, preoperative cholangitis, preoperative biliary drainage, preoperative serum bilirubin level, preoperative serum albumin level, nature of disease (malignant versus benign), type of operation (conventional versus pylorus-preserving pancreaticoduodenectomy), any portal vein resection, operative blood loss, and any perioperative transfusion. Multivariate analysis was performed by logistic regression analysis. Statistical analysis was performed using statistical software (Statistical Package for the Social Sciences; Windows 9.0; SPSS Inc., Chicago, US). A *P* value <0.05 was considered statistically significant.

Results

Patients included 85 men and 55 women, with a mean age of 61.7 years (range, 16-91 years; SD, 13.1 years). There were 43 (30.7%) elderly patients aged 70 years or older. Fifty-nine (42.1%) patients had one or more chronic co-morbid illnesses, which included cardiovascular disease (*n*=32), chronic respiratory disease (*n*=10), and diabetes mellitus (*n*=28). Preoperative biliary drainage was performed in 77 (55.0%) patients, either by endoscopic stenting (*n*=50) or percutaneous transhepatic biliary drainage (*n*=27). Ninety-seven (69.3%) patients underwent conventional Whipple's operation, whereas the other 43 (30.7%) patients underwent pylorus-preserving pancreaticoduodenectomy. Concomitant procedures included portal vein resection for six patients and hepatic resection for two patients. The mean duration of operation was 8.6 hours (range, 5.5-15.0 hours; SD, 2.4 hours). The pathological diagnoses of the 140 patients are depicted in Table 1.

Postoperative mortality

Overall there were four (2.9%) hospital deaths, three after pancreaticoduodenectomy alone (two for carcinoma of the head of the pancreas and one for chronic pancreatitis) and one after pancreaticoduodenectomy combined with right extended hepatectomy for a carcinoma of the bile duct extending into the right hepatic duct. The precipitating causes of death were intra-abdominal sepsis without anastomotic leakage (*n*=1), intra-abdominal sepsis secondary to

Table 1. Pathological diagnoses of 140 patients who underwent pancreaticoduodenectomy

Pathology	Patients No. (%)
<i>Malignant</i>	
Carcinoma of pancreas	60 (42.9)
Carcinoma of ampulla	40 (28.6)
Carcinoma of bile duct	18 (12.9)
Carcinoma of duodenum	3 (2.1)
<i>Benign</i>	
Chronic pancreatitis	11 (7.9)
Tuberculosis of pancreas*	2 (1.4)
Adenoma of ampulla	6 (4.3)

* Preoperative diagnosis was pancreatic carcinoma in both cases

pancreaticojejunostomy leakage (n=1), acute myocardial infarction (n=1), and massive gastrointestinal haemorrhage (n=1). There were no hospital deaths among the six patients with portal vein resection. Three of the four hospital deaths occurred within 30 days after surgery, giving a 2.1% operative mortality rate. Dividing the study period into two halves between July 1989 to June 1995 (n=48) and July 1995 to July 2001 (n=92), the hospital mortality rate has been reduced from 4.2% (n=2) in the early half of the study period to 2.2% (n=2) in the latter half, but the difference was not statistically significant.

Table 2 shows comparisons of the hospital mortality rates between subgroups categorised by the aforementioned clinical and operative parameters. None of the parameters had a significant impact on the hospital mortality rate by univariate analysis, except that there was a trend towards a higher hospital mortality rate in patients with intra-operative blood loss ≥ 1.5 L compared with those with less blood loss (7.5% versus 1.0%; $P=0.07$). It is noteworthy that the hospital mortality rate in the 43 elderly patients aged 70 years or older was not significantly higher than that of the 97 younger patients (2.3% versus 3.1%).

Postoperative morbidity

Complications were encountered in 54 (38.6%) of the 140 patients (Table 3). The two most common complications were intra-abdominal abscess (13.6%) and leakage of pancreaticojejunal anastomosis (12.9%). Table 4 shows the results of univariate analysis of risk factors for postoperative morbidity. Male sex, presence of co-morbid illness, preoperative cholangitis, pylorus-preserving

pancreaticoduodenectomy, intra-operative blood loss ≥ 1.5 L, and perioperative blood transfusion were associated with significantly increased morbidity. On multivariate analysis, the presence of co-morbid illness (risk ratio [RR], 2.823; 95% confidence interval [CI], 1.541-4.385; $P=0.01$), preoperative cholangitis (RR, 2.565; 95% CI, 1.166-5.643; $P=0.02$), and intra-operative blood loss ≥ 1.5 L (RR, 2.236; 95% CI, 1.132-6.213; $P=0.03$) were independent risk factors for postoperative morbidity.

Discussion

Pancreaticoduodenectomy is a surgical procedure that has been widely studied with respect to its perioperative outcomes during the past decade, but data in the literature are derived mainly from western centres.^{6-9,12} The concentration of patients undergoing the procedure in tertiary referral centres is considered an important factor for the low operative mortality rate observed in recent western studies. In fact, several studies have demonstrated a significant impact of hospital volume on the perioperative outcomes after pancreaticoduodenectomy.^{8-11,13,14} Based on the western experience, an overseas panel of experts have recommended concentration of major surgical procedures such as pancreaticoduodenectomy in high-volume hospitals in a recent review of surgical services in Hong Kong.¹⁷ However, there is a paucity of data on the results of pancreaticoduodenectomy in Hong Kong, which may not be comparable with that of western centres in view of the much smaller volume of patients undergoing this operation in local institutions. Hence, a retrospective study was performed to evaluate the standards of this operation in a tertiary

Table 2. Hospital mortality according to preoperative and operative factors

Factor		Hospital deaths No. (%)	P value
Age	<70 years (n=97)	3 (3.1)	0.64
	≥ 70 years (n=43)	1 (2.3)	
Sex	Male (n=85)	3 (3.5)	0.49
	Female (n=55)	1 (1.8)	
Co-morbid illness	No (n=81)	2 (2.5)	0.65
	Yes (n=59)	2 (3.4)	
Preoperative cholangitis	No (n=129)	4 (3.1)	0.72
	Yes (n=11)*	0 (0)	
Preoperative biliary drainage	No (n=63)	2 (3.2)	0.66
	Yes (n=77)	2 (2.6)	
Nature of disease	Benign (n=19)	1 (5.3)	0.47
	Malignant (n=121)	3 (2.5)	
Preoperative bilirubin	<50 mmol/L (n=66)	2 (3.0)	0.69
	≥ 50 mmol/L (n=74)	2 (2.7)	
Preoperative albumin	<40 g/L (n=65)	2 (3.1)	0.66
	≥ 40 g/L (n=75)	2 (2.7)	
Operation	Conventional PD† (n=97)	4 (4.1)	0.31
	Pylorus-preserving PD (n=43)	0 (0)	
Portal vein resection	No (n=134)	4 (3.0)	0.84
	Yes (n=6)	0 (0)	
Operative blood loss	<1.5 L (n=100)	1 (1.0)	0.07
	≥ 1.5 L (n=40)	3 (7.5)	
Perioperative transfusion	No (n=85)	1 (1.2)	0.13
	Yes (n=55)	3 (5.5)	

* Includes eight patients who initially presented with cholangitis and three patients who developed cholangitis as a result of a blocked stent

† PD pancreaticoduodenectomy

Table 3. Complications of 140 patients who underwent pancreaticoduodenectomy

Complication	Patients* No. (%)
Cardiac complications (arrhythmia, myocardial infarction)	5 (3.6)
Chest infection	15 (10.7)
Gastrointestinal bleeding	5 (3.6)
Wound infection	15 (10.7)
Intra-abdominal abscess	19 (13.6)
Pancreaticojejunostomy leakage	18 (12.9)
Hepaticojejunostomy leakage	2 (1.4)
Postoperative haemorrhage	3 (2.1)
Delayed gastric emptying (>7 days)	13 (9.3)
Any complication	54 (38.6)

* Some patients had more than one complication

referral centre in Hong Kong. Furthermore, with an aim of improving the operative results, we also analysed the factors that may influence mortality or morbidity after the operation.

The hospital mortality rate for this series of 140 patients operated during a 12-year period was 2.9%. The average case volume per year in our institution during the study period was 12 per year, but the case volume has increased from eight cases per year in the first 6 years to 15 per year in the final 6 years. In a study of the results of pancreaticoduodenectomy in 39 hospitals in the US, low-, medium-, and high-volume centres for pancreaticoduodenectomy were defined as 1 to 5 cases per year, 6 to 20 cases per year, and more than 20 cases per year, respectively, and the corresponding hospital mortality rates were 19%, 12%, and

2.2%, respectively.⁹ Other recent western studies using similar definitions have reported similar mortality rates in hospitals with different volumes of pancreatic resection.^{10,18} Our institution would be classified as a medium-volume centre according to such definition, but our hospital mortality rate was comparable to those of high-volume western centres.^{9,10,14} The largest single-institution experience of pancreaticoduodenectomy reported thus far in the literature was from a centre with 650 cases of pancreaticoduodenectomy between 1990 and 1996 (ie >100 cases per year), and the hospital mortality rate in that series was 1.4%.¹² The mortality rate in our centre was slightly higher, but the difference was not remarkable.

The low hospital mortality rate observed in our experience is likely to be related to the management of all patients by a specialised team of hepatobiliary and pancreatic surgeons, even though the case volume was not high compared with western standards. A recent study in the UK has demonstrated significantly lower postoperative mortality rate after resection of pancreatic and periampullary tumours in specialist pancreatic units compared with general surgical units (average mortality rate 4.9% versus 9.8%).¹¹ A tertiary referral centre is likely to offer better facilities and expertise in perioperative care, such as more sophisticated diagnostic imaging and radiological interventions, specialised anaesthetic services, and a well-equipped intensive care unit. However, the experience of the surgical team is of equal, if not more, importance when a complex operation is

Table 4. Morbidity according to preoperative and operative factors

Factor		Patients No. (%)	P value
Age	<70 years (n=97)	37 (38.1)	0.88
	≥70 years (n=43)	17 (39.5)	
Sex	Male (n=85)	39 (45.9)	0.03
	Female (n=55)	15 (27.3)	
Co-morbid illness	No (n=81)	22 (27.2)	0.004
	Yes (n=59)	32 (54.2)	
Preoperative cholangitis	No (n=129)	46 (35.7)	0.02
	Yes (n=11)*	8 (72.7)	
Preoperative biliary drainage†	No (n=63)	25 (39.7)	0.81
	Yes (n=77)	29 (37.7)	
Nature of disease	Benign (n=19)	10 (52.6)	0.18
	Malignant (n=121)	44 (36.4)	
Preoperative bilirubin	<50 mmol/L (n=66)	25 (37.9)	0.72
	≥50 mmol/L (n=74)	29 (39.2)	
Preoperative albumin	<40 g/L (n=65)	28 (43.1)	0.36
	≥40 g/L (n=75)	26 (34.7)	
Operation	Conventional PD‡ (n=97)	31 (32.0)	0.02
	Pylorus-preserving PD (n=43)	23 (53.5)	
Portal vein resection	No (n=134)	51 (38.1)	0.88
	Yes (n=6)	3 (50.0)	
Operative blood loss	<1.5 L (n=100)	31 (31.0)	0.01
	≥1.5 L (n=40)	23 (57.5)	
Perioperative transfusion	No (n=85)	27 (31.8)	0.04
	Yes (n=55)	27 (49.1)	

* Includes eight patients who initially presented with cholangitis and three patients who developed cholangitis as a result of a blocked stent

† No significant difference between patients without preoperative biliary drainage and patients with preoperative biliary drainage in wound infection rate (7.9% vs 12.9%; $P=0.30$) or intra-abdominal abscess (12.7% vs 14.3%; $P=0.68$)

‡ PD pancreaticoduodenectomy

being performed only once a month or less frequently. It is not only the operative technique but also the perioperative management that determine patients' outcomes. In a recent study, hospital rather than individual surgeon's case volume was identified as the most important determinant of hospital mortality rate after resection of pancreatic cancer.¹⁸ The authors suggested that the combined 'experience effect' of the whole team of surgeons is more important than the number of operations performed by a particular surgeon, and the development of a systematic approach in perioperative management by a specialised team may be an important factor for better perioperative outcomes.¹⁸

The low operative mortality rate in this study, together with the data from western studies regarding the impact of hospital volume on perioperative outcomes, seem to support the concentration of complex surgical procedures such as pancreaticoduodenectomy in tertiary referral centres in Hong Kong. However, without a study that compares the operative outcomes of pancreaticoduodenectomy between tertiary referral centres and general surgical units in Hong Kong, it is impossible to draw a conclusion. The influence of any confounding factors such as patient characteristics that may affect operative results in different institutions needs to be adjusted in such a study.

Except for a trend towards a higher hospital mortality rate with excessive operative blood loss, no significant factors were found to affect the mortality rate in this study. A previous study of 13 deaths among 221 patients with pancreaticoduodenectomy found that operative blood loss was a significant risk factor for postoperative mortality.¹⁹ The overall mortality rate in our series was so low that it is unlikely to yield any statistically significant risk factor with such an analysis. However, some of the results of the analysis do carry certain implications. The hospital mortality rate of elderly patients aged 70 years or older was similar to that of younger patients. This finding is in accordance with previous studies of oesophagectomy and hepatectomy in elderly patients in our institution.^{20,21} The oldest patient who underwent pancreaticoduodenectomy in this series was a 91-year-old man, who recovered without any complications. Our results indicate that advanced age alone should not be considered a contraindication for pancreaticoduodenectomy. This finding has an important implication for the selection of patients for pancreaticoduodenectomy at a time when surgeons are faced with an increasing number of elderly patients in the Hong Kong population. Of course, the importance of careful preoperative assessment and meticulous postoperative management of elderly patients cannot be overemphasised. No mortality was observed in the six cases of pancreaticoduodenectomy with portal vein resection, which was indicated because of tumour involvement. Studies in the early 1990s reported high mortality rates (6%-17%) and poor survival results with portal vein resection in pancreatic cancer.²²⁻²⁴ However, more recent studies have found no significant difference in the operative mortality rate or long-term survival between patients who did and those who did not

undergo portal vein or superior mesenteric vein resection for tumour involvement.^{25,26} Although experience in our centre with portal vein resection is limited, the authors believe that pancreatic carcinoma with isolated portal vein involvement should not be considered a contraindication to surgery.²⁷

While the operative mortality rate in this series was low, the operative morbidity rate (38.6%) was high. Our experience is comparable with that of western centres, which reported morbidity rates of approximately 40% after pancreaticoduodenectomy despite remarkably reduced mortality rates in recent years.^{6,7,12,28} Leakage of pancreaticoenteric anastomosis was one of the most common complications in this study, with an incidence of 12.6%. Pancreatic leakage rates of 10% to 20% after pancreaticoduodenectomy have been reported in major western centres, and have not declined significantly in the past 30 years.²⁸ Despite intensive effort by pancreatic surgeons to prevent pancreatic anastomotic leakage through modification of surgical techniques or use of prophylactic octreotide, none of the measures have thus far been proved to be effective in reducing the pancreatic leakage rate.²⁹ Pancreatic leakage is a potentially serious complication that can lead to intra-abdominal sepsis and haemorrhage, and it has been associated with a mortality rate of 20% to 40% in the past.³⁰ The high morbidity rate but low mortality rate in this study indicates that successful management of postoperative complications such as pancreatic anastomotic leakage and intra-abdominal abscess plays an important role in achieving the low mortality. The concerted efforts of the surgeons, intensive care staff, interventional radiologists, and clinical microbiologists in the management of postoperative complications are critical to the favourable mortality outcome.

Further improvement in the operative results of pancreaticoduodenectomy relies on measures to reduce postoperative morbidity. Analysis of risk factors of morbidity revealed that the presence of co-morbid illness, preoperative cholangitis, and excessive blood loss were independent factors related to increased morbidity. The morbidity rate was similar between elderly and younger patients. Hence, it is the presence of co-morbid illness rather than age alone that determines postoperative outcome. Better preparation of patients with co-morbid illnesses and vigilant postoperative care may help reduce morbidity, but complications should be anticipated and managed in a timely fashion in such patients to avoid mortality. Patients who presented with cholangitis may have colonisation of bacteria in the bile even after control of sepsis, and thus are at risk of postoperative intra-abdominal sepsis. This is a non-preventable risk factor, but adequate preoperative biliary drainage and use of prophylactic antibiotics may help minimise postoperative complications in such patients. For patients with jaundice but without cholangitis, the role of preoperative biliary drainage is more controversial. The data in this study indicated that neither preoperative biliary drainage nor preoperative bilirubin level was a risk factor for postoperative morbidity. Based on retrospective studies,

some authors have reported increased postoperative morbidity and mortality after pancreaticoduodenectomy in patients with preoperative biliary drainage,³¹ but others have not observed increased morbidity associated with preoperative biliary drainage.^{32,33} The role of biliary drainage for jaundiced patients before pancreaticoduodenectomy needs to be evaluated with a prospective randomised study. Reduction of operative blood loss by meticulous surgical techniques is probably the most practical measure that surgeons can employ to reduce postoperative morbidity. Other authors have demonstrated that operative blood loss is a major risk factor for complications after pancreaticoduodenectomy.¹⁹ Excessive blood loss increases surgical stress and also entails the need for blood transfusion, both of which have been shown to exert an immunosuppressive effect and to increase postoperative morbidity, especially septic complications.^{34,35}

Conclusion

This study shows that pancreaticoduodenectomy can be performed with a low mortality rate in a tertiary referral centre in Hong Kong. When performed by a specialised team of surgeons, the perioperative results were comparable to those reported from well-established western centres, despite a lower case volume due to a lower prevalence of pancreatic cancer and chronic pancreatitis in the local population. However, operative morbidity could be improved. Further reduction in intra-operative blood loss by meticulous surgical techniques may be an effective measure to reduce morbidity.

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