

Impact of cirrhosis on surgical outcome after pancreaticoduodenectomy

Ayman El Nakeeb, Ahmad M Sultan, Tarek Salah, Mohamed El Hemaly, Emad Hamdy, Ali Salem, Ahmed Moneer, Rami Said, Ahmed AbuEleneen, Mostafa Abu Zeid, Talaat Abdallah, Mohamed Abdel Wahab

Ayman El Nakeeb, Ahmad M Sultan, Tarek Salah, Mohamed El Hemaly, Emad Hamdy, Ali Salem, Ahmed Moneer, Rami Said, Ahmed AbuEleneen, Mostafa Abu Zeid, Talaat Abdallah, Mohamed Abdel Wahab, Gastroenterology surgical center, Mansoura University, Mansoura 35516, Egypt

Author contributions: El Nakeeb A designed the research; El Nakeeb A, Salah T, Salem A, El Hemaly M, Hamdy E, Sultan AM, Moneer A, Said R, AbuEleneen A, Abu Zeid M, Abdallah T and Abdel Wahab M performed the research; El Nakeeb A and Sultan AM analysed the data; El Nakeeb A and Abdallah T wrote the paper.

Correspondence to: Ayman El Nakeeb, MD, Associate Professor of general surgery, Gastroenterology surgical center, Mansoura University, Gehan street, Mansoura 35516,

Egypt. elnakeebayman@yahoo.com

Telephone: +20-10-6752021 Fax: +20-50-2251543

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Abstract

AIM: To elucidate surgical outcomes of pancreaticoduodenectomy (PD) in patients with liver cirrhosis.

METHODS: We studied retrospectively all patients who underwent PD in our centre between January 2002 and December 2011. Group A comprised patients with cirrhotic livers, and Group B comprised patients with non-cirrhotic livers. The cirrhotic patients had Child-Pugh classes A and B (patient's score less than 8). Pre-operative demographic data, intra-operative data and postoperative details were collected. The primary outcome measure was hospital mortality rate. Secondary outcomes analysed included duration of the operation, postoperative hospital stay, postoperative morbidity and survival rate.

RESULTS: Only 67/442 patients (15.2%) had cirrhotic livers. Intraoperative blood loss and blood transfusion

were significantly higher in group A ($P = 0.0001$). The mean surgical time in group A was significantly longer than that in group B ($P = 0.0001$). Wound complications ($P = 0.02$), internal haemorrhage ($P = 0.05$), pancreatic fistula ($P = 0.02$) and hospital mortality ($P = 0.0001$) were significantly higher in the cirrhotic patients. Postoperative stay was significantly longer in group A ($P = 0.03$). The median survival was 19 mo in group A and 24 mo in group B. Portal hypertension (PHT) was present in 16/67 cases of cirrhosis (23.9%). The intraoperative blood loss and blood transfusion were significantly higher in patients with PHT ($P = 0.001$). Postoperative morbidity (0.07) and hospital mortality ($P = 0.007$) were higher in cirrhotic patients with PHT.

CONCLUSION: Patients with periampullary tumours and well-compensated chronic liver disease should be routinely considered for PD at high volume centres with available expertise to manage liver cirrhosis. PD is associated with an increased risk of postoperative morbidity in patients with liver cirrhosis; therefore, it is only recommended in patients with Child A cirrhosis without portal hypertension.

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Key words: Periampullary tumour; Liver cirrhosis; Portal hypertension; Pancreaticoduodenectomy

Core tip: Traditionally, cirrhosis has been considered a contraindication to major gastrointestinal surgery. Hospital mortality rates have been reported to be 17.5% to 38% for cirrhotic patients undergoing gastrointestinal surgery. Pancreaticoduodenectomy is associated with an increased risk of postoperative morbidity in patients with liver cirrhosis; therefore, it is recommended only in patients with Child A cirrhosis. Cirrhotic patients with portal hypertension were associated with poorer

outcome than cirrhotic patients without portal hypertension. Patients with periampullary tumours and well-compensated chronic liver disease should be routinely considered for radical surgery at high volume centres with available expertise to manage liver cirrhosis.

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INTRODUCTION

Pancreaticoduodenectomy (PD) is a complex procedure; however, it is the only curative procedure for patients with malignant diseases of the pancreas and periampullary region. The procedure is also recommended in some benign pancreatic tumours^[1-3]. Although PD is performed in many hospitals, its associated morbidity and mortality rates are still high. Recently, the operative mortality rate after PD has dramatically decreased to less than 5%, while the incidence of postoperative complications remains high: from 30% to 60%^[3-7]. Recent studies have suggested that many factors influence postoperative morbidity and prognosis after PD, including age, sex, preoperative jaundice, operative time, intraoperative blood loss, type of pancreatic reconstruction, anastomotic technique, consistency of pancreatic stump, pancreatic duct diameter, use of somatostatin, mass size, safety margin, lymph node ratio and surgeon experience^[5-9].

Cirrhosis represents a common pathological pathway for a wide variety of chronic liver diseases. The progression of liver injury to cirrhosis can occur over weeks to years. Hepatitis C virus (HCV) is the most important cause of liver cirrhosis in Egypt^[10,11]. Traditionally, cirrhosis has been considered a contraindication to major gastrointestinal surgery. The hospital mortality rates have been reported to be 17.5% to 38% for cirrhotic patients undergoing any gastrointestinal surgery^[12-14]. Studies from the 1980s reported a mortality rate of approximately 25% and a morbidity rate of 35% for patients with cirrhosis undergoing open cholecystectomy^[15,16]. Postoperative mortality for cirrhotic patients undergoing cholecystectomy has decreased significantly over the last two decades, partly because of the use of laparoscopy^[17-19].

Many studies have observed that patients with cirrhosis tend to have a significant risk of developing postoperative complications after major abdominal operations, frequently leading to their eventual death^[15,16,20]. Patients with cirrhosis have an increased risk of complications during surgery (bleeding because of portal hypertension and coagulopathy, liver dysfunction, and ascites, which often lead to sepsis), which is related to the severity of

liver disease. It is a challenge to determine which patients are the best candidates for surgery^[20,21]. Now, major surgical procedures can be safely performed in patients with cirrhosis with intensive preoperative care and with minimised intraoperative blood loss because surgical techniques and medical management have been improved significantly^[16,19,20].

The impact of cirrhosis on postoperative morbidity and mortality for gastrointestinal cancer resection has not been well described^[12,22-25]. The aim of this study was to elucidate surgical outcomes of PD in patients with liver cirrhosis.

MATERIALS AND METHODS

Study design

We studied retrospectively all cirrhotic patients who underwent PD for malignant and benign diseases in pancreatic head and periampullary region in our Gastroenterology Surgical Center, Mansoura University, Egypt, from January 2002 to December 2011. The clinical condition of the patients was graded according to the Child-Pugh classification system^[26]. In our centre, the inclusion criteria for PD included patients with resectable Periampullary tumours with CTP classes A and B (patient's score less than 8), and no other hepatic pathology. Exclusion criteria for surgery included patients with CTP classes B (patient's score > 8), and C, patients with poor liver function, patients with bleeding risky oesophageal varices or gastric varices, and patients with thrombosed portal veins, malnutrition or coagulopathy.

The medical records of patients, including their well-designed pancreatic surgical sheet, were reviewed. Informed consent for the surgical procedures was obtained from each patient. The local ethical committee approved this study.

The patients who underwent PD formed two groups: Group A (PD in patients with cirrhotic livers) and Group B (PD in patients with normal livers).

Preoperative assessment

Preoperative diagnostic workup for all patients included clinical assessment, laboratory investigations (complete blood count, liver functions, HCV and HBV markers, creatinine, serum amylase and tumour markers, such as CEA and CA19-9) and radiological investigations [abdominal ultrasound, magnetic resonance cholangiopancreatography (MRCP) and abdominal computerised tomography CT].

Preoperative endoscopic retrograde cholangio-pancreatography (ERCP) was carried out in selected patients (patients with serum levels of total bilirubin greater than 10 mg/dL or patients with hepatic dysfunction (transaminase: more than threefold the normal *i.e.*, more than 120 IU/mL).

The diagnosis of cirrhosis was proven on ultrasound findings, CT findings and intraoperatively. Liver biopsies were performed in some cases. The presence of preop-

erative portal hypertension was evaluated retrospectively: direct measurement of portal pressure was not performed routinely in this study, and portal hypertension was indirectly defined as oesophageal varices detected by endoscopy, or splenomegaly [major diameter > 12 cm with platelet count less than 100000/mm³, according to the Barcelona Clinic Liver Cancer (BCLC) group criteria]^[22-25].

Surgical procedures

PD was carried out under general anaesthesia; hepatotoxic drugs were avoided. Standard Whipple type operation or pylorus preserving PD (PPPD) was performed. All patients underwent standard regional lymphadenectomy, which included resection of nodes within the outlines of the hepatoduodenal ligament, the right side of the superior mesenteric artery and the inferior vena cava. The presence of cirrhosis did not modify the standard procedure; however, we preferred to use suture ligation rather than cauterisation when possible. Pancreatic reconstruction was performed by either pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ), based on surgeon preference. Biliary drainage was achieved by end-to-side hepaticojejunostomy (retrocolic). However, gastric drainage was achieved by gastrojejunostomy (GJ) (antecolic or retrocolic) (manual or using a stapler) in the standard Whipple operation or duodenojejunostomy in PPPD (end-to-side or end-to-end).

Postoperative management

All patients were managed in the intensive care unit (ICU) for at least one day before transfer to the ward. All patients received antibiotics intraoperatively and for 4 d postoperatively. Prophylactic sandostatin was given subcutaneously and continued postoperatively for 4 d in risky patients, which included patients with liver cirrhosis. The drain was removed in all enrolled patients if no bile leak, pancreatic leak or pus occurred. Outputs from Ryle tube were recorded daily, and it was removed if the patients passed flatus, had no distension or the daily output was less than 500 mL. The patients resumed oral feeding, started by a fluid diet, followed by a regular diet once the bowel movement restarted and they could tolerate oral feeding.

Liver functions were measured on post-operative day (POD) 1, and POD 6. Abdominal ultrasound was performed routinely for all patients, and repeated if we suspected intraabdominal collection. Ultrasound (US) guided tubal drainage was done if there was abdominal collection.

Definitions

Postoperative pancreatic fistula was defined as proposed by the International Study Group of Pancreatic Fistula (ISGPF) as any measurable volume of fluid on or after POD 3 with amylase content greater than three times the serum amylase activity, and classified into grades A, B, and C^[7,27,28].

Biliary leak was defined as the presence of bile in the

drainage fluid that persisted to POD 4. Delayed gastric emptying was defined as output from a nasogastric tube of greater than 500 mL per day that persisted beyond POD 10, the failure to maintain oral intake by POD 14 or reinsertion of a nasogastric tube^[7,23]. Postoperative ascites was defined as effusion of more than 400 mL/d through the drain after POD 4.

Follow up

Patients were followed up after 2 wk, 1 mo, 6 mo, 1 year and then annually. Patients' follow-up was based on medical records, their last hospital visit and personal communication conducted by telephone calls.

Data collection

Preoperative demographic and clinical data, surgical procedure, intra-operative data, pathologic diagnosis, postoperative course, early and late complications details and survival were collected.

Statistical analysis

The primary outcome measure was hospital mortality rate. Secondary outcomes analysed included duration of the operation, postoperative hospital stay, postoperative morbidity and survival rate. Statistical analysis of the data in this study was performed using SPSS software, version 17. For continuous variables, descriptive statistics were calculated and were reported as the mean \pm SD. Categorical variables were described using frequency distributions. Independent sample *t*-test was used to detect differences in the means of continuous variables and χ^2 test was used in cases with low expected frequencies. Survival was calculated and plots constructed according to the Kaplan-Meier method and life table method. A log-rank test was used for comparison of survival in different subgroups. *P* values < 0.05 were considered to be significant.

RESULTS

Characteristics of patients

PD was performed in 442 patients in our Gastroenterology Surgical Center, Mansoura University, Egypt, between January 2002 and December 2011. During this study, only 67 patients (15.2%) had cirrhotic livers [48 (71.6%) men and 19 (28.4%) women, with a mean age 54.07 \pm 9.43 years] (group A), and the other 375 patients (84.8%) had non-cirrhotic livers (group B).

In group A, cirrhosis was diagnosed as secondary to hepatitis C in 44 patients (65.7%), hepatitis B in eight patients (11.9%), both hepatitis C and B in five patients (7.5%) and pure bilharzial periportal fibrosis in 10 patients (14.9%, Table 1).

Portal hypertension was present in 16/67 cases (23.9%) and absent in the remaining 51 (76.1%). Of these 16 cases, four patients had Child-Pugh class B (all patients had splenomegaly with platelet count less than 100000/mm³ and oesophageal varices grade 1) and 12 patients had Child-Pugh class A (all patients had splenomegaly with

Table 1 Demographic data for cirrhotic patients *n* (%)

Variables	Statistics
Number	67 (15.2)
Age	
Mean (yr)	54.07 ± 9.43
< 60 yr	48 (71.6)
> 60 yr	19 (28.4)
Sex	
Male	52 (77.6)
Female	15 (22.4)
Cause	
HCV	44 (65.7)
HBV	8 (11.9)
Combined	5 (7.5)
Pure periportal fibrosis	10 (14.9)
Child classification	
Child A	63 (94)
Child B (patient's score less than 8)	4 (6)
With portal hypertension	16 (23.9)
Without portal hypertension	51 (76.1)

HCV: Hepatitis C virus; HBV: Hepatitis B virus.

platelet count less than 100000/mm³, and two patients had oesophageal varices).

There was no statistical difference between patient groups with regard to age, BMI, Preoperative SGPT, bilirubin, haemoglobin, preoperative drainage or preoperative CA19-9. There was statistical difference between patient groups with regard to gender: more male patients were in cirrhotic group ($P = 0.006$). Preoperative albumin values were significantly lower in group A than in group B ($P = 0.01$). The mean preoperative CEA was significantly higher in group A than in group B (67.31 ± 69.78 vs 30.97 ± 62.57 respectively, $P = 0.0001$, Table 2).

PD was decided for cirrhotic patients (Child A or B with patient's score less than 8) for whom surgery could be performed (the tumour was not locally advanced, and they had no distant metastases).

Operative data

There was no statistical difference between the groups in terms of tumour size, pancreatic texture, pancreatic duct diameter and site of the tumour. The median intraoperative blood loss and blood transfusion were significantly different between the groups. Blood loss was 500 mL (100-2500 mL) in the cirrhotic group vs 200 mL (50-2000) in the non-cirrhotic group, $P = 0.0001$ and blood transfusion was 1 (0-4 units) in the cirrhotic group vs 0 (0-4 units) in the non-cirrhotic group, $P = 0.0001$. Estimated intraoperative bleeding of more than 500 mL occurred in 36 patients (53.7%) in group A and 142 (37.9%) patients in group B; the difference between the two groups was statistically significant ($P = 0.015$). Thirty eight patients (58.7%) in group A required a blood transfusion, and 145 patients (38.7%) in group B required a blood transfusion intraoperatively. The mean operative time in group A was 5.81 ± 0.87 h, which was significantly longer than that in group B, which was 5.1 ± 0.99 h ($P = 0.0001$) (Table 3).

Table 2 Preoperative data *n* (%)

Variables	Cirrhotic group Group A	Non cirrhotic group Group B	<i>P</i> value
Age			
Mean (yr)	54.07 ± 9.43	52.47 ± 10.73	NS
< 60 yr	48 (71.6)	286 (76.3)	NS
> 60 yr	19 (28.4)	89 (23.7)	
Sex			
Male	52 (77.6)	225 (60)	0.006
Female	15 (22.4)	150 (40)	
BMI			
< 25	53 (79.1)	285 (76)	NS
> 25	14 (20.9)	90 (24)	
Preoperative albumin (gm%)	3.69 ± 0.5	3.96 ± 0.48	0.01
Preoperative SGPT (IU/L)	71.68 ± 45.74	77.4 ± 71.29	NS
Preoperative bilirubin (mg%)	6.72 ± 8.01	8.79 ± 8.9	NS
Preoperative HG (gm/dL)	13.26 ± 11.57	13.43 ± 13.05	NS
Preoperative CEA			
Mean (ng/mL)	67.31 ± 69.78	30.97 ± 62.57	0.0001
< 5 ng/mL	14 (20.9)	182 (48.5)	0.0001
> 5 ng/mL	53 (79.1)	193 (51.5)	
Preoperative CA19-9			
Mean (U/mL)	103.89 ± 202.18	100.23 ± 208.85	NS
< 37 U/mL	35 (52.2)	207 (55.2)	NS
> 37 U/mL	32 (47.8)	168 (44.8)	
Preoperative ERCP	42 (62.7)	231 (50.4)	NS

NS: Not significant; BMI: Body mass index; ERCP: Endoscopic retrograde cholangio-pancreatography; SGPT: Alanine transaminase.

Postoperative data

The mean postoperative stay was significantly longer in group A (12.97 ± 11.2 d vs 10.71 ± 7.41 d, $P = 0.03$). In group A, 70 postoperative complications developed in 31 patients (46.26%). While in group B, 188 postoperative complications occurred in 85 patients (22.66%). Patient morbidity was more frequent in group A than in group B. A statistically significant difference was observed in wound complications ($P = 0.02$), occurrence of internal haemorrhage ($P = 0.05$) and development of a postoperative pancreatic fistula (POPF, $P = 0.02$). POPF occurred in 13 patients (19.4%) in group A and in 37 patients (9.9%) in group B. The POPF was grade C in 11 patients, five of them in cirrhotic group who died from sepsis and six in the non cirrhotic group, three of whom died from sepsis (Table 4).

In group A, two patients developed encephalopathy, seven patients developed postoperative ascites that was treated by diuretics and three patients (4.5%) developed liver cell failure. Twelve patients (17.5%) developed intra-abdominal collection, for whom ultrasound guided tubal drainage was performed. Eight patients (11.5%) required re-exploration, four because of internal haemorrhage, one for bleeding gastrojejunostomy, one for bleeding PG and two for debridement and drainage.

In group B, 40 patients (10.7%) developed intra-abdominal collection and were managed by ultrasound guided tubal drainage. Twenty seven patients (7.2%) required re-exploration, seven because of internal haemorrhage, 12 for bleeding gastrojejunostomy, six for bleeding

Table 3 Operative data n (%)

Variables	Cirrhotic group Group A	Non cirrhotic group Group B	P values
Median blood loss (mL)	500 (100-2500)	200 (50-2000)	0.0001
< 500 mL	31 (46.3)	233 (62.1)	0.01
> 500 mL	36 (53.7)	142 (37.9)	
Blood transfusion			
Median (unite)	1 (0-4)	0 (0-4)	0.0001
Number of patients	38 (56.7)	145 (38.7)	0.006
Tumour size			
Mean (cm)	2.61 ± 1.2	2.82 ± 1.13	NS
< 2 cm	33 (49.3)	144 (38.4)	
> 2 cm	34 (50.7)	231 (61.6)	
Pancreatic texture			
Soft	48 (71.6)	246 (65.6)	NS
Firm	19 (28.4)	129 (34.4)	
Pancreatic duct diameter			
Mean (mm)	4.04 ± 2.96	4.24 ± 2.68	NS
< 3 mm	39 (58.2)	208 (55.5)	NS
> 3 mm	28 (41.8)	195 (44.5)	
Site of tumour			
Ampullary	25 (37.3)	116 (30.9)	
Pancreatic head mass	34 (50.7)	222 (59.2)	NS
Cholangiocarcinoma	2 (3)	13 (3.5)	
Duodenal tumour	6 (9)	24 (6.4)	
Operative time (h)	5.81 ± 0.87	5.1 ± 0.99	0.0001

NS: Not significant.

PG, one for debridement and drainage (one patient) and completion spleno-pancreatectomy was required in one patient who had PF complicated by internal haemorrhage because of erosion of the gastroduodenal artery.

Postoperative complications, including delayed gastric emptying, intra-abdominal collection, biliary leakage, pulmonary complication, bleeding gastrojejunostomy and bleeding PG, were not significantly different between both groups (Table 4).

Cirrhotic patients with portal hypertension were associated with poorer outcome than cirrhotic patients without portal hypertension. The median intraoperative blood loss and blood transfusion were significantly more in cirrhotic patients with portal hypertension than in cirrhotic patients without portal hypertension [blood loss was 1000 mL (200-2500 mL) *vs* 300 mL (100-2500 mL), *P* = 0.001 respectively and blood transfusion was two units (0-4 units) *vs* one unite (0-4 units), *P* = 0.02 respectively]. Twelve (75%) of the cirrhotic patients with portal hypertension required a blood transfusion, while 26 (51%) cirrhotic patients without portal hypertension required a blood transfusion intraoperatively. Patients who had portal hypertension developed 30 postoperative complications in the form of pancreatic leakage in six patients (37.5%), ascites in three patients (18.8%), wound infection in four patients (25%), intra-abdominal collection in four patients (25%), delayed gastric emptying in four patients (25%) and deterioration of liver function in two cases (12.5%, Table 5).

Hospital mortality was significantly higher in group A than in group B [8 (11.9%) *vs* 6 (1.6%), *P* = 0.0001].

Table 4 Postoperative data n (%)

Variables	Cirrhotic group Group A	Non cirrhotic group Group B	P values
Time to resume oral intake (d)	5.98 ± 5.11	6.08 ± 5.71	NS
Drain removal (d)	11.2 ± 9.89	9.41 ± 6.76	NS
Drain amount (mL)	1106.76 ± 1388.91	676.42 ± 1871.36	NS
Complications			
Pancreatic fistula	13 (19.4)	37 (9.9)	0.02
Grade A	5 (7.5)	16 (4.3)	
Grade B	3 (4.5)	15 (4)	NS
Grade C	5 (7.5)	6 (1.6)	
Delayed gastric emptying	10 (14.9)	41 (10.9)	NS
Biliary leakage	4 (6)	19 (5.1)	NS
Wound infection	10 (14.9)	24 (6.4)	0.02
Burst wound	4 (6)	2 (0.5)	0.0001
Internal haemorrhage	4 (6)	7 (1.9)	0.05
Bleeding	1 (1.5)	12 (3.2)	NS
gastrojejunostomy			
Bleeding	1 (1.5)	6 (1.6)	NS
pancreaticogastrostomy			
Abdominal collection	12 (17.9)	40 (10.7)	NS
Encephalopathy	2 (3)	0	0.001
Ascites	7 (10.44)	0	0.0001
Re-exploration	8 (11.9)	27 (7.2)	NS
Postoperative albumin (gm%)	2.81 ± 0.56	2.97 ± 0.43	0.01
Postoperative bilirubin (mg%)	4.54 ± 5.1	3.54 ± 3.89	NS
Postoperative SGPT (IU/L)	113.08 ± 50.1	58.35 ± 82.1	0.0001
Hospital mortality	8 (11.9)	6 (1.6)	0.0001
Liver cell failure	4 (6)	0	
Sepsis	4 (6)	4 (1)	
Pulmonary embolism	0	2 (0.5%)	
Postoperative stay (d)	12.97 ± 11.2	10.71 ± 7.41	0.03
Median survival (mo)	19	24	0.009
1 yr	42	59	
2 yr	13	29	
3 yr	8	19	

NS: Not significant.

Mortality in the cirrhotic group, 6/63 patients died had Child A and 2/4 patients had Child B (Table 4). Hospital mortality in cirrhotic patients with portal hypertension was higher than in cirrhotic patients without hypertension [4/16 (25%) *vs* 4/51 (7.8%), *P* = 0.07, Table 5].

Long term survival

The median follow up time for this study was 22 mo (range; 1-123 mo).The median survival was 19 mo in group A and 24 mo in group B. The 1, 2, and 3 year survival rates were 42%, 13%, and 3% respectively in group A and 59%, 29%, and 19%, respectively, in group B. There was a statistically significant difference between the two groups (*P* = 0.009, Table 4).

DISCUSSION

Recently, the operative mortality rate after PD has dramatically decreased to less than 5%, while the incidence

Table 5 Outcomes of cirrhotic patients n (%)

Variables	Cirrhotic Group	Patients without PHT (51 patients)	Patients with PHT (16 patients)	P values
Age				
Mean (yr)	54.07 ± 9.43	54.66 ± 10.05	52.18 ± 7.04	NS
< 60 yr	48 (71.6)	35 (68.6)	13 (81.3)	NS
> 60 yr	19 (28.4)	16 (31.4)	3 (18.8)	
Sex				
Male	52 (77.6)	40 (78.4)	12 (75)	NS
Female	15 (22.4)	11 (21.6)	4 (25)	
Median blood loss (mL)	500 (100-2500)	300 (100-2500)	1000 (200-2500)	0.001
< 500 mL	31 (46.3)	26 (51)	5 (31.3)	NS
> 500 mL	36 (53.7)	25 (49)	11 (68.8)	
Blood transfusion				
Median (unite)	1 (0-4)	1 (0-4)	2 (0-4)	0.020
Number of patients	38 (56.7)	26 (51)	12 (75)	
Operative time (h)	5.81 ± 0.87	5.8 ± 0.91	5.68 ± 0.72	NS
Hospital stay (d)	12.97 ± 11.2	14.5 ± 10.2	12.49 ± 11.55	NS
Pancreatic fistula	13 (19.4)	7 (13.7)	6 (37.5)	NS
Grade A	5 (7.5)	3 (5.9)	2 (12.5)	NS
Grade B	3 (4.5)	1 (2)	2 (12.5)	
Grade C	5 (7.5)	3 (5.9)	2 (12.5)	
Delayed gastric emptying	10 (14.9)	6 (11.8)	4 (25)	NS
Biliary leakage	4 (6)	3 (5.9)	1 (6.3)	NS
Wound infection	10 (14.9)	6 (11.8)	4 (25)	NS
Burst wound	4 (6)	2 (3.9)	2 (12.5)	NS
Internal haemorrhage	4 (6)	3 (5.9)	1 (6.3)	NS
Bleeding gastrojejunostomy	1 (1.5)	0	1 (6.3)	NS
Bleeding pancreaticogastrostomy	1 (1.5)	0	1 (6.3)	NS
Abdominal collection	12 (17.9)	8 (15.7)	4 (25)	NS
Encephalopathy	2 (3)	1 (2)	1 (6.3)	NS
Ascites	7 (10.44)	4 (7.8)	3 (18.8)	NS
Re-exploration	8 (11.9)	4 (7.8)	4 (25)	NS
Hospital mortality	8 (11.9)	4 (7.8)	4 (25)	NS
Liver cell failure	4 (6)	2 (3.9)	2 (12.5)	
Sepsis	4 (6)	2 (3.9)	2 (12.5)	
Pulmonary embolism	0			
Median survival (mo)	19	21	18	NS
1 yr	42	41	46	
2 yr	13	15	4	
3 yr	8	9	0	

NS: Not significant; PHT: Portal hypertension.

of postoperative complications remains high, from 30% to 60%^[1-4]. However, PD remains the only curative treatment for periampullary tumours. In the majority of cases, morbidity and mortality after PD are related to surgical management of the pancreatic stump and anatomical feature of the stump^[4-6]. PD may have a high risk of developing considerable complications, including POPF, intraabdominal bleeding, delayed gastric emptying, or intraabdominal collection^[1-6].

The incidence and prevalence of cirrhosis has been increasing in many countries for the past four decades, due to the increase incidence of viral hepatitis, alcoholic intake and non-alcohol related fatty liver disease^[10,11,29,30]. These individuals are at an increased risk of bleeding, infection, hepatic decompensation, including hepatic coma after a major abdominal operation. Therefore, PD in these patients must be performed in a high volume center^[29-34]. Indication for cancer treatment in cirrhotic patients has expanded, because surgical techniques and medical management have been improved remarkably. It has been suggested that PD in cirrhotic patient carries a

high risk of morbidity and mortality. Appropriate perioperative evaluation of cirrhotic patients will lead to their safer management^[13,20,31-36].

Few studies with small numbers of patients have been published to show the impact of cirrhosis on the surgical outcome after pancreatic resection^[20,31-34,37]. No evidence-based guidelines were obtained regarding the management of resectable periampullary tumour in cirrhotic patients^[1,35-40]. Artinyan *et al*^[12] reported that cirrhosis is a risk factor for postoperative morbidity and mortality after general surgical procedures. However, the impact of cirrhosis on surgical outcome in gastrointestinal malignancies has not been described.

In our study, we decided to perform PD in child A and B patients with periampullary tumours. One way to avoid a high operative mortality in Child B and C is not to operate. The severity of liver disease is the most important factor predicting postoperative surgical outcome. Patients with liver cirrhosis have an inappropriate response to surgical stress secondary to the loss of liver reserve and because of other systemic derangements that

are the result of hepatic dysfunction (such as hemodynamic impairments)^[32]. A case control study by Warnick *et al*^[31] compared outcomes in 32 cirrhotic patients (30 Child A and Child B) *vs* matched controls (non cirrhotic) undergoing pancreatic resection surgery, they concluded that the cirrhotic group had a significantly higher rate of complications than the non-cirrhotic group (47% *vs* 22%; $P = 0.035$), and required reoperation (34% *vs* 12%, $P = 0.039$). These patients also had a prolonged hospital stay (27.9 d *vs* 24.3 d), a significantly longer ICU stay (8.6 d *vs* 3.7 d; $P = 0.033$) and required twice as many transfusions. Overall, the hospital mortality was 3 patients, 1 with Child A (3% of all Child A patients) and 2 with Child B cirrhosis. The demanding medical efforts required by these patients demand that they are treated exclusively in high-volume centres^[29].

In this study, we found that intraoperative blood loss was significantly higher in cirrhotic patients. Estimated intraoperative bleeding of more than 500 ml occurred in 36 patients (53.7%) in group A and 142 (37.9%) patients in group B, the difference between the two groups was statistically significant ($P = 0.015$). In cirrhotic patients, there are a bleeding tendency and portal hypertension explained the increased intraoperative blood loss. We have overcome this bleeding tendency using vitamin K injection and fresh frozen plasma. We used suture ligation rather than cauterisation when possible. Currently, the ultrasonically activated (Harmonic) scalpel and LigaSure™ have proved to be effective and safe instruments for dissection and haemostasis in both open and laparoscopic surgical procedures^[17,19,38,40].

Pancreatic leakage remains the most important cause of morbidity, and also contributes significantly to prolonged hospitalization, increased health care costs and mortality. It remains a challenge at high volume centres for pancreatic surgery^[4,5]. The incidence of pancreatic anastomotic leakage after PD among different series ranged from 5% to 30%^[2,6]. Many factors influence PF after PD, including age, sex, preoperative jaundice, operative time, intraoperative blood loss, type of pancreatic reconstruction, anastomotic technique, consistency of pancreatic stump, pancreatic duct diameter, use of somatostatin and surgeon experience^[6-11]. In our study, POPF occurred in 13 patients (19.4%) in group A and in 37 patients (9.9%) in group B ($P = 0.02$). The POPF was grade C in 11 patients, five in the cirrhotic group who died from sepsis, and six in the non-cirrhotic group, three of whom died from sepsis. This is because the healing power of cirrhotic patients is reduced compared with non-cirrhotic patients.

In this study, two patients developed encephalopathy and seven patients developed postoperative ascites in the cirrhotic group. Encephalopathy may be induced by infection, diuretics, metabolic alkalosis, constipation, hypoxia, sepsis, bleeding and electrolyte imbalance in the perioperative period. Correction of electrolyte imbalance, treatment of infection, branched chain amino acid and restriction of sedatives help to prevent encephalopa-

thy^[32-34].

The degree of portal hypertension can be correlated with the severity of cirrhosis, which is estimated by the Child-Pugh score. As a result, an improvement in liver function is associated with decrease in portal hypertension. Cucchetti *et al*^[24] reported that cirrhotic patients with portal hypertension were associated with poorer outcome. Patients with portal hypertension were often Child-Pugh B and C patients, and when considering only Child-Pugh A class, the results were similar with or without portal hypertension. Some authors concluded that portal hypertension should not be considered as a contraindication for hepatic resection^[24,25]. In our study, cirrhotic patients with portal hypertension were associated with poorer outcome than cirrhotic patients without portal hypertension. Intraoperative blood loss and blood transfusion were significantly higher in cirrhotic patients with portal hypertension than in cirrhotic patients without portal hypertension. Patients who had portal hypertension developed 30 postoperative complications in the form of pancreatic leakage, ascites, wound infection, intra-abdominal collection, delayed gastric emptying and deterioration of liver function.

The hospital mortality rates after various surgical operations among cirrhotic patients range from 8.3% to 25% (even in well selected cases) compared to 1.1% in non-cirrhotic patients^[34-37]. Mortality is the consequence of a high rate of postoperative liver cell failure (especially in cases of intra-abdominal surgery) and an increased risk of bacterial infection^[36]. Warnick *et al*^[31] reported that, overall, 3 patients died following surgery. In Child A cirrhotic patient, the mortality is, however, comparable to non-cirrhotic patients. Artinyan *et al*^[12] reported that a query of the National Inpatient Sample Database (2005-2008) identified 106729 patients who underwent resection for GI malignancy; 1479 (1.4%) had cirrhosis. Cirrhotic patients had higher risk of hospital mortality (8.9% *vs* 2.8%, $P < 0.001$) and longer postoperative stay (11.5 ± 0.26 d *vs* 10.0 ± 0.03 d, $P < 0.001$). Mortality was highest in patients with moderate to severe liver cirrhosis (21.5% *vs* 6.5%, $P < 0.001$). On multivariate analysis, cirrhosis was an independent predictor of hospital mortality. That study also suggested that resection of gastrointestinal malignancy can be performed safely in well-selected cirrhotic patients with mild liver dysfunction. In our study, the hospital mortality was significantly higher in cirrhotic patients than in non-cirrhotic patients [8/67 (11.9%) *vs* 6/375 (1.6%), $P = 0.0001$] and the hospital mortality was higher in Child B patients than Child A. The cause of death in cirrhotic group was liver cell failure in four patients (6%) and sepsis in four patients (6%). Hospital mortality in cirrhotic patients with portal hypertension was higher than in cirrhotic patients without hypertension [4/16 (25%) *vs* 4/51 (7.8%), $P = 0.07$]. In our series, postoperative mortality was low probably because we have experience in pancreatic surgery: in our centre we perform around forty cases per year^[41,42].

In this study, the median survival was 19 mo for cir-

rhctic patients, which is comparable to the 15.8 mo reported by Fuks *et al*³⁹ for PD in patients with cirrhosis.

The limitations of this study were the retrospective design and the limited number of cases. Further studies are needed to confirm the impact of cirrhosis and portal hypertension in surgical outcome after PD and to show risk factors.

In a conclusion, PD is associated with an increased risk of postoperative morbidity in patients with liver cirrhosis; therefore, it is recommended only in patients with Child A cirrhosis. Cirrhotic patients with portal hypertension were associated with poorer outcome than cirrhotic patients without portal hypertension. Patients with periampullary tumour and well-compensated chronic liver disease should be routinely considered for radical surgery at high volume centres with available expertise to manage liver cirrhosis.

COMMENTS

Background

Indication for cancer treatment in cirrhotic patients has expanded. Patients with periampullary tumours and well-compensated chronic liver disease should be routinely considered for pancreaticoduodenectomy (PD) at high volume centres with available expertise to manage liver cirrhosis. PD is associated with an increased risk of postoperative morbidity in patients with liver cirrhosis; therefore, it is only recommended in patients with Child A cirrhosis without portal hypertension.

Research frontiers

Intraoperative blood loss and blood transfusion were significantly more in cirrhotic. The mean surgical time in group A was significantly longer than that in group B. Wound complications, internal haemorrhage, pancreatic fistula and hospital mortality were significantly higher in cirrhotic patients. Postoperative stay was significantly longer in cirrhotic. The median survival was in cirrhotic patients after PD. Portal hypertension (PHT) was present in 16/67 cirrhotic patients (23.9%). The intraoperative blood loss and blood transfusion were significantly more in portal hypertension (PHT). Postoperative morbidity and hospital mortality were higher in cirrhotic with PHT.

Innovations and breakthroughs

Patients with periampullary tumour and well-compensated chronic liver disease should routinely be considered for radical surgery at high volume centres with expertise available to manage liver cirrhosis.

Applications

PD is associated with an increased risk of postoperative morbidity in patients with liver cirrhosis, and therefore it is recommended only in patients with Child A cirrhosis. Cirrhotic patients with portal hypertension were associated with poorer outcome than cirrhotic patients without portal hypertension. Patients with periampullary tumour and well-compensated chronic liver disease should routinely be considered for radical surgery at high volume centres with expertise available to manage liver cirrhosis.

Peer review

It is interesting and important to investigate surgical outcomes of PD in patients with liver cirrhosis. PD is recommended only in patients with Child A cirrhosis.

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